complications

MDPI

Review

Mitochondrial Bioenergetic Dysfunction as a Driver in Postoperative Low Cardiac Output Syndrome: Mechanistic Insights and Clinical Implications After Cardiac Surgery

Dhienda C. Shahannaz [1] and Tadahisa Sugiura [2,*]

[1] Digestive Disease & Surgery Institute, Cleveland Clinic, Cleveland, OH 44195, USA; dhiendaladdynasrul@gmail.com
[2] Department of Cardiothoracic and Vascular Surgery, Montefiore Medical Center, Albert Einstein College of Medicine, Greene Medical Arts Pavilion 5th Floor, 3400 Bainbridge Avenue, Bronx, NY 10467, USA
* Correspondence: tsugiura@montefiore.org; Tel.: +1-718-405-8249

Abstract

Background: Low Cardiac Output Syndrome (LCOS) remains a common and clinically significant complication after cardiac surgery, characterized by impaired myocardial performance and inadequate systemic oxygen delivery despite optimized preload, afterload, and rhythm control. Although LCOS has traditionally been attributed to ischemia–reperfusion injury, myocardial stunning, inflammation, and neurohormonal dysregulation, accumulating evidence suggests that subcellular energetic impairment may contribute to postoperative myocardial dysfunction. Objective: This review evaluates mitochondrial dysfunction as a potential pathophysiological substrate that may underlie or exacerbate postoperative LCOS, integrating experimental, translational, and clinical findings relevant to adult cardiac surgery. Methods: A focused narrative review of preclinical and clinical literature was performed, emphasizing mitochondrial bioenergetics, calcium handling, redox signaling, and mitochondrial quality control in the context of cardiopulmonary bypass, ischemia–reperfusion, and postoperative myocardial injury. Results: Cardiomyocytes rely predominantly on mitochondrial oxidative phosphorylation, which supplies approximately 95% of myocardial ATP under physiological conditions. Surgical ischemia–reperfusion, cardioplegia, and systemic inflammatory activation are associated with transient mitochondrial disturbances, including impaired electron transport, increased reactive oxygen species generation, calcium overload, and mitochondrial permeability transition pore opening. These changes may contribute to reduced ATP availability, delayed myocardial recovery, contractile inefficiency, and increased susceptibility to arrhythmias. Emerging evidence suggests that circulating mitochondrial biomarkers, such as cell-free mitochondrial DNA, correlate with postoperative organ dysfunction, supporting the presence of systemic mitochondrial stress after cardiac surgery. Conclusions: Postoperative LCOS may partially reflect a reversible state of myocardial energetic failure. Recognition of mitochondrial involvement complements established hemodynamic and inflammatory models and offers a biologically plausible framework for variability in postoperative cardiac recovery.

Keywords: low cardiac output syndrome; cardiac surgery; mitochondrial dysfunction; ischemia–reperfusion injury; cardiopulmonary bypass; myocardial stunning; bioenergetics; Survivor Activator Factor Enhancement (SAFE) pathway; STAT3; oxidative stress

Check for updates

Academic Editor: Mario D'Oria

Received: 19 January 2026
Revised: 11 May 2026
Accepted: 4 June 2026
Published: 30 June 2026

Copyright: © 2026 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license.

1. Introduction

Low Cardiac Output Syndrome (LCOS) remains one of the most clinically significant complications following adult cardiac surgery, contributing to prolonged intensive care unit stays [1,2], increased requirements for inotropic support [3,4] or mechanical circulatory assistance [5,6], and higher postoperative morbidity and mortality [7,8]. LCOS is generally defined as inadequate cardiac pump function resulting in insufficient systemic oxygen delivery, often necessitating pharmacologic or mechanical intervention. Reported incidence varies widely, reaching up to approximately 27%, depending on patient characteristics, surgical complexity, and the absence of universally standardized diagnostic criteria across studies [9]. Definitions of LCOS vary according to cardiac index thresholds, inotropic requirements, lactate elevation, and need for mechanical circulatory support, contributing to substantial heterogeneity in reported incidence and outcome comparisons. Despite decades of refinement in surgical techniques and perioperative care, LCOS has proven difficult to eliminate. Contributing factors include the absence of a uniform definition, an evolving surgical population characterized by advanced age and reduced cardiac reserve, and the fact that current management strategies remain largely supportive rather than mechanistically targeted.

The pathophysiology of LCOS is widely recognized as multifactorial. Established contributors include ischemia–reperfusion injury during aortic cross-clamping [10,11], myocardial stunning [5,10], systemic and myocardial inflammation [12,13], neurohormonal activation [14,15], and alterations in preload, afterload, and heart rate [16,17]. Advances in myocardial protection strategies [18,19], cardioplegia formulations [20–22], and perioperative hemodynamic management [23–25] have mitigated some of these insults, yet LCOS continues to occur even in cases with apparently adequate surgical correction and optimized macrocirculatory parameters. This persistence highlights unresolved gaps in current pathophysiological models and suggests that mechanisms beyond gross perfusion and structural myocardial integrity may influence postoperative cardiac performance.

LCOS is most frequently encountered following procedures associated with prolonged ischemic exposure or increased myocardial stress, including coronary artery bypass grafting, valve surgery, combined CABG-valve procedures, complex aortic surgery, and reoperative cardiac surgery [26]. Clinically, LCOS manifests through hypotension, reduced cardiac index, oliguria, elevated lactate levels, metabolic acidosis, impaired end-organ perfusion, and dependence on inotropic or mechanical circulatory support [27,28]. Persistent LCOS is associated with prolonged intensive care unit stay, renal dysfunction, arrhythmias, multiorgan failure, and increased perioperative mortality [29,30].

Within this context, mitochondrial function has emerged as a biologically plausible contributor to postoperative myocardial dysfunction [31–33]. The heart's extraordinary energy demand renders cardiomyocyte performance highly dependent on intact mitochondrial bioenergetics, calcium handling, and redox balance. Beyond ATP generation, mitochondria regulate excitation–contraction coupling, intracellular calcium homeostasis, and cell survival signaling [34–47]—processes that are acutely stressed during cardiac surgery. Even transient perturbations in mitochondrial function may therefore disproportionately impair myocardial performance without causing irreversible myocyte loss [48–51].

Cardiac surgery exposes the myocardium to multiple stressors capable of disrupting mitochondrial homeostasis [49–52]. Ischemia–reperfusion associated with cardiopulmonary bypass [53] and cardioplegic arrest [54,55] alters electron transport chain efficiency, increases reactive oxygen species generation, and destabilizes mitochondrial membrane potential [52]. Reperfusion-related calcium overload further challenges mitochondrial integrity by sensitizing the mitochondrial permeability transition pore, promoting a state of bioenergetic inefficiency rather than frank necrosis. These changes may manifest clinically

as delayed or incomplete functional recovery despite preserved coronary perfusion and structurally intact myocardium [36,37].

From a clinical perspective, mitochondrial vulnerability provides a coherent explanation for several characteristic features of LCOS. A mismatch between myocardial energy supply and demand—rather than an absolute loss of contractile units—may underlie reduced stroke volume, impaired contractile reserve, heightened afterload sensitivity, and diminished responsiveness to inotropic therapy. Mitochondrial dysfunction has also been implicated in postoperative arrhythmogenesis [55–57], further compounding low-output states. Importantly, these phenomena align with the observed temporal profile of LCOS, which often evolves after reperfusion and improves gradually rather than immediately.

Translational observations linking perioperative mitochondrial stress to postoperative organ dysfunction support the clinical relevance of this framework, reinforcing the concept that mitochondrial impairment is not merely an experimental construct but a feature of the surgical stress response. Framed conservatively, mitochondrial dysfunction does not replace established inflammatory or hemodynamic paradigms of LCOS; rather, it offers an integrative cellular layer through which these processes may exert sustained effects on myocardial performance.

This review synthesizes current mechanistic, translational, and clinical evidence linking mitochondrial dysfunction to postoperative LCOS, emphasizing mitochondrial bioenergetics as an integrative framework for delayed myocardial recovery, heterogeneous treatment response, and persistent postoperative dysfunction beyond conventional hemodynamic paradigms, while maintaining a conservative interpretation regarding causality.

2. Methods

This manuscript is a focused narrative review synthesizing mechanistic, translational, and clinical evidence addressing mitochondrial dysfunction as a modifier of postoperative low cardiac output syndrome (LCOS) following adult cardiac surgery. The intent was to integrate established perioperative LCOS paradigms with emerging myocardial bioenergetic data, rather than to perform a formal systematic review or meta-analysis.

The primary objective of this review was to integrate established perioperative LCOS concepts with emerging evidence in myocardial bioenergetics and mitochondrial physiology, with emphasis on translational relevance for adult cardiac surgery.

2.1. Literature Search Strategy

A targeted literature search was conducted using PubMed/MEDLINE, Scopus, and Web of Science, encompassing publications from database inception through the most recent update prior to manuscript submission. Search terms included combinations of:

1. Low cardiac output syndrome, cardiac surgery, cardiopulmonary bypass;
2. Ischemia–reperfusion injury, myocardial stunning;
3. Mitochondrial dysfunction, myocardial bioenergetics, ATP depletion;
4. Oxidative stress, mitochondrial permeability transition pore;
5. Cardioplegia, myocardial protection, perioperative hypothermia.

Reference lists of key clinical trials, translational studies, and authoritative reviews were manually screened to identify additional relevant literature. The literature search included studies involving adult coronary artery bypass grafting, valve surgery, combined cardiac procedures, aortic surgery, cardioplegic arrest, and cardiopulmonary bypass-associated myocardial dysfunction.

2.2. Study Selection

The search encompassed publications from database inception through January 2026. Following duplicate removal and relevance screening, approximately 312 articles were reviewed in full text, of which 168 studies were ultimately synthesized qualitatively based on mechanistic relevance, translational value, and perioperative applicability. Study selection emphasized mechanistic relevance, reproducibility across experimental systems, translational applicability to adult cardiac surgery, and consistency with established perioperative physiology.

Studies were included if they met one or more of the following criteria:

1. Reported clinical outcomes related to LCOS or myocardial dysfunction after adult cardiac surgery.
2. Investigated ischemia–reperfusion injury or myocardial stunning with relevance to surgical ischemic intervals.
3. Examined mitochondrial bioenergetics, calcium handling, or oxidative injury in cardiac surgical or closely related experimental models.
4. Provided translational insight linking subcellular energetic impairment to postoperative myocardial performance.

Studies were excluded if they focused exclusively on pediatric populations, non-cardiac surgery, non-myocardial mitochondrial disease unrelated to perioperative injury, or lacked translational relevance to postoperative myocardial dysfunction. Given the conceptual and mechanistic focus of the manuscript, formal PRISMA-guided quantitative synthesis was not performed.

2.3. Evidence Synthesis

Given heterogeneity in study design, endpoints, and biological scale, data were synthesized qualitatively. Emphasis was placed on temporal perioperative relevance, reproducibility across experimental and clinical contexts, and biological plausibility within established LCOS frameworks.

Mitochondrial dysfunction was interpreted as a pathophysiologic amplifier influencing recovery trajectories, rather than as an isolated etiologic mechanism. Where direct adult cardiac surgical LCOS evidence was limited, mechanistic conclusions were conservatively extrapolated from myocardial ischemia–reperfusion, transplantation, and closely related cardiovascular experimental models. Non-cardiac surgical and isolated cellular findings were included only when mechanistically indispensable and are interpreted cautiously with respect to perioperative cardiac surgery applicability.

2.4. Presentation of Findings

Tables and figures were developed to align perioperative stressors with myocardial recovery patterns and LCOS relevance, emphasizing clinical interpretability for cardiothoracic surgeons. Visual schematics were designed to illustrate mechanistic convergence without implying direct causality beyond available evidence (Figure 1).

2.5. Limitations

This review is limited by reliance on indirect clinical correlates and translational data, reflecting the current state of human myocardial bioenergetic research. In addition, many experimental mitochondrial studies disproportionately involve male animal models or predominantly male cardiac surgical cohorts, limiting interpretation of potential sex-based differences in mitochondrial resilience, inflammatory signaling, and postoperative recovery trajectories.

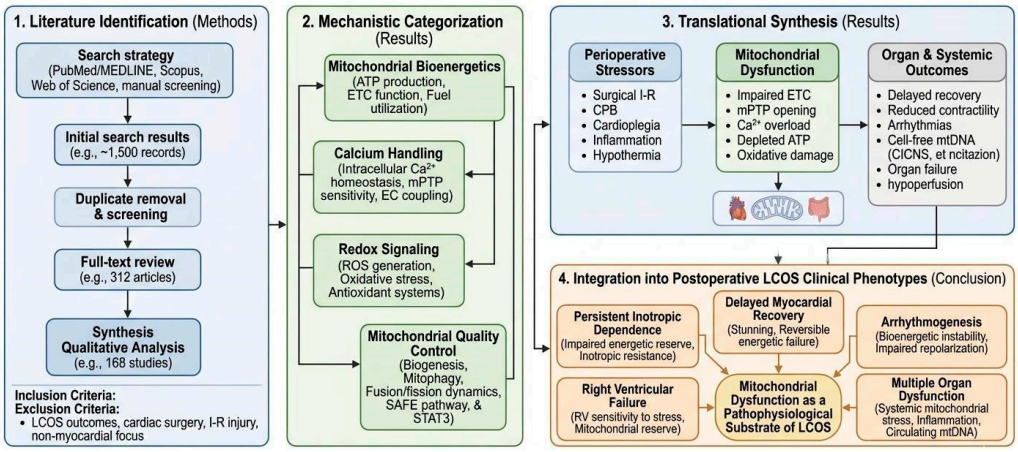


Figure 1. Narrative review framework illustrating literature identification, mechanistic categorization, translational synthesis, and integration into postoperative LCOS clinical phenotypes.

2.6. Figure Preparation Statement

All figures and illustrations were conceptualized and created by the authors using standard graphics and data-visualization software (including Adobe Photoshop version 27, Adobe Illustrator version 30.2, PowerPoint version 2024, GraphPad Prism, and Canva version 2.0). No artificial intelligence-based image generation or automated figure design tools were used in the preparation of graphical content. All schematics are original and were manually constructed based on the authors' interpretation of the cited literature. No proprietary scientific illustration platforms (e.g., BioRender) were used, and no third-party copyrighted materials are included.

3. LCOS After Cardiac Surgery: Pathophysiological Context

Postoperative low cardiac output syndrome (LCOS) arises from interacting myocardial, inflammatory (such as cytokine storm) [58], neurohormonal, and microcirculatory disturbances [59] following cardiac surgery. Although ischemia–reperfusion injury, myocardial stunning, and systemic inflammation are well-established contributors, these processes rarely act in isolation. Their dynamic interaction determines the severity, duration, and reversibility of postoperative myocardial dysfunction.

Rather than reflecting a single dominant lesion, LCOS represents a transient inability of the heart to match energetic supply with mechanical demand in the early postoperative period where a predictable nadir (low point) occurs between 6–18 h post-surgery [60]. This framework accommodates the clinical observation that delayed recovery frequently occurs despite restored coronary perfusion and apparently adequate macrocirculatory parameters.

3.1. Ischemia–Reperfusion Injury

Ischemia–reperfusion (I/R) injury is inherent to cardiac surgery involving cardiopulmonary bypass and aortic cross-clamping [61,62]. Temporary interruption of coronary blood flow followed by abrupt reperfusion imposes substantial metabolic stress on cardiomyocytes [63,64]. Clinically, this transition is associated with transient depression of myocardial performance even in the absence of irreversible necrosis [65,66].

Importantly, post-reperfusion dysfunction often reflects impaired myocardial efficiency rather than loss of viable myocardium [67–70]. The magnitude of dysfunction varies according to ischemic duration, myocardial protection strategies, temperature management, and patient-specific vulnerability [71–73]. These features align with the time-dependent recovery characteristic of LCOS, reflecting the progressive resolution of reperfusion-associated oxidative stress, restoration of mitochondrial ATP stores depleted

during aortic cross-clamping, and re-establishment of intracellular calcium homeostasis through sarcoplasmic reticulum re-sequestration—processes essential for normalization of excitation–contraction coupling [60,72]. Detailed subcellular mechanisms linking I/R to mitochondrial dysfunction are addressed in Section 5 and are not reiterated here.

3.2. Myocardial Stunning and Inflammation

Myocardial stunning is defined by reversible post-ischemic contractile dysfunction despite preserved cellular viability and adequate perfusion [74,75]. Clinically, it manifests as reduced systolic performance requiring temporary pharmacologic or mechanical support [2,66].

Systemic and myocardial inflammation amplifies this process. Cardiopulmonary bypass triggers cytokine release, leukocyte activation, and endothelial dysfunction, which together impair contractile efficiency and prolong recovery [76,77]. Protective signaling cascades, including the Survivor Activating Factor Enhancement (SAFE) and Reperfusion Injury Salvage Kinase (RISK) pathways, modulate this inflammatory–metabolic interface [78,79]. Their mechanistic roles and translational constraints are discussed in Section 8.

3.3. Neurohormonal and Microcirculatory Factors

Neurohormonal activation further sustains LCOS. Sympathetic stimulation and engagement of the renin–angiotensin–aldosterone system initially support perfusion but ultimately increase myocardial oxygen demand and energetic stress [80–88].

At the microcirculatory level, heterogeneous perfusion persists despite normalization of global hemodynamic indices [89]. Capillary shunting [90] and endothelial dysfunction [91] limit effective oxygen delivery, creating a mismatch between macrocirculatory adequacy and cellular respiration [92,93]. This mismatch contributes to persistent LCOS despite optimized conventional targets [75,93].

3.4. Integrative Perspectives

Collectively, ischemia–reperfusion injury [94], myocardial stunning with inflammatory amplification [95,96], and neurohormonal–microcirculatory [97] disturbances converge to impair myocardial energetic efficiency. Mitochondrial dysfunction does not replace established LCOS paradigms [51,98] but provides a unifying mechanistic layer that explains delayed recovery and heterogeneous treatment response. These pathophysiological processes converge on mitochondrial bioenergetics, as detailed below.

4. Mitochondria in Cardiac Energy Homeostasis

Mitochondria integrate energetic supply with calcium signaling and redox balance to sustain myocardial performance [37]. Beyond ATP generation, they coordinate excitation–contraction coupling, metabolic adaptation, and cell survival [35–47]. In cardiac surgery, abrupt shifts in oxygen availability and workload render mitochondrial integrity a critical determinant of postoperative recovery. This section establishes a conceptual framework for mitochondrial function. Specific perioperative injury mechanisms are addressed in Section 5.

4.1. ATP Generation and Metabolic Coordination

The myocardium is uniquely dependent on continuous aerobic energy production, requiring precise coordination between substrate availability, oxidative metabolism, and mechanical demand [35–37]. Mitochondria facilitate this coordination by dynamically adjusting respiratory activity and substrate utilization to meet changing workloads [99–101]. This metabolic adaptability allows the healthy heart to maintain efficiency across a wide range of physiological conditions [102].

In the perioperative setting, this coordination may become transiently uncoupled. Even when global perfusion and hemodynamic parameters appear adequate, delays in restoring mitochondrial energetic efficiency can limit the heart's ability to meet immediate postoperative demand [61,103–105]. From a systems perspective, impaired energy coordination—rather than absolute ischemia—may underlie reduced myocardial reserve and delayed recovery observed in some patients after cardiac surgery.

4.2. Calcium Handling and Excitation–Contraction Coupling

Mitochondria play an essential modulatory role in intracellular calcium handling by linking cytosolic calcium flux to metabolic output [36,37,42,43]. Through this coupling, ATP production is matched to contractile demand, ensuring efficient excitation–contraction coupling under physiological conditions [36,37].

Disruption of this integration alters the balance between energy supply and mechanical workload [37,42,43]. When mitochondrial responsiveness to calcium signaling is impaired, myocardial efficiency declines, manifesting as reduced systolic performance and increased energetic cost of contraction [106–109]. This conceptual framework aligns with clinical observations of postoperative myocardial dysfunction that occurs despite preserved structural integrity and adequate perfusion.

4.3. Redox Signaling and Cell Survival

Mitochondria also function as regulators of intracellular redox signaling, maintaining a balance between adaptive signaling and oxidative stress [37]. Physiological redox signaling supports cellular adaptation and survival, whereas dysregulated redox balance compromises metabolic efficiency and cellular resilience [35–47].

In the postoperative heart, loss of redox equilibrium can amplify energetic inefficiency and impair recovery without necessarily causing immediate cell death [110–114]. Thus, redox imbalance represents a functional—not exclusively structural—threat to myocardial performance [37,42,43,110–114]. Mitochondrial redox regulation therefore constitutes a critical interface between metabolic stress and clinical expression of low cardiac output.

Collectively, mitochondria integrate energy production, calcium signaling, and redox balance to sustain myocardial performance [37,42,43,110–114]. Framed conceptually, mitochondrial dysfunction represents a state of impaired energetic coordination rather than isolated organelle failure [115–117]. At the molecular level, this imbalance reflects cumulative effects on electron transport efficiency, mitochondrial calcium buffering capacity, and redox-sensitive signaling nodes [35–47], which are detailed in subsequent sections. This perspective provides a mechanistic bridge between traditional hemodynamic explanations and the subcellular processes that influence postoperative myocardial recovery, setting the stage for detailed discussion of mitochondrial injury mechanisms and clinical consequences in subsequent sections.

5. Mechanisms of Mitochondrial Dysfunction in the Perioperative Heart

Perioperative mitochondrial dysfunction reflects converging stressors rather than a single dominant insult [118–121]. Ischemia–reperfusion, calcium dysregulation, and oxidative stress form an interdependent cascade that transiently compromises myocardial bioenergetic efficiency.

5.1. Ischemia–Reperfusion-Associated Mitochondrial Stress and Oxidative Injury

During ischemia, mitochondrial electron transport slows and membrane potential partially dissipates [30–33]. Reperfusion exposes mitochondria to abrupt oxidative and metabolic load before full functional recovery is achieved [122,123]. Early reperfusion is

therefore characterized by inefficient oxidative phosphorylation, transient ATP depletion, and excess reactive oxygen species generation [124].

Oxidative injury targets mitochondrial proteins, lipids, and mitochondrial DNA, perpetuating energetic inefficiency [37,38,125–127]. These changes typically remain reversible in adult cardiac surgery, consistent with delayed functional recovery rather than irreversible myocyte loss [128,129].

5.2. Calcium Overload and Mitochondrial Permeability Transition

Mitochondrial calcium uptake normally couples workload with ATP production. In the perioperative heart, excessive cytosolic calcium overwhelms this regulatory function and sensitizes the mitochondrial permeability transition pore [130–133]. Even transient pore opening disrupts membrane potential and ATP synthesis without immediate cell death [134–139].

This mechanism provides a cellular explanation for reduced contractile reserve, electrical instability, and poor inotropic responsiveness observed in LCOS [140–147]. As illustrated in Figure 2, perioperative calcium dysregulation promotes mPTP sensitization and transient pore opening, leading to mitochondrial energetic mismatch that underlies postoperative LCOS [140–151]. Clinically, this mitochondrial dysfunction manifests as diminished contractile reserve [51,109,142,152], arrhythmia susceptibility [40,55,56], and delayed myocardial recovery [66,67,94], as discussed in Section 6.

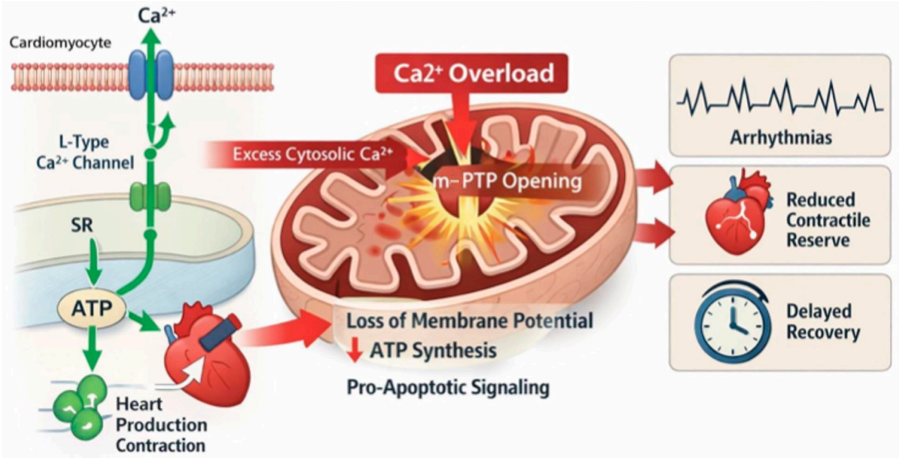


Figure 2. Mechanism of mitochondrial calcium handling and mPTP activation. Excess cytosolic calcium during reperfusion increases mitochondrial calcium load [51,69,134], sensitizing the mPTP [67,124,129]. Sustained mPTP opening dissipates membrane potential, halts ATP synthesis, and triggers pro-apoptotic signaling [49,71,95]. Green arrows indicate physiological calcium signaling; red arrows indicate pathologic overload.

This visual reinforces the critical interplay between calcium homeostasis and mitochondrial ATP production, emphasizing why therapeutic modulation of mPTP remains an attractive strategy [152,153].

5.3. Oxidative Stress and Mitochondrial DNA Damage

Mitochondria are both the primary source and principal target of ROS during reperfusion [35–39]. Excess ROS damages mitochondrial proteins, lipids, and mitochondrial DNA (mtDNA), further destabilizing oxidative phosphorylation [36–38,51,53,67,86]. Because mtDNA lacks histone protection and has limited repair capacity, oxidative injury perpetuates a feed-forward cycle of energetic inefficiency [153].

Release of mtDNA into the circulation also activates innate immune pathways, linking mitochondrial injury to systemic inflammation and postoperative organ dysfunction [154].

These observations reinforce the concept that mitochondrial stress contributes not only to myocardial dysfunction but also to the broader perioperative inflammatory milieu.

5.4. Integration with Protective Signaling Pathways

Endogenous cardioprotective pathways converge at the mitochondrial level to modulate these injurious processes. The Survivor Activating Factor Enhancement (SAFE) and Reperfusion Injury Salvage Kinase (RISK) pathways influence mitochondrial respiration, redox balance, and membrane stability during reperfusion [32,155–157]. Their actions reflect modulation rather than elimination of injury, shaping the trajectory of energetic recovery. To integrate these molecular insights, Figure 3 provides a schematic overview of how ischemia–reperfusion, calcium overload, and ROS converge on mitochondrial dysfunction, modulated by protective signaling cascades. These pathways are discussed in mechanistic detail in Section 8.

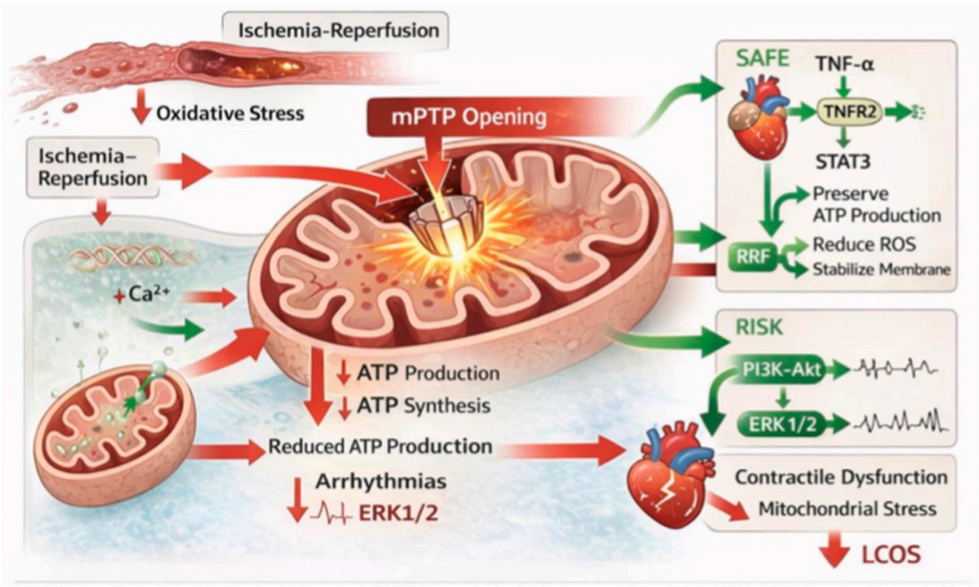


Figure 3. Mechanistic overview of mitochondrial dysfunction in postoperative LCOS. Ischemia–reperfusion induces ROS generation and calcium overload, sensitizing mPTP opening and impairing ATP production. Protective pathways (SAFE and RISK) mitigate injury via STAT3, Akt, and ERK1/2 signaling [32,51,67,95]. Arrows indicate stimulatory or inhibitory interactions; red highlights injurious events, green protective signals.

This system-level framework positions mitochondrial stress as a reversible modifier of LCOS rather than a primary etiologic driver. Perioperative insults variably affect mitochondrial recovery, thereby influencing the severity, duration, and clinical trajectory of postoperative low cardiac output syndrome.

In the setting of cardiac surgery, procedural factors, systemic responses, and patient-specific vulnerability collectively shape mitochondrial bioenergetic stress and recovery capacity. The following table synthesizes evidence from contemporary mechanistic and clinical studies to link these perioperative determinants with myocardial recovery patterns and clinically relevant LCOS phenotypes.

Table 1 summarizes key perioperative factors that influence mitochondrial bioenergetic stress and recovery after cardiac surgery. For each factor, the predominant direction of mitochondrial perturbation is indicated, followed by typical postoperative recovery trajectories and their clinical relevance to low cardiac output syndrome. The table links operative variables, systemic responses, and patient-specific vulnerabilities to delayed

myocardial recovery, impaired contractile reserve, and LCOS phenotypes through mitochondrial mechanisms.

Table 1. Perioperative Factors Influencing Mitochondrial Recovery Trajectories After Cardiac Surgery.

Perioperative Factor	Direction of Mitochondrial Stress	Typical Recovery Pattern	Clinical Relevance to LCOS
Ischemic duration (cross-clamp time/CPB time)	↑ ROS, transient ATP depletion, Ca^{2+} overload via prolonged ischemia–reperfusion	Delayed or heterogeneous recovery with longer durations → greater energetic stress	Longer cross-clamp/CPB times correlate with postoperative myocardial dysfunction and contractile depression due to mitochondrial oxidative stress and energetic mismatch [51]
Cold temperature (hypothermia during cardioplegia)	↓ metabolic rate but potential cold-induced mitochondrial perturbation	Heterogeneous: shorter metabolic demand but possible delayed ETC reactivation	Hypothermia reduces metabolic rate and ROS production, extending ischemic tolerance (Q_{10} effect), but may prolong recovery of oxidative phosphorylation [51].
Cardioplegia strategy (substrate and delivery)	Variable: affects ROS burst, Ca^{2+} handling, ATP preservation	Variable (protocol dependent)	Cardioplegia with balanced substrates and additives that protect mitochondria (e.g., antioxidants) may attenuate mitochondrial dysfunction; inconsistent results in clinical studies [158].
Systemic inflammation (CPB exposure)	↑ cytokines → mitochondrial respiratory impairment	Delayed/heterogeneous	CPB-induced inflammatory cascade negatively impacts mitochondrial respiration and recovery, linking subcellular dysfunction with clinical LCOS features [51].
Pre-existing comorbidities (diabetes, HF, age)	Baseline mitochondrial deficits → ↑ Ca^{2+} overload & ROS	Delayed, increased inter-patient variability	Patients with baseline mitochondrial vulnerability have slower recovery, greater energetic mismatch, and higher risk of arrhythmias/contractile dysfunction [51,158].
Ischemic preconditioning/remote conditioning	↓ ROS, improved Ca^{2+} handling & signaling	Rapid/improved recovery	RIPC and pharmacologic preconditioning modulate mitochondrial stress, showing improved functional outcomes in some cardiac surgery models [159].

This synthesis highlights that not all perioperative stresses are equal: some exert reversible energetic strain while others predispose to prolonged mitochondrial dysfunction that aligns with clinical LCOS manifestations. Understanding these patterns may guide tailored myocardial protection and postoperative support strategies. ↑ means an increase, ↓ means reduction, → means "leading to".

5.5. Clinical Relevance to LCOS

Collectively, ischemia–reperfusion-induced mitochondrial stress, calcium-dependent mPTP sensitization, and oxidative mtDNA damage impair myocardial energetic efficiency in a reversible manner. This framework explains key clinical features of LCOS, including delayed onset, incomplete response to hemodynamic optimization, arrhythmia susceptibility, and gradual recovery. Mitochondrial dysfunction thus serves as a unifying cellular substrate that complements—rather than replaces—established inflammatory and hemodynamic models of postoperative low cardiac output.

6. Mitochondrial Dysfunction and Clinical Features of LCOS

This section focuses on clinical translation, linking mitochondrial dysfunction to observed postoperative LCOS phenotypes rather than reiterating mechanistic pathways detailed earlier. Beyond patient-specific and systemic factors, operative myocardial protection strategies and ischemic duration further shape the temporal trajectory of mitochondrial recovery. Table 2 summarizes how cardioplegia approaches and ischemic exposure patterns influence postoperative myocardial recovery characteristics relevant to LCOS.

Table 2. Cardioplegia Strategy, Ischemic Duration, and Time-Dependent Myocardial Recovery Patterns Relevant to LCOS.

Cardioplegia Strategy	Typical Ischemic Exposure Context	Predominant Mitochondrial Stress Pattern	Expected Time-Dependent Recovery Pattern	Clinical LCOS Implication	Strength of Evidence
Cold crystalloid cardioplegia [18,19,21,22,61]	Often used during prolonged or intermittent arrest; greater dependence on re-dosing during extended cross-clamp [18,19]	Marked ETC reactivation delay (mechanistic synthesis)/impaired mitochondrial oxidative recovery, impaired oxidative phosphorylation on reperfusion; Ca^{2+} handling perturbation and ROS burst despite reduced metabolic demand [51,54,63,67,94]	Delayed but frequently reversible recovery over 24–72 h [65,66,68,95]	Myocardial stunning [2,73], delayed contractile recovery, higher early inotrope requirement [6,58]	Predominantly retrospective observational cardiac surgery studies with extensive translational ischemia–reperfusion literature; supported by several comparative perioperative cohorts
Cold blood cardioplegia [18,19,21,22]	Common in moderate to prolonged arrest, intermittent or continuous delivery [18,19]	Improved substrate delivery yet persistent reperfusion ROS generation; partial preservation of mitochondrial redox balance [53,54,62]	Intermediate recovery trajectory, faster than crystalloid but still time-dependent [18,19]	Reduced severity of stunning; associated with reduced severity of LCOS surrogates compared with crystalloid [18,21]	Mixed prospective and retrospective clinical observational studies with supportive translational mitochondrial and myocardial protection data
Warm blood cardioplegia [61,64]	Typically short to moderate arrest, often continuous or terminal warm reperfusion [64]	Higher baseline metabolism [68] → greater Ca^{2+} overload risk if interruption occurs [67,69]; less ETC restart delay when reperfusion is controlled	Earlier recovery (hours) when ischemia is limited; vulnerable if arrest is prolonged [64,65]	Faster weaning from inotropes; risk of LCOS if ischemia unexpectedly extends [6,67,69,73]	Small prospective clinical studies and comparative observational cohorts supported by experimental myocardial metabolism literature

Table 2. *Cont.*

Cardioplegia Strategy	Typical Ischemic Exposure Context	Predominant Mitochondrial Stress Pattern	Expected Time-Dependent Recovery Pattern	Clinical LCOS Implication	Strength of Evidence
Intermittent cardioplegia (any type) [61]	Repeated ischemia–reperfusion cycles during cross-clamp [53,62]	Recurrent ROS bursts, cumulative mPTP sensitization [67], mtDNA injury vulnerability [52]	Heterogeneous recovery, dependent on cumulative ischemic burden [65,66]	Variable LCOS phenotype [2,79]; arrhythmia susceptibility and fluctuating output [56]	Predominantly translational and mechanistic ischemia–reperfusion evidence with heterogeneous retrospective clinical observational support
Continuous cardioplegia (any type) [61,64]	Sustained myocardial arrest with minimized ischemic fluctuation	Reduced ROS oscillation [53], more stable mitochondrial membrane potential [67]	More uniform recovery [64], less delayed dysfunction	Lower incidence of severe LCOS, smoother postoperative course [2,6]	Limited prospective observational cardiac surgery studies with supportive physiologic and translational myocardial protection data
Cardioplegia with metabolic substrates/antioxidants (general) [25,32,97]	Used adjunctively in moderate to prolonged arrest; Selenium [25], Oxidative stress modulation [32,97]	Improved mitochondrial redox balance, partial mitigation of oxidative stress and ETC inhibition [25,32,113]	Facilitated myocardial recovery [25], particularly in metabolically vulnerable myocardium/stunning reversal [65]	Reduced inotrope dependence; potential attenuation of LCOS severity [6,25]	Translational and experimental evidence with limited prospective perioperative clinical validation and small heterogeneous human studies

Table 2 summarizes qualitative recovery patterns rather than absolute ischemic thresholds. Associations reflect integrated evidence from clinical observational studies, translational research, and established ischemia–reperfusion and myocardial stunning literature. Mitochondrial dysfunction is presented as a unifying mechanistic layer modulating LCOS expression rather than a competing paradigm. → means "leading to".

6.1. Energetic Mismatch and Reduced Contractile Reserve

In the perioperative period, mitochondrial dysfunction most commonly manifests as a mismatch between myocardial energy supply and mechanical demand [51,54,94]. Transient impairment of oxidative phosphorylation limits ATP availability at a time when calcium-dependent excitation–contraction coupling remains energetically demanding [104,108,142]. As a result, contractile reserve is reduced despite preserved coronary perfusion and adequate macrocirculatory support.

Clinically, this energetic mismatch presents as myocardial stunning, reduced stroke volume, and reliance on temporary inotropic or mechanical support [2,95,128]. Patients with pre-existing mitochondrial vulnerability—such as advanced age, diabetes, or chronic heart failure—exhibit more pronounced impairment and slower recovery [48,102].

6.2. Arrhythmias and Impaired Inotropic Response

Mitochondrial dysfunction contributes directly to postoperative arrhythmogenesis [51]. Energetic insufficiency and redox imbalance destabilize ion channel function and disrupt excitation–contraction coupling, increasing susceptibility to atrial and ventricular arrhythmias that further depress cardiac output [55,56].

In parallel, reduced ATP availability limits responsiveness to inotropic therapy [2,142]. Pharmacologic augmentation of calcium cycling increases energy demand without proportionate improvement in output when mitochondrial reserve is constrained, explaining persistent LCOS despite optimized hemodynamics [17].

6.3. Delayed Myocardial Recovery

The clinical course of LCOS often reflects delayed mitochondrial recovery rather than ongoing ischemia [65,68,128]. Residual mitochondrial stress prolongs contractile dysfunction for hours to days postoperatively [65,68,128]. Recovery trajectories vary according to baseline mitochondrial health and perioperative stress burden, shaping LCOS duration, arrhythmic risk, and responsiveness to therapy [40,65,68].

Together, energetic mismatch, electrical instability, and delayed recovery define the clinical expression of mitochondrial dysfunction in LCOS, providing a coherent translational link between cellular bioenergetics and postoperative cardiac performance [2,9,17]. Table 3 summarizes key clinical manifestations of LCOS alongside their underlying mitochondrial mechanisms, highlighting links between bioenergetic stress, arrhythmias, and contractile inefficiency. Understanding these mechanistic correlates informs both risk stratification and potential mitochondria-targeted interventions.

Table 3. Clinical Features and Mitochondrial Correlates in LCOS.

Clinical Feature of LCOS	Mitochondrial Biomarker or Functional Correlate	Underlying Energetic or Calcium Dysregulation	Relevant Mitochondrial-Linked Signaling Pathway (SAFE/RISK)	Potential Biomarker/Indicator	Key Quantitative Data (from Research)
Postoperative Atrial Fibrillation (POAF)	↓ Pre-op mitochondrial respiration (atrial tissue)	Impaired mitochondrial respiration and ATP production with ischemia–reperfusion injury and calcium overload → energetic mismatch and contractile inefficiency [160]	Engagement of cardioprotective signaling (e.g., SAFE/RISK) is documented to modulate mitochondrial energetic stress, though not fully compensatory in LCOS. Pathway involvement is inferred rather than directly measured in LCOS populations [161]	Elevated circulating cell-free mitochondrial DNA (cf-mtDNA) after CPB; altered mitochondrial respiration indices in atrial tissue [162,163]	POAF incidence 44% in patients with metabolic syndrome; lower ADP-stimulated mitochondrial respiration independently associated with AF onset ($p = 0.0028$) [162,163]
Reduced contractile reserve/myocardial stunning	Impaired respiratory chain activity and ATP generation in subsarcolemmal mitochondria following ischemia–reperfusion; calcium overload-induced energetic mismatch.	Impaired respiratory chain activity and ATP generation in subsarcolemmal mitochondria following ischemia–reperfusion; calcium overload-induced energetic mismatch.	Engagement of SAFE and RISK pathways shown to modulate mitochondrial calcium handling and redox balance, though not fully compensatory in LCOS.	Altered lactate/ATP or phosphocreatine ratios; postoperative elevations in cf-mtDNA [162,163]	Ischemia duration correlates with impaired respiratory chain function and altered mitochondrial Ca^{2+} handling in human cardiac tissue [161,163]
Low stroke volume requiring inotropic or mechanical support	Reduced oxidative phosphorylation efficiency limits ATP supply during increased calcium cycling demand.	Energetic mismatch due to reduced oxidative phosphorylation efficiency; impaired ATP generation relative to calcium cycling demand (seen mechanistically in I/R stress) [160].	RISK pathway kinases (Akt/ERK1/2) are studied in reperfusion models as modulators of mitochondrial function, though clinical direct LCOS studies are limited.	Elevated cf-mtDNA post CPB; systemic inflammatory and cardiac stress (including arrhythmias) [162,163]	No standardized mitochondrial biomarker threshold for LCOS; consistent posoperative mitochondrial stress signals reported across translational studies [158–160]

Table 3. *Cont.*

Clinical Feature of LCOS	Mitochondrial Biomarker or Functional Correlate	Underlying Energetic or Calcium Dysregulation	Relevant Mitochondrial-Linked Signaling Pathway (SAFE/RISK)	Potential Biomarker/Indicator	Key Quantitative Data (from Research)
Blunted responsiveness to inotropic therapy	Mitochondrial ATP supply fails to meet increased energetic demand induced by enhanced calcium cycling	Energetic insufficiency from mitochondrial respiration impairment to contractile augmentation (ATP supply does not match increased demand from enhanced Ca^{2+} cycling). Mechanistic parallels drawn from I/R injury models [160].	Although no direct clinical SAFE/RISK measurement in LCOS patients exists, these pathways are known to influence mitochondrial respiration and redox balance under stress.	Increased cf-mtDNA and metabolic shifts (e.g., lactate, pyruvate) after cardiac surgery suggest mitochondrial stress and may correlate with poorer functional response [162,163]	Mechanistic parallels derived from ischemia–reperfusion models rather than LCOs-specific trials [51,160]
Delayed myocardial recovery (hours-days)	Prolonged mitochondrial respiration recovery after reperfusion injury, calcium overload, and oxidative stress	Prolonged mitochondrial recovery from reperfusion injury, Ca^{2+} overload, and oxidative damage contributes to delayed ATP generation/energetic normalization and redox homeostasis/contractile recovery. Translational data support role of mitochondrial adaptation mechanisms [51]	Time-dependent engagement of protective signaling such as SAFE and RISK pathways modulates mitochondrial function post-injury [161].	Serial increases in cf-mtDNA after surgery that decline over days but remain elevated in complicated recovery suggest ongoing mitochondrial stress [162,163]	Cf-mtDNA levels decline over days post-surgery but remain elevated in complicated recoveries [51,161,163].
Increased LCOS Risk with Comorbidities (age, diabetes, heart failure)	Baseline mitochondrial deficit increases susceptibility to perioperative calcium overload and oxidative stress [51].	Reduced mitochondrial reserve and impaired adaptive capacity	Altered efficacy of cardioprotective signaling in metabolic disease; LCOS linkage inferred from translational evidence [163].	Higher post-operative cf-mtDNA levels; impaired metabolic markers. specific LCOS populations under investigation [163].	Comorbidities recognized as amplifiers of postoperative mitochondrial stress and LCOS risk [51,161,163].

Table 3 Correlation of clinical features of LCOS with mitochondrial dysfunction. Columns indicate: (i) feature, (ii) mitochondrial biomarker, (iii) underlying energetic or calcium dysregulation, (iv) relevant signaling pathway (SAFE/RISK), (v) potential biomarker (e.g., cf-mtDNA). ↓ means reduction, → means "leading to".

7. Biomarkers and Indicators of Mitochondrial Stress

Identification of mitochondrial stress offers an opportunity for early detection and risk stratification in LCOS. Rather than reflecting gross hemodynamic failure, mitochondrial biomarkers capture subclinical energetic injury that may precede overt deterioration.

7.1. Cell-Free Mitochondrial DNA

Cell-free mitochondrial DNA (cf-mtDNA) has emerged as a sensitive marker of mitochondrial injury following cardiac surgery. Elevated postoperative cf-mtDNA levels correlate with ischemia–reperfusion severity, arrhythmias, LCOS, and multiorgan dysfunction. Unlike conventional hemodynamic parameters, cf-mtDNA reflects early subcellular injury and systemic mitochondrial stress [52,154,162,163]. However, clinical implementation remains limited by lack of assay standardization, variability in sampling methodology

and timing, and absence of universally accepted perioperative reference thresholds in adult cardiac surgical populations.

Beyond its diagnostic role, cf-mtDNA may also participate in innate immune activation, reinforcing inflammatory responses that compound postoperative myocardial dysfunction [154].

7.2. Emerging Metabolic and Oxygen Tension Markers

Complementary biomarkers include tissue oxygen tension, lactate dynamics, and redox indicators such as $NADH/NAD^+$ ratios [33,87]. These metrics provide real-time insight into cellular oxygen utilization and oxidative phosphorylation efficiency, often preceding systemic lactate elevation [2].

Integration of cf-mtDNA with metabolic and oxygenation markers enhances detection of patients at risk for delayed myocardial recovery and persistent LCOS.

7.3. Clinical Integration

In clinical practice, mitochondrial biomarkers offer a proactive framework for identifying energetic vulnerability, guiding postoperative monitoring, and informing individualized support strategies. Their utility is greatest when interpreted conservatively—as indicators of risk and recovery trajectory rather than definitive causal drivers—supporting translational relevance without overstating mechanistic certainty. Accordingly, cf-mtDNA currently remains investigational and should be interpreted as a translational biomarker rather than a validated standalone clinical diagnostic tool. Table 4 lists clinically relevant biomarkers reflecting mitochondrial stress in LCOS, their pathophysiological basis, and potential translational applications. Routine monitoring of these markers may enable early detection of energetic insufficiency and guide personalized mitochondria-targeted interventions.

Table 4. Biomarkers of Mitochondrial Stress in Postoperative LCOS.

Biomarker	Source/Compartment	Physiological/Pathophysiological Significance	Timing of Detection	Potential Clinical Utility in LCOS
Circulating free mitochondrial DNA (cf-mtDNA)	Mitochondrial DNA released into plasma or pericardial fluid [51,126]	Reflects mitochondrial membrane disruption and DAMP-mediated inflammatory amplification after ischemia–reperfusion and CPB [51]	Early postoperative (within hours after CPB)	Risk stratification for LCOS severity, postoperative AF, and inflammatory LCOS phenotypes [51]
Lactate/Pyruvate ratio	Systemic blood metabolite ratio [100,106]	Indicates impaired mitochondrial oxidative phosphorylation and reliance on anaerobic glycolysis [100,106]	Immediate–early postoperative period [2]	Early marker of energetic insufficiency and inadequate myocardial oxygen utilization [2]
Mixed venous oxygen saturation (SvO_2)	Venous blood (pulmonary artery)	Reflects global oxygen extraction imbalance due to impaired cardiac output and mitochondrial oxygen utilization [86]	Continuous peri- and postoperative monitoring [16]	Differentiates flow-limited vs. utilization-limited LCOS states [16]
ATP content (myocardial tissue/surrogate metabolic markers)	Cardiomyocyte mitochondria (direct or inferred)	Represents cellular energetic reserve depletion following ischemia–reperfusion [65,67]	Intraoperative or early postoperative [51]	Mechanistic indicator of myocardial stunning and delayed contractile recovery [51]

Table 4. *Cont.*

Biomarker	Source/Compartment	Physiological/Pathophysiological Significance	Timing of Detection	Potential Clinical Utility in LCOS
Reactive oxygen species–related oxidative stress markers	Plasma/myocardial tissue	Excess ROS generation during reperfusion causes ETC dysfunction and calcium mishandling [53,69]	Early reperfusion phase [53,69]	Identifies oxidative LCOS phenotype and potential benefit from antioxidant or conditioning strategies [32,87]
Calcium overload–associated markers	Cardiomyocyte cytosol/mitochondria [66,125]	Mitochondrial Ca^{2+} overload triggers permeability transition and energetic collapse [56]	Early reperfusion	Links reperfusion injury to contractile dysfunction and arrhythmogenesis [56]

Table 4 Key biomarkers of mitochondrial stress in postoperative LCOS. Includes: (i) marker, (ii) source (e.g., cf-mtDNA), (iii) physiological/pathophysiological significance, (iv) timing of detection, (v) potential clinical utility.

8. Protective Signaling Pathways Converging on Mitochondria

Protective signaling pathways modulate mitochondrial resilience during perioperative stress, influencing the balance between injury and recovery in LCOS. Rather than preventing mitochondrial stress entirely, these pathways shape its magnitude and reversibility.

8.1. SAFE Pathway (TNF-α/STAT3)—Contextual, Dose-Dependent

The Survivor Activating Factor Enhancement (SAFE) pathway is initiated by low-level cytokine signaling and converges on STAT3 activation [125]. Within mitochondria, STAT3 supports respiratory efficiency, limits excessive oxidative stress, and stabilizes membrane integrity [116,125]. These effects appear to be non-transcriptional and highly context dependent [125,127].

Importantly, SAFE signaling exhibits a narrow therapeutic window [125]. Protective effects are associated with TNFR2-mediated signaling, whereas excessive or prolonged cytokine activation may exacerbate injury [125,145].

8.2. RISK Pathway Convergence

The Reperfusion Injury Salvage Kinase (RISK) pathway operates in parallel, engaging PI3K-Akt and ERK1/2 signaling to inhibit mPTP opening and promote cell survival [125,126]. RISK and SAFE pathways interact at the mitochondrial level, reinforcing prosurvival signaling during early reperfusion [125,127].

Despite strong experimental support, clinical translation remains variable, particularly in patients with advanced age or metabolic disease [27,127,146]. Figure 4 depicts the convergence of SAFE and RISK pathways on mitochondrial targets, highlighting key effectors that preserve ATP production, limit ROS, and prevent mPTP-mediated injury [125,127]. Understanding this network provides a framework for targeted therapies and reinforces mitochondria as a central hub for postoperative cardiac protection [51,125,127].

8.3. Clinical Relevance and Current Limitations

SAFE and RISK pathways should be viewed as modulators of mitochondrial recovery rather than guaranteed protective mechanisms. Their influence helps explain gradual postoperative improvement and interpatient variability in LCOS resolution. However, comorbidity sensitivity, translational inconsistency, and incomplete mechanistic definition limit their current therapeutic application [51,155,156]. Framed conservatively, these pathways underscore the central role of mitochondria as integrative targets of endogenous cardioprotection without overstating clinical causality.

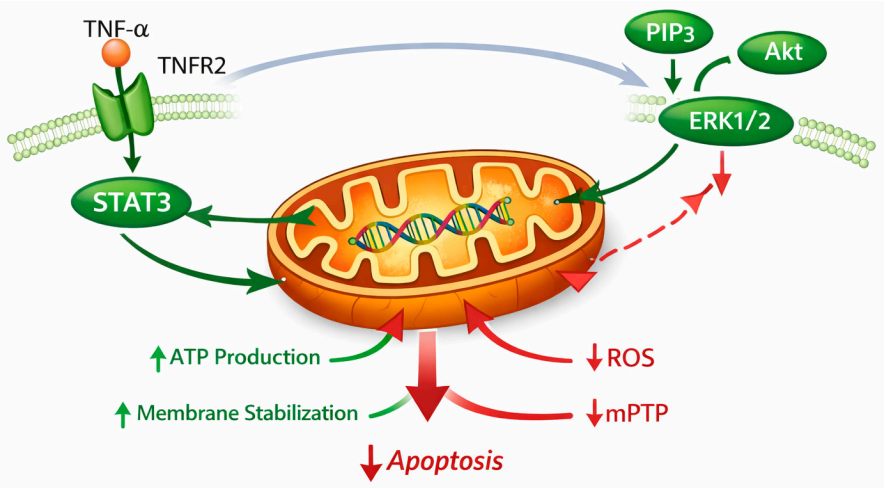


Figure 4. SAFE and RISK signaling convergence on mitochondria. SAFE pathway (TNF-α/STAT3) and RISK pathway (PI3K/Akt/ERK1/2) jointly stabilize mitochondrial membrane potential, reduce ROS, and limit apoptotic signaling [71,153,154]. Interactions and feedback loops between pathways are indicated with bidirectional arrows; protective effects are green, injurious pathways in red.

9. Therapeutic Implications and Future Directions

Postoperative low cardiac output syndrome (LCOS) remains a significant clinical challenge, affecting up to ~27% of adult patients following cardiac surgery [73]. Its pathophysiology is multifactorial, incorporating ischemia–reperfusion (I/R) injury, inflammatory activation, myocardial stunning, neurohormonal alterations, and cellular energetic deficits. Central to this process is mitochondrial dysfunction, which manifests as ATP depletion, calcium dysregulation, oxidative stress, and impaired metabolic signaling [67,117]. While mitochondria are integral to cardiomyocyte survival, current evidence positions them as modifiers of injury and recovery, rather than primary therapeutic targets.

9.1. Myocardial Protection Strategies

Clinically, cardioprotective strategies aim to modulate, rather than override, intrinsic mitochondrial responses. Two major pathways illustrate this principle [139]:

1. SAFE pathway (TNF-α/STAT3): Activation of TNF-α through TNFR2, low-dose cytokine signaling, or other stimuli such as sphingosine-1-phosphate or melatonin triggers STAT3 phosphorylation. STAT3 then translocates to mitochondria, enhancing electron transport chain efficiency, regulating ROS production, and limiting mPTP opening, ultimately supporting ATP generation and reducing apoptosis. Importantly, these protective effects are context- and dose-dependent, emphasizing careful modulation over indiscriminate pathway activation.
2. RISK pathway (PI3K-Akt/ERK1/2): Activated predominantly during early reperfusion, RISKs converge on mitochondrial targets to stabilize membrane potential, preserve oxidative capacity, and suppress apoptosis. Although preclinical data are compelling, human translation is limited by age, comorbidities, and metabolic variability, reinforcing a conservative therapeutic interpretation.

Interventions exploiting these pathways include ischemic preconditioning [31,57], postconditioning maneuvers [32,57], and pharmacologic modulation (e.g., polyphenols, melatonin) [32,57,139], which aim to augment intrinsic protective signaling without directly overriding mitochondrial control. These approaches exemplify the broader principle: mitochondria respond to upstream modulation but are not independent targets.

9.2. Mitochondria as Modifiers, Not Primary Targets

The conceptual pivot here is that mitochondria in LCOS act as bioenergetic and signaling hubs. Dysfunction contributes to contractile impairment, arrhythmogenesis, and delayed postoperative recovery, yet therapeutic strategies should enhance the heart's endogenous adaptive capacity, rather than attempt to directly "engineer" mitochondrial function. For example, approaches such as mitochondrial transplantation or targeted ROS scavenging remain experimental. Although promising in preclinical models, these strategies face important translational barriers including delivery standardization, immunologic and off-target safety considerations, manufacturing reproducibility, and limited regulatory pathway definition for perioperative clinical implementation [134,160,161].

Mitochondrial modulation also has systemic implications. Elevated cell-free mtDNA, disturbances in mitochondrial oxygen tension, and oxidative stress reflect ongoing tissue injury and provide early indicators of LCOS risk. Clinically, these markers may help stratify patients for protective interventions, but should be interpreted as dynamic readouts of cellular resilience rather than direct intervention points.

9.3. Need for Clinical Validation and Future Directions

Despite mechanistic insights, translation of mitochondria-focused therapies into routine perioperative care remains limited. Future directions include:

- Biomarker-guided interventions: Using mtDNA, ROS metrics, or mitochondrial oxygenation to tailor post-surgical support [110].
- Optimized pharmacologic conditioning: Refining dose, timing, and context for SAFE/RISK pathway modulation to maximize protection while minimizing off-target inflammatory activation [151].
- Integration with systemic strategies: Combining mitochondrial modulation with hemodynamic optimization, anti-inflammatory therapy, and metabolic support to address the multifactorial nature of LCOS [150,151].

In conclusion, mitochondria in LCOS are modulators of cardiomyocyte survival, with protective signaling pathways offering contextual and reversible therapeutic leverage. Emphasis on conservative, evidence-aligned modulation—rather than speculative, direct mitochondrial engineering—ensures translational feasibility and aligns with current clinical standards.

9.4. Contribution to Current Literature

This review contributes to the current LCOS literature by integrating mitochondrial bioenergetics into established perioperative cardiac surgery paradigms through a clinically oriented translational framework. Unlike prior reviews focusing predominantly on inflammatory or hemodynamic mechanisms, this manuscript synthesizes experimental mitochondrial physiology, ischemia–reperfusion biology, calcium handling, oxidative stress, and perioperative myocardial recovery into a unified conceptual model relevant to adult cardiac surgery. Importantly, mitochondrial dysfunction is framed conservatively as a mechanistic amplifier and recovery modifier rather than an isolated causal pathway, thereby maintaining alignment with current clinical evidence while identifying biologically plausible therapeutic and biomarker opportunities.

10. Conclusions

Mitochondrial dysfunction emerges as a unifying, mechanistically coherent framework for understanding Low Cardiac Output Syndrome (LCOS) following adult cardiac surgery. This review consolidates evidence that perioperative stressors—ischemia–reperfusion, calcium overload, and oxidative insult—disrupt mitochondrial bioenergetics, creating a re-

versible mismatch between ATP supply and myocardial energy demand. Such dysfunction does not replace established hemodynamic, inflammatory, or neurohormonal models of LCOS; rather, it provides a conservative, cellular substrate that integrates these paradigms into a more complete mechanistic understanding.

Integration with existing LCOS models highlights how mitochondrial perturbations amplify clinically observed phenomena: delayed postoperative contractile recovery, arrhythmogenic susceptibility, and reduced responsiveness to conventional inotropes. Transient opening of the mitochondrial permeability transition pore (mPTP), oxidative damage to mitochondrial DNA, and impaired calcium handling collectively impair excitation–contraction coupling, reproducing the energetic deficits observed in myocardial stunning and persistent low output states. Protective signaling pathways—particularly the Survivor Activating Factor Enhancement (SAFE) and Reperfusion Injury Salvage Kinase (RISK) cascades—demonstrate that the perioperative heart possesses intrinsic modulatory capacity. SAFE-mediated STAT3 activation supports electron transport chain efficiency, stabilizes redox balance, and limits apoptotic signaling, while RISK pathways converge to preserve mitochondrial membrane potential and reinforce anti-apoptotic defenses.

Clinically, mitochondrial-focused biomarkers, including cell-free mitochondrial DNA and tissue-level oxygen tension metrics, provide early, mechanistically grounded indicators of subclinical energetic compromise. These translational insights suggest opportunities for perioperative interventions: mitochondria-targeted pharmacologic strategies, metabolic modulation, and tailored cardioprotective conditioning may accelerate recovery and reduce LCOS incidence, particularly in patients with pre-existing mitochondrial vulnerability such as diabetes, chronic heart failure, or advanced age.

In summary, positioning mitochondrial dysfunction at the interface of cellular bioenergetics, calcium homeostasis, and redox signaling offers a conservative yet revolutionary framework for perioperative cardiac care. This paradigm aligns with structured, evidence-based clinical reasoning while opening avenues for translational innovation, ultimately linking biomolecular insight to improved postoperative outcomes. By integrating subcellular mechanisms into the broader LCOS landscape, this review provides both a practical lens for clinicians and a foundation for future research aimed at optimizing cardiac resilience and functional recovery.

Postoperative LCOS reflects more than isolated hemodynamic failure. Evidence synthesized in this review suggests that perioperative mitochondrial dysfunction acts as a reversible bioenergetic amplifier linking ischemia–reperfusion injury, calcium dysregulation, oxidative stress, and delayed myocardial recovery. Framed conservatively, mitochondrial impairment provides an integrative mechanistic layer that may explain persistent postoperative dysfunction despite adequate macrocirculatory correction. Recognition of this bioenergetic dimension may improve future strategies for myocardial protection, perioperative monitoring, and targeted postoperative support in adult cardiac surgery.

Author Contributions: Conceptualization, D.C.S. and T.S.; writing—original draft preparation, D.C.S.; writing—review and editing, D.C.S. and T.S. All authors have read and agreed to the published version of the manuscript.

Funding: This work received no specific funding or grant support. The authors declare no financial or institutional conflicts of interest.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analyzed in this study.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

ADP	Adenosine diphosphate
AF	Atrial fibrillation
Akt	Protein kinase B
ATP	Adenosine triphosphate
Ca^{2+}	Calcium ion
cf-mtDNA	Cell-free mitochondrial DNA
CPB	Cardiopulmonary bypass
DAMP	Damage-associated molecular pattern
ETC	Electron transport chain
ERK1/2	Extracellular signal–regulated kinases 1 and 2
HF	Heart failure
I/R	Ischemia–reperfusion
LCOS	Low Cardiac Output Syndrome
mPTP	Mitochondrial permeability transition pore
mtDNA	Mitochondrial DNA
$NADH/NAD^+$	Reduced nicotinamide adenine dinucleotide/oxidized nicotinamide adenine dinucleotide
PI3K	Phosphoinositide 3-kinase
POAF	Postoperative atrial fibrillation
Q_{10}	Temperature coefficient (Q10 effect)
RISK	Reperfusion Injury Salvage Kinase
ROS	Reactive oxygen species
SAFE	Survivor Activating Factor Enhancement
STAT3	Signal transducer and activator of transcription 3
SvO_2	Mixed venous oxygen saturation
TNF-α	Tumor necrosis factor alpha
TNFR2	Tumor necrosis factor receptor 2

References

1. Abedinov, F. Risk Factors for Very Long ICU Stay after Cardiac Surgery and Effects on the Quality of Life. *Proc. Bulg. Acad. Sci.* **2024**, *77*, 8. [CrossRef]
2. Belletti, A.; Lomivorotov, V.V.; Zangrillo, A.; Pieri, M. Low cardiac output syndrome after adult cardiac surgery. *Signa Vitae* **2025**, *21*, 1–16. [CrossRef]
3. Kumar, M.; Sharma, R.; Sethi, S.K.; Bazaz, S.; Sharma, P.; Bhan, A.; Kher, V. Vasoactive Inotrope Score as a tool for clinical care in children post cardiac surgery. *Indian J. Crit. Care Med.* **2014**, *18*, 653–658. [CrossRef] [PubMed] [PubMed Central]
4. Laimoud, M.; Maghirang, M.; Alanazi, M.; Mutlaq, S.M.; Althibait, S.A.; Alanazi, B.; Alomran, M.; Halees, Z. Predictors and clinical outcomes of post-coronary artery bypass grafting cerebrovascular strokes. *Egypt. Heart J.* **2022**, *74*, 76. [CrossRef] [PubMed]
5. Mahajna, A.; Ott, S.; Haneya, A.; Leick, J.; Pilarczyk, K.; Shehada, S.E.; Bolotin, G.; Lorusso, R. Current insights on temporary mechanical circulatory support in adults with post-cardiotomy cardiogenic shock. *Eur. Heart J. Suppl.* **2025**, *27*, iv12–iv22. [CrossRef] [PubMed]
6. Miles, T.J.; Blackburn, K.W.; Moon, M.R.; Chatterjee, S. Optimal inotropic support strategy in low cardiac output syndrome. *Semin. Thorac. Cardiovasc. Surg.* **2025**, *38*, 93–101. [CrossRef] [PubMed]
7. Akbasli, I.T.; Tandon, A.; Cassedy, A.; Allan, C.K. Preoperative, operative, and immediate postoperative predictors of onset of low cardiac output syndrome in congenital heart disease. *Res. Sq.* **2025**, *41*, 601. [CrossRef] [PubMed]
8. Duncan, A.E.; Kartashov, A.; Robinson, S.B.; James, R.A.; Halvorson, S.; Bokesch, P. Risk factors, resource use, and cost of postoperative low cardiac output syndrome. *J. Thorac. Cardiovasc. Surg.* **2020**, *163*, 1890–1898.e10. [CrossRef] [PubMed]
9. Schoonen, A.; van Klei, W.A.; van Wolfswinkel, L.; van Loon, K. Definitions of low cardiac output syndrome after cardiac surgery and their effect on the incidence of intraoperative LCOS: A literature review and cohort study. *Front. Cardiovasc. Med.* **2022**, *9*, 926957. [CrossRef] [PubMed] [PubMed Central]
10. Crescenzi, G.; Torracca, L.; Pierri, M.D.; Capestro, F.; Rosica, C.; Oliva, F.M.; Landoni, G. Esmolol as a cardioprotective agent to reduce low cardiac output syndrome after cardiac surgery. *Signa Vitae* **2024**, *20*, 69. [CrossRef]

11. Wardoyo, S.; Djer, M.M.; Busro, P.W. Evaluation of myocardial injury from use of aortic cross-clamp and cardiopulmonary bypass duration in patients undergoing tetralogy of Fallot corrective surgery. *Paediatr. Indones.* **2025**, *65*, 147–155. [CrossRef]
12. Hein, Z.M. Cardiovascular Manifestations of Multisystem Inflammatory Syndrome in Children (MIS-C). *Afr. J. Biomed. Res.* **2025**, *28*, 103–113. [CrossRef]
13. Koyuncu, A.O.; Yesiltas, M.A.; Ozsoy, S.D.; Mert, A.M. Comparison of Systemic Inflammation Indices With Post- Cardiac Surgery Mortality and Morbidity. *Heart Surg. Forum* **2025**, *28*, 46933. [CrossRef]
14. Baldan, B.U.; Hegeman, R.R.M.J.J.; Bos, N.M.J.P.; Smeenk, H.G.; Klautz, R.J.M.; Klein, P. Comparative Analysis of Therapeutic Strategies in Post-Cardiotomy Cardiogenic Shock: Insight into a High-Volume Cardiac Surgery Center. *J. Clin. Med.* **2024**, *13*, 2118. [CrossRef] [PubMed]
15. Jia, B.; Yan, S.; Luo, Y.; Cheng, J.; Cheng, J.; Fei, J.; Gao, Y.; Liao, X.; Bian, L.; Wang, J.; et al. Post-pericardiectomy ECMO for constrictive pericarditis: A case series and literature review. *BMC Anesth.* **2025**, *25*, 110. [CrossRef] [PubMed]
16. Feinstein, Y.; Hoskote, A.; Pollak, U. Principles of Postoperative Management in the Paediatric Cardiac Intensive Care: Low Cardiac Output State (LCOS) and Lesion-Specific Management. In *ESPNIC Children's Intensive Care Textbook*; Brierley, J., Tissieres, P., Deep, A., Eds.; Springer: Cham, Switzerland, 2025. [CrossRef]
17. Chen, A.L.; Kindzelski, B.A.; Robinson, J.P.; Altshuler, J.M.; Schwann, T.A.; Vivacqua, A. Deciphering Low Cardiac Output Syndrome: Insights and Management in Post-Cardiac Surgery. *Heart Surg. Forum* **2024**, *27*, E1237–E1244. [CrossRef]
18. Avşar, M.K.; Güzel, Y.; Önsel, İ.Ö.; Kurat, B.; Yucel, I.K.; Zeybek, C.; Yorgancular, D. Myocardial Protection in Complete AVSD repair: A Decade of Comparative Outcomes between Custodiol-HTK and Blood Cardioplegia. *J. Card. Surg.* **2025**, *2025*, 1280973. [CrossRef]
19. Yücel, M.; Benli, E.D.; Erdoğan, K.E.; Saglam, M.F.; Deniz, G.; Comakli, H.; Uguz, E. Evaluation of myocardial protection in Prolonged Aortic Cross-Clamp times: Del Nido and HTK cardioplegia in adult cardiac surgery. *Medicina* **2025**, *61*, 1420. [CrossRef] [PubMed]
20. Burkhardt, B.E.; Hummel, J.; Rücker, G.; Stiller, B. Inotropes for the prevention of low cardiac output syndrome and mortality for paediatric patients undergoing surgery for congenital heart disease: A network meta-analysis. *Cochrane Database Syst. Rev.* **2024**, *2024*, CD013707. [CrossRef] [PubMed]
21. Hosseini, A.; Shahzamani, M.; Maghami-Mehr, A.; Khosravi, F.; Emadi, N. Comparison of Clinical Outcomes of Two Different Cardioplegic Solutions in Patients Undergoing Coronary Artery Bypass Graft Surgery; A randomize clinical trial. *Adv. Biomed. Res.* **2025**, *14*, 138. [CrossRef] [PubMed]
22. Brzeska, B.; Karolak, W.; Żelechowski, P.; Łoś, A.; Ulatowski, N.; Pawlaczyk, R. Del Nido cardioplegia versus other contem-porary solutions for myocardial protection—Aliterature review. *Eur. J. Transl. Clin. Med.* **2023**, *6*, 41–57. [CrossRef]
23. Hong, L.; Xu, H.; Ge, C.; Tao, H.; Shen, X.; Song, X.; Guan, D.; Zhang, C. Prediction of low cardiac output syndrome in patients following cardiac surgery using machine learning. *Front. Med.* **2022**, *9*, 973147. [CrossRef] [PubMed]
24. Bechri, I.; Derkaoui, A.; Shimi, A.; Khatouf, M. Low cardiac output syndrome after cardiac surgery: A retrospective analysis. *Int. J. Med. Med. Res.* **2023**, *9*, 6–14. [CrossRef]
25. Mohsen, G.; Catena, D.; Lee, Z.Y.; Notz, Q.; Jiang, X.; Velten, M.; O'brien, B.; Kleine-Brueggeney, M.; Ott, S.; Heyland, D.K.; et al. Impact of perioperative selenium supplementation on perioperative hemodynamics in patients undergoing cardiac surgery: A post hoc analysis of the Sustain CSX trial. *J. Clin. Anesth.* **2025**, *107*, 112011. [CrossRef] [PubMed]
26. Zhang, Z.; Yang, W.; Wang, L.; Zhu, C.; Cui, S.; Wang, T.; Gu, X.; Liu, Y.; Qiu, P. Unraveling the role and mechanism of mitochondria in postoperative cognitive dysfunction: A narrative review. *J. Neuroinflammation* **2024**, *21*, 293. [CrossRef] [PubMed]
27. Fan, X.; Tang, Y.; Zhang, G.; Zhang, J.; Xue, Q.; Zhang, B.; Xu, Z.; Han, L. Risk factors of chronic left ventricular dysfunction after cardiac valve surgery. *J. Thorac. Dis.* **2020**, *12*, 4854–4859. [CrossRef] [PubMed] [PubMed Central]
28. Hoffman, T.M.; Wernovsky, G.; Atz, A.M.; Kulik, T.J.; Nelson, D.P.; Chang, A.C.; Bailey, J.M.; Akbary, A.; Kocsis, J.F.; Kaczmarek, R.; et al. Efficacy and safety of milrinone in preventing low cardiac output syndrome in infants and children after corrective surgery for congenital heart disease. *Circulation* **2003**, *107*, 996–1002. [CrossRef] [PubMed]
29. Jana, S.; Wijesinghe, M.; DiCaro, M.V.; Lei, K.; Houshmand, N.; Ahsan, C. Cardiogenic Shock Management in the Modern Era: A Narrative Review of Percutaneous Mechanical Circulatory Support Devices. *J. Cardiovasc. Dev. Dis.* **2026**, *13*, 9. [CrossRef] [PubMed]
30. Yeşiler, F.İ.; Akmatov, N.; Nurumbetova, O.; Beyazpınar, D.S.; Şahintürk, H.; Gedik, E.; Zeyneloğlu, P. Incidence of and Risk Factors for Prolonged Intensive Care Unit Stay After Open Heart Surgery Among Elderly Patients. *Cureus* **2022**, *14*, e31602. [CrossRef] [PubMed] [PubMed Central]
31. Rony Atoui, M.D.; Felix Ma, M.D.; Yves Langlois, M.D.; Jean-Francois Morin, M.D. Risk Factors for Prolonged Stay in the Intensive Care Unit and on the Ward After Cardiac Surgery. *J. Card. Surg.* **2008**, *23*, 99–106. [CrossRef] [PubMed]
32. Guerrero-Orriach, J.L.; Carmona-Luque, M.D.; Gonzalez-Alvarez, L. Heart Failure after Cardiac Surgery: The Role of Halogenated Agents, Myocardial Conditioning and Oxidative Stress. *Int. J. Mol. Sci.* **2022**, *23*, 1360. [CrossRef] [PubMed]

33. Stark, R.J.; Schrimpe-Rutledge, A.C.; Codreanu, S.G.; Sherrod, S.D.; McLean, J.A.; Krispinsky, L.T.; Lamb, F.S. Endothelial-dependent vascular reactivity after cardiopulmonary bypass is associated with unique metabolomic signatures. *Shock.* **2024**, *62*, 656–662. [CrossRef] [PubMed]
34. Sugiura, T.; Shahannaz, D.C.; Ferrell, B.E. Current status of cardiac regenerative therapy using induced pluripotent stem cells. *Int. J. Mol. Sci.* **2024**, *25*, 5772. [CrossRef] [PubMed]
35. Sugiura, T.; Shahannaz, D.C.; Ferrell, B.E.; Yoshida, T. Advancements in cardiac regenerative therapy: Scalable human iPSC-derived cardiomyocyte differentiation and maturation. *Glob. Transl. Med.* **2025**, *4*, 1–15. [CrossRef]
36. Ji, H.; Cao, T.; Tan, Z.; Zheng, R.; Bian, Z.; Lin, W.; Yuan, C.; Shao, Y.; Li, H.; Du, J. Adipocyte extracellular vesicle mitochondrial cargo is linked to cardiomyocyte dysfunction in type 2 diabetes–related heart failure with preserved ejection fraction. *Free Radic. Biol. Med.* **2025**, *244*, 435–451. [CrossRef] [PubMed]
37. Shahannaz, D.C.; Sugiura, T.; Ferrell, B.E. Enhancing mitochondrial maturation in IPSC-DerivedCardiomyocytes: Strategies for Metabolic Optimization. *BioChem* **2025**, *5*, 23. [CrossRef]
38. Sugiura, T.; Nawaz, S.; Shahannaz, D.C.; Ferrell, B.E.; Yoshida, T. From injury to repair: The therapeutic potential of induced pluripotent stem cells in heart failure. *Regen. Med. Rep.* **2025**, *2*, 22–30. [CrossRef]
39. Shahannaz, D.C.; Sugiura, T.; Ferrell, B.E. The role of large language models in induced pluripotent stem cell-derived cardiomyocytes research and clinical translation. *J. Clin. Transl. Res.* **2025**, *11*, 4. [CrossRef]
40. Shahannaz, D.C.; Sugiura, T.; Ferrell, B.E.; Yoshida, T. Arrhythmogenic Risk in IPSC-Derived Cardiomyocytes: Current limitations and therapeutic Perspectives. *Medicina* **2025**, *61*, 2056. [CrossRef] [PubMed]
41. Shahannaz, D.C.; Sugiura, T.; Ferrell, B.E.; Yoshida, T. Engineering Mitochondrial Biogenesis in iPSC-CMs: CRISPR-Guided Approaches for Advanced Cardiomyocyte Development. *J. Cardiovasc. Dev. Dis.* **2026**, *13*, 77. [CrossRef] [PubMed]
42. Shahannaz, D.C.; Sugiura, T.; Ferrell, B.E.; Yoshida, T. Targeting mitochondrial dynamics via EV delivery in regenerative cardiology: Mechanistic and therapeutic perspectives. *Cells* **2025**, *14*, 1738. [CrossRef] [PubMed]
43. Shahannaz, D.C.; Sugiura, T.; Yoshida, T. Mitochondria-Enriched Extracellular Vesicles (EVs) for Cardiac Bioenergetics Restoration: A Scoping Review of Preclinical Mechanisms and Source-Specific Strategies. *Int. J. Mol. Sci.* **2025**, *26*, 11052. [CrossRef] [PubMed]
44. Shahannaz, D.C.; Sugiura, T. EV-Encapsulated Mitochondrial miRNAs: Enhancing Cardiomyocyte Bioenergetics. *Int. J. Mol. Sci.* **2026**, *27*, 2224. [CrossRef] [PubMed]
45. Shahannaz, D.C.; Sugiura, T. Engineering Smart Biomaterial Interfaces for iPSC-CM Maturation: A Biophysical and Metabolic Reprogramming Approach to Regenerative Cardiac Medicine. *Int. J. Mol. Sci.* **2026**, *27*, 2637. [CrossRef] [PubMed]
46. Shahannaz, D.C.; Sugiura, T. Phospholipid Transfer Protein (PLTP) in Cholesterol Handling: Implications for Mitochondrial Lipid Homeostasis in Human iPSC-Derived Cardiomyocytes. *Int. J. Mol. Sci.* **2026**, *27*, 3617. [CrossRef] [PubMed]
47. Shahannaz, D.C.; Sugiura, T. Next-Generation Metabolic Reprogramming in iPSC-Derived Cardiomyocytes: CRISPR-EV Synergy for Precision Cardiac Regeneration. *Biomolecules* **2026**, *16*, 467. [CrossRef] [PubMed]
48. Tocchi, A.; Quarles, E.K.; Basisty, N.; Gitari, L.; Rabinovitch, P.S. Mitochondrial dysfunction in cardiac aging. *Biochim. Biophys. Acta* **2015**, *1847*, 1424–1433. [CrossRef] [PubMed] [PubMed Central]
49. Lin, K.L.; Chen, S.D.; Lin, K.J.; Liou, C.W.; Chuang, Y.C.; Wang, P.W.; Chuang, J.H.; Lin, T.K. Quality Matters? The Involvement of Mitochondrial Quality Control in Cardiovascular Disease. *Front. Cell Dev. Biol.* **2021**, *9*, 636295. [CrossRef] [PubMed] [PubMed Central]
50. Mishra, P.K.; Adameova, A.; Hill, J.A.; Baines, C.P.; Kang, P.M.; Downey, J.M.; Narula, J.; Takahashi, M.; Abbate, A.; Piristine, H.C.; et al. Guidelines for evaluating myocardial cell death. *Am. J. Physiol. Heart Circ. Physiol.* **2019**, *317*, H891–H922. Erratum in *Am. J. Physiol. Heart Circ. Physiol.* **2019**, *317*, H1390. https://doi.org/10.1152/ajpheart.zh4-2975-corr.2019. [CrossRef] [PubMed] [PubMed Central]
51. Cherry, A.D. Mitochondrial Dysfunction in Cardiac Surgery. *Anesth. Clin.* **2025**, *43*, 357–375. [CrossRef] [PubMed]
52. Manghelli, J.L.; Kelly, M.O.; Carter, D.I.; Gelman, A.E.; Damiano, R.J.; Melby, S.J. Pericardial mitochondrial DNA levels are associated with atrial fibrillation after cardiac surgery. *Ann. Thorac. Surg.* **2020**, *111*, 1593–1600. [CrossRef] [PubMed]
53. Zakkar, M.; Guida, G.; Suleiman, M.S.; Angelini, G.D. Cardiopulmonary bypass and oxidative stress. *Oxidative Med. Cell. Longev.* **2015**, *2015*, 189863. [CrossRef] [PubMed]
54. Geissler, H.J.; Allen, S.J.; Davis, K.L.; Sauer, H.; Laine, G.A.; Kuhn-Régnier, F.; Dapunt, O.; de Vivie, E.R.; Mehlhorn, U. Impact of cardiopulmonary bypass and cardioplegic arrest on myocardial efficiency. *Crit. Care* **1999**, *3*, 21. [CrossRef] [PubMed Central]
55. Brown, D.; Moukdar, F. Are Post-Operative Arrhythmias in Patients with Metabolic Syndrome a Sign of Dysfunctional Mitochondria? *J. Am. Coll. Cardiol.* **2013**, *62*, 1474–1475. [CrossRef] [PubMed]
56. Jeganathan, J.; Saraf, R.; Mahmood, F.; Pal, A.; Bhasin, M.K.; Huang, T.; Mittel, A.; Knio, Z.; Simons, R.; Khabbaz, K.; et al. Mitochondrial dysfunction in atrial tissue of patients developing postoperative atrial fibrillation. *Ann. Thorac. Surg.* **2017**, *104*, 1547–1555. [CrossRef] [PubMed]
57. Sánchez, F.J.; Pueyo, E.; Diez, E.R. Strain echocardiography to predict postoperative atrial fibrillation. *Int. J. Mol. Sci.* **2022**, *23*, 1355. [CrossRef] [PubMed]

58. Chandler, H.K.; Kirsch, R. Management of the low cardiac output syndrome following surgery for congenital heart disease. *Curr. Cardiol. Rev.* **2016**, *12*, 107–111. [CrossRef] [PubMed]
59. Budiwardhana, N.; Murni, I.K.; Marwali, E.M.; Busro, P.W.; Rizkia, F.I.; Seolaeman, M.F.; Widyastuti, Y. Correlation between Syndecan-1 in Inter Category of RACHS-1 Score and Immediate Clinical Outcomes. *Congenit. Heart Dis.* **2025**, *20*, 645–654. [CrossRef]
60. Aslan, N.; Yildizdas, D. Low Cardiac Output Syndrome After Cardiac Surgery: A Life-Threatening Condition from the Perspective of Pediatric Intensivists. *Türk. Kardiyol. Derneği. Arşivi.* **2022**, *50*, 284–292. [CrossRef] [PubMed]
61. Eris, C.; Erdolu, B.; Engin, M.; As, A.K.; Ustundag, Y. The effects of aortic clamping strategy on myocardial protection and early postoperative outcomes during coronary artery bypass grafting operations. *Heart Surg. Forum* **2021**, *24*, E217–E222. [CrossRef] [PubMed]
62. Becker, A.C.; Lantz, C.W.; Forbess, J.M.; Epting, C.L.; Thorp, E.B. Cardiopulmonary Bypass–Induced inflammation and myocardial ischemia and reperfusion injury stimulates accumulation of soluble MER*. *Pediatr. Crit. Care Med.* **2021**, *22*, 822–831. [CrossRef] [PubMed]
63. Drennan, S.E.; Burge, K.Y.; Szyld, E.G.; Eckert, J.V.; Mir, A.M.; Gormley, A.K.; Schwartz, R.M.; Daves, S.M.; Thompson, J.L.; Burkhart, H.M.; et al. Clinical and laboratory predictors for the development of low cardiac output syndrome in infants undergoing cardiopulmonary bypass: A pilot study. *J. Clin. Med.* **2021**, *10*, 712. [CrossRef] [PubMed]
64. von Zeppelin, M.; Hecker, F.; Keller, H.; Hlavicka, J.; Walther, T.; Moritz, A.; Arsalan, M.; Holubec, T. Gradual Reperfusion in Cardioplegia-Induced Cardiac Arrest. *Medicina* **2024**, *60*, 1564. [CrossRef] [PubMed] [PubMed Central]
65. Kloner, R.A. Stunned and hibernating myocardium: Where are we nearly 4 decades later? *J. Am. Heart Assoc.* **2020**, *9*, e015502. [CrossRef] [PubMed]
66. Al-Awar, A.; Khan, A.W.; Hussain, S. Myocardial stunning: Mechanisms, molecular insights, and gaps in knowledge. *Biosci. Rep.* **2025**, *45*, BSR20253410. [CrossRef] [PubMed] [PubMed Central]
67. Lesnefsky, E.J.; Chen, Q.; Tandler, B.; Hoppel, C.L. Mitochondrial Dysfunction and myocardial Ischemia-Reperfusion: Implications for novel therapies. *Annu. Rev. Pharmacol. Toxicol.* **2016**, *57*, 535–565. [CrossRef] [PubMed]
68. Braunwald, E.; Kloner, R.A. The stunned myocardium: Prolonged, postischemic ventricular dysfunction. *Circulation* **1982**, *66*, 1146–1149. [CrossRef] [PubMed]
69. Buja, L.M. Pathobiology of Myocardial Ischemia and Reperfusion Injury: Models, Modes, Molecular Mechanisms, Modulation, and Clinical Applications. *Cardiol. Rev.* **2023**, *31*, 252–264. [CrossRef] [PubMed] [PubMed Central]
70. Frank, A.; Bonney, M.; Bonney, S.; Weitzel, L.; Koeppen, M.; Eckle, T. Myocardial Ischemia reperfusion injury. *Semin. Cardiothorac. Vasc. Anesth.* **2012**, *16*, 123–132. [CrossRef] [PubMed]
71. Pedriali, G.; Ramaccini, D.; Bouhamida, E.; Wieckowski, M.R.; Giorgi, C.; Tremoli, E.; Pinton, P. Perspectives on mitochondrial relevance in cardiac ischemia/reperfusion injury. *Front. Cell Dev. Biol.* **2022**, *10*, 1082095. [CrossRef] [PubMed]
72. Baumann, M.; Bender, E.; Stömmer, G.; Gross, G.; Brand, K. Effects of warm and cold ischemia on mitochondrial functions in brain, liver and kidney. *Mol. Cell Biochem.* **1989**, *87*, 137–145. [CrossRef] [PubMed]
73. Lomivorotov, V.V.; Efremov, S.M.; Kirov, M.Y.; Fominskiy, E.V.; Karaskov, A.M. Low-Cardiac-Output Syndrome After Cardiac Surgery. *J. Cardiothorac. Vasc. Anesth.* **2017**, *31*, 291–308. [CrossRef] [PubMed]
74. Bolli, R. Mechanism of myocardial "stunning". *Circulation* **1990**, *82*, 723–738. [CrossRef] [PubMed]
75. Anselmi, A. Myocardial ischemia, stunning, inflammation, and apoptosis during cardiac surgery: A review of evidence. *Eur. J. Cardio-Thorac. Surg.* **2004**, *25*, 304–311. [CrossRef] [PubMed]
76. Banerjee, D.; Feng, J.; Sellke, F.W. Strategies to attenuate maladaptive inflammatory response associated with cardiopulmonary bypass. *Front. Surg.* **2024**, *11*, 1224068. [CrossRef] [PubMed]
77. Sahulee, R.; McKinstry, J. Pharmacologic therapies for the low cardiac output syndrome in children after cardiac surgery: Evidence of their efficacy and trends in their use. *Vessel. Plus* **2022**, *6*, 5. [CrossRef]
78. Elnaiem, W.; Elnour, A.M.; Koko, A.E.A.; Madany, M.; Hemmeda, L. Efficacy and safety of inhaled nitric oxide administered during cardiopulmonary bypass for pediatric cardiac surgery: A systematic review and meta-analysis. *Ann. Med. Surg.* **2023**, *85*, 2865–2874. [CrossRef] [PubMed]
79. Song, B.; Dang, H.; Dong, R. Analysis of risk factors of low cardiac output syndrome after congenital heart disease operation: What can we do. *J. Cardiothorac. Surg.* **2021**, *16*, 135. [CrossRef] [PubMed]
80. Manolis, A.A.; Manolis, T.A.; Manolis, A.S. Neurohumoral Activation in Heart Failure. *Int. J. Mol. Sci.* **2023**, *24*, 15472. [CrossRef] [PubMed] [PubMed Central]
81. Hartupee, J.; Mann, D.L. Neurohormonal activation in heart failure with reduced ejection fraction. *Nat. Rev. Cardiol.* **2017**, *14*, 30–38. [CrossRef] [PubMed] [PubMed Central]
82. Jackson, G. ABC of heart failure: Pathophysiology. *BMJ* **2000**, *320*, 167–170. [CrossRef] [PubMed]
83. Volpe, M.; Tocci, G.; Pagannone, E. L'attivazione del sistema renina-angiotensina-aldosterone nello scompenso cardiaco [Activation of the renin-angiotensin-aldosterone system in heart failure]. *Ital. Heart J.* **2005**, *6*, 16S–23S. [PubMed]

84. Rana, K.B.; Ansari, A.; Sharma, P.; Yadav, L.; Shahbaz, A. Frequency of Low Cardiac Output Syndrome Following on Pump Coronary Artery Bypass Grafting Surgery and it's Association with Degree of Pre-operative Left Ventricular Dysfunction. *Kathmandu Univ. Med. J. (KUMJ)* **2023**, *21*, 79–84. [PubMed]
85. Crimi, E.; Rajkumar, K.; Coleman, S.; Fernando, R.; Marchant, B.; Garner, C.; Gaillard, J.; Hicks, M.H.; Maves, R.C.; Khanna, A.K.; et al. Cardiovascular Physiology during Mechanical Circulatory Support: Implications for management and monitoring. *J. Clin. Med.* **2025**, *14*, 6935. [CrossRef] [PubMed]
86. Guerrero Orriach, J.L.; Navarro Arce, I.; Hernandez Rodriguez, P.; Ponferrada, A.R.; Manso, A.M.; Aliaga, M.R.; Fernandez, A.R.; Belmonte, J.J.E.; Estevez, B.; Luque, A.G.; et al. Preservation of renal function in cardiac surgery patients with low cardiac output syndrome: Levosimendan vs beta agonists. *BMC Anesth.* **2019**, *19*, 212. [CrossRef] [PubMed]
87. Meneas, C.; Sall, F.; Nader, J. Pathophysiology of Perioperative Low Cardiac Output Syndrome in Cardiac Surgery: What do we know? *J. Surg.* **2022**, *7*, 1537. [CrossRef]
88. den Os, M.M.; van den Brom, C.E.; van Leeuwen, A.L.I.; Dekker, N.A.M. Microcirculatory perfusion disturbances following cardiopulmonary bypass: A systematic review. *Crit. Care* **2020**, *24*, 218. [CrossRef] [PubMed] [PubMed Central]
89. Koning, N.J.; Simon, L.E.; Asfar, P.; Baufreton, C.; Boer, C. Systemic microvascular shunting through hyperdynamic capillaries after acute physiological disturbances following cardiopulmonary bypass. *Am. J. Physiol. Heart Circ. Physiol.* **2014**, *307*, H967–H975. [CrossRef] [PubMed]
90. Greenwood, J.C.; Jang, D.H.; Spelde, A.E.; Gutsche, J.T.; Horak, J.; Acker, M.A.; Kilbaugh, T.J.; Shofer, F.S.; Augoustides, J.G.T.; Bakker, J.; et al. Low Microcirculatory Perfused Vessel Density and High Heterogeneity are Associated with Increased Intensity and Duration of Lactic Acidosis After Cardiac Surgery with Cardiopulmonary Bypass. *Shock.* **2021**, *56*, 245–254. [CrossRef] [PubMed] [PubMed Central]
91. Ince, C. Hemodynamic coherence and the rationale for monitoring the microcirculation. *Crit. Care* **2015**, *19*, S8. [CrossRef] [PubMed]
92. Wang, G.; Lian, H.; Zhang, H.; Wang, X. Microcirculation and mitochondria: The critical unit. *J. Clin. Med.* **2023**, *12*, 6453. [CrossRef] [PubMed]
93. Dekker, N.A.M.; Veerhoek, D.; Koning, N.J.; van Leeuwen, A.L.I.; Elbers, P.W.G.; van den Brom, C.E.; Vonk, A.B.A.; Boer, C. Postoperative microcirculatory perfusion and endothelial glycocalyx shedding following cardiac surgery with cardiopulmonary bypass. *Anaesthesia* **2019**, *74*, 609–618. [CrossRef] [PubMed] [PubMed Central]
94. Chang, X.; Lochner, A.; Wang, H.H.; Wang, S.; Zhu, H.; Ren, J.; Zhou, H. Coronary microvascular injury in myocardial infarction: Perception and knowledge for mitochondrial quality control. *Theranostics* **2021**, *11*, 6766–6785. [CrossRef] [PubMed]
95. Soares, R.O.S.; Losada, D.M.; Jordani, M.C.; Évora, P.; Castro-E-Silva, O. Ischemia/Reperfusion injury Revisited: An overview of the latest pharmacological strategies. *Int. J. Mol. Sci.* **2019**, *20*, 5034. [CrossRef] [PubMed]
96. Wang, J.; Toan, S.; Zhou, H. New insights into the role of mitochondria in cardiac microvascular ischemia/reperfusion injury. *Angiogenesis* **2020**, *23*, 299–314. [CrossRef] [PubMed]
97. Bennett, C.F.; Latorre-Muro, P.; Puigserver, P. Mechanisms of mitochondrial respiratory adaptation. *Nat. Rev. Mol. Cell Biol.* **2022**, *23*, 817–835. [CrossRef] [PubMed]
98. Tomar, N.; Zhang, X.; Kandel, S.M.; Sari, S.; Yang, C.; Liong, M.; Audi, S.H.; Cowley, A.W., Jr.; Dash, R.K. Substrate-dependent differential regulation of mitochondrial bioenergetics in the heart and kidney cortex and outer medulla. *Biochim. Biophys. Acta (BBA) Bioenerg.* **2021**, *1863*, 148518. [CrossRef] [PubMed]
99. Weinrich, T.W.; Kam, J.H.; Ferrara, B.T.; Thompson, E.P.; Mitrofanis, J.; Jeffery, G. A day in the life of mitochondria reveals shifting workloads. *Sci. Rep.* **2019**, *9*, 13898. [CrossRef] [PubMed]
100. Gambardella, J.; Lombardi, A.; Santulli, G. Metabolic flexibility of mitochondria plays a key role in balancing glucose and fatty acid metabolism in the diabetic heart. *Diabetes* **2020**, *69*, 2054–2057. [CrossRef] [PubMed]
101. Prakash, S.; Choudhury, P.; Bisht, S. Diabetic cardiomyopathy and COVID-19: Intersecting pathways and amplified cardiovascular risk. *Front. Pharmacol.* **2025**, *16*, 1683159. [CrossRef] [PubMed] [PubMed Central]
102. Muoio, D.M. Metabolic inflexibility: When mitochondrial indecision leads to metabolic gridlock. *Cell* **2014**, *159*, 1253–1262. [CrossRef] [PubMed]
103. Brealey, D.; Brand, M.; Hargreaves, I.; Heales, S.; Land, J.; Smolenski, R.; Davies, N.A.; Cooper, C.E.; Singer, M. Association between mitochondrial dysfunction and severity and outcome of septic shock. *Lancet* **2002**, *360*, 219–223. [CrossRef] [PubMed]
104. Koklesova, L.; Liskova, A.; Samec, M.; Zhai, K.; Al-Ishaq, R.K.; Bugos, O.; Šudomová, M.; Biringer, K.; Pec, M.; Adamkov, M.; et al. Protective Effects of Flavonoids Against Mitochondriopathies and Associated Pathologies: Focus on the Predictive Approach and Personalized Prevention. *Int. J. Mol. Sci.* **2021**, *22*, 8649. [CrossRef] [PubMed] [PubMed Central]
105. Parker, A.M.; Lees, J.G.; Murray, A.J.; Velagic, A.; Lim, S.Y.; Blasio, M.J.D.; Ritchie, B.H. Precision medicine. *JACC Basic. Transl. Sci.* **2025**, *10*, 101345. [CrossRef] [PubMed]
106. Zhou, B.; Tian, R. Mitochondrial dysfunction in pathophysiology of heart failure. *J. Clin. Investig.* **2018**, *128*, 3716–3726. [CrossRef] [PubMed]

107. Ranjbarvaziri, S.; Kooiker, K.B.; Ellenberger, M.; Fajardo, G.; Zhao, M.; Roest, A.S.V.; Woldeyes, R.A.; Koyano, T.T.; Fong, R.; Ma, N.; et al. Altered cardiac energetics and mitochondrial dysfunction in hypertrophic cardiomyopathy. *Circulation* **2021**, *144*, 1714–1731. [CrossRef] [PubMed]
108. Pang, Y.; Li, Y.; Zhang, Y.; Wang, H.; Lang, J.; Han, L.; Liu, H.; Xiong, X.; Gu, L.; Wu, X. Effects of inflammation and oxidative stress on postoperative delirium in cardiac surgery. *Front. Cardiovasc. Med.* **2022**, *9*, 1049600. [CrossRef] [PubMed] [PubMed Central]
109. Carew, N.T.; Schmidt, H.M.; Yuan, S.; Galley, J.C.; Hall, R.; Altmann, H.M.; Hahn, S.A.; Miller, M.P.; Wood, K.C.; Gabris, B.; et al. Loss of cardiomyocyte CYB5R3 impairs redox equilibrium and causes sudden cardiac death. *J. Clin. Investig.* **2022**, *132*, e147120. [CrossRef] [PubMed] [PubMed Central]
110. Lekkos, K.; Hu, Z.; Nguyen, P.D.; Honkoop, H.; Sengul, E.; Alonaizan, R.; Koth, J.; Ying, J.; Lemieux, M.E.; Kenward, A.; et al. Oxidative phosphorylation is required for cardiomyocyte re-differentiation and long-term fish heart regeneration. *Nat. Cardiovasc. Res.* **2025**, *4*, 1363–1380. [CrossRef] [PubMed]
111. Lygate, C.A. Maintaining energy provision in the heart: The creatine kinase system in ischaemia–reperfusion injury and chronic heart failure. *Clin. Sci.* **2024**, *138*, 491–514. [CrossRef] [PubMed]
112. Toro-Pérez, J.; Rodrigo, R. Contribution of oxidative stress in the mechanisms of postoperative complications and multiple organ dysfunction syndrome. *Redox Rep.* **2021**, *26*, 35–44. [CrossRef] [PubMed] [PubMed Central]
113. Zong, Y.; Li, H.; Liao, P.; Chen, L.; Pan, Y.; Zheng, Y.; Zhang, C.; Liu, D.; Zheng, M.; Gao, J. Mitochondrial dysfunction: Mechanisms and advances in therapy. *Sig. Transduct. Target. Ther.* **2024**, *9*, 124. [CrossRef] [PubMed]
114. Hinton, A., Jr.; Claypool, S.M.; Neikirk, K.; Senoo, N.; Wanjalla, C.N.; Kirabo, A.; Williams, C.R. Mitochondrial structure and function in human heart failure. *Circ. Res.* **2024**, *135*, 372–396. [CrossRef] [PubMed]
115. Sharma, E.; Abadi, L.F.; Kombe Kombe, J.A.; Kandala, M.; Parker, J.; Winicki, N.; Kelesidis, T. Overview of methods that determine mitochondrial function in human disease. *Metabolism* **2025**, *170*, 156300. [CrossRef] [PubMed]
116. Yusuf, J.A.; Akanbi, S.T.; Ijibadejo, M.S.; Sulaiman, S.E.; Olorunlowu, D.R.; Akinola, A.O.; Abe, A.P.; Opoola, E.K.; Adejobi, E.O.; Adigun, T.D. A review of mitochondrial dysfunction, pathophysiology and therapeutic prospects in neurodegenerative diseases. *Discov. Neurosci.* **2025**, *20*, 25. [CrossRef]
117. Chen, M.; Yan, R.; Ding, L.; Luo, J.; Ning, J.; Zhou, R. Research Advances of Mitochondrial Dysfunction in Perioperative Neurocognitive Disorders. *Neurochem. Res.* **2023**, *48*, 2983–2995. [CrossRef] [PubMed]
118. Meza Monge, K.; Shapiro, A.L.B.; Coughlan, C.; Mungo, B.; Schulick, R.; Pratap, A.; Kovacs, E.J.; Idrovo, J.-P. From Bench to Bedside: New frontiers in understanding and Treating Postoperative Delirium. *J. Clin. Med.* **2025**, *14*, 8418. [CrossRef] [PubMed]
119. Ju, L.S.; Morey, T.E.; Seubert, C.N.; Martynyuk, A.E. Intergenerational perioperative Neurocognitive disorder. *Biology* **2023**, *12*, 567. [CrossRef] [PubMed]
120. Katseni, K.; Chalkias, A.; Kotsis, T.; Dafnios, N.; Arapoglou, V.; Kaparos, G.; Logothetis, E.; Iacovidou, N.; Karvouni, E.; Katsenis, K. The Effect of Perioperative Ischemia and Reperfusion on Multiorgan Dysfunction following Abdominal Aortic Aneurysm Repair. *BioMed. Res. Int.* **2015**, *2015*, 598980. [CrossRef] [PubMed]
121. Jiang, M.; Xie, X.; Cao, F.; Wang, Y. Mitochondrial metabolism in myocardial remodeling and mechanical unloading: Implications for ischemic heart disease. *Front. Cardiovasc. Med.* **2021**, *8*, 789267. [CrossRef] [PubMed]
122. Bernardi, P.; Gerle, C.; Halestrap, A.P.; Jonas, E.A.; Karch, J.; Mnatsakanyan, N.; Pavlov, E.; Sheu, S.S.; Soukas, A.A. Identity, structure, and function of the mitochondrial permeability transition pore: Controversies, consensus, recent advances, and future directions. *Cell Death Differ.* **2023**, *30*, 1869–1885. [CrossRef] [PubMed]
123. Hu, S.; Tang, X.; Zhu, F.; Liang, C.; Wang, S.; Wang, H.; Li, P.; Li, Y. Disruption of mitochondrial DNA integrity in cardiomyocyte injury upon ischemia/reperfusion. *Genes. Dis.* **2024**, *12*, 101282. [CrossRef] [PubMed]
124. Poulaki, A.; Giannouli, S. Mitochondrial lipids: From membrane organization to apoptotic facilitation. *Int. J. Mol. Sci.* **2022**, *23*, 3738. [CrossRef] [PubMed]
125. Halphen, D.G. Ongoing strategies against mitochondrial diseases: Prevention and development of genetic therapies. *Rev. Odontológica Mex.* **2015**, *19*, e142–e144. [CrossRef]
126. Vaidya, Y.; Cavanaugh, S.M.; Dhamoon, A.S. Myocardial Stunning and Hibernation. In *StatPearls [Internet]*; StatPearls Publishing: Treasure Island, FL, USA, 2025. Available online: https://www.ncbi.nlm.nih.gov/books/NBK537026/ (accessed on 24 January 2026).
127. Canty, J.M. Myocardial injury, troponin release, and cardiomyocyte death in brief ischemia, failure, and ventricular remodeling. *Am. J. Physiol. Heart Circ. Physiol.* **2022**, *323*, H1–H15. [CrossRef] [PubMed]
128. Hurst, S.; Hoek, J.; Sheu, S.S. Mitochondrial Ca^{2+} and regulation of the permeability transition pore. *J. Bioenerg. Biomembr.* **2017**, *49*, 27–47. [CrossRef] [PubMed] [PubMed Central]
129. Bauer, T.M.; Murphy, E. Role of Mitochondrial Calcium and the Permeability Transition Pore in Regulating Cell Death. *Circ. Res.* **2020**, *126*, 280–293. [CrossRef] [PubMed] [PubMed Central]

130. Morciano, G.; Naumova, N.; Koprowski, P.; Valente, S.; Sardão, V.A.; Potes, Y.; Rimessi, A.; Wieckowski, M.R.; Oliveira, P.J. The mitochondrial permeability transition pore: An evolving concept critical for cell life and death. *Biol. Rev. Camb. Philos. Soc.* **2021**, *96*, 2489–2521. [CrossRef] [PubMed]
131. Kwong, J.Q.; Molkentin, J.D. Physiological and pathological roles of the mitochondrial permeability transition pore in the heart. *Cell Metab.* **2015**, *21*, 206–214. [CrossRef] [PubMed]
132. Halestrap, A.P. Calcium, mitochondria and reperfusion injury: A pore way to die. *Biochem. Soc. Trans.* **2006**, *34*, 232–237. [CrossRef] [PubMed]
133. Briston, T.; Roberts, M.; Lewis, S.; Powney, B.; M Staddon, J.; Szabadkai, G.; Duchen, M.R. Mitochondrial permeability transition pore: Sensitivity to opening and mechanistic dependence on substrate availability. *Sci. Rep.* **2017**, *7*, 10492. [CrossRef] [PubMed]
134. Toosky, M.; Kheradvar, A. Assessment of mitochondrial viability under calcium Stress: Insights for mitochondrial transplantation. *Mitochondrion* **2025**, *86*, 102098. [CrossRef] [PubMed]
135. Endlicher, R.; Drahota, Z.; Štefková, K.; Červinková, Z.; Kučera, O. The Mitochondrial Permeability Transition Pore—Current knowledge of its structure, function, and regulation, and optimized methods for evaluating its functional state. *Cells* **2023**, *12*, 1273. [CrossRef] [PubMed]
136. Javadov, S.; Karmazyn, M. Mitochondrial permeability transition pore opening as an endpoint to initiate cell death and as a putative target for cardioprotection. *Cell. Physiol. Biochem.* **2007**, *20*, 1–22. [CrossRef] [PubMed]
137. Garcia-Dorado, D.; Ruiz-Meana, M.; Inserte, J.; Rodriguez-Sinovas, A.; Piper, H.M. Calcium-mediated cell death during myocardial reperfusion. *Cardiovasc. Res.* **2012**, *94*, 168–180. [CrossRef] [PubMed]
138. Nesci, S.; Rubattu, S. Mitochondrial Permeability Transition pore: The cardiovascular disease's molecular Achilles heel. *Biomedicines* **2025**, *13*, 3014. [CrossRef] [PubMed]
139. Hausenloy, D.; Wynne, A.; Duchen, M.; Yellon, D. Transient mitochondrial permeability transition pore opening mediates preconditioning-induced protection. *Circulation* **2004**, *109*, 1714–1717. [CrossRef] [PubMed]
140. Luptak, I.; Sverdlov, A.L.; Panagia, M.; Qin, F.; Pimentel, D.R.; Croteau, D.; Siwik, D.A.; Ingwall, J.S.; Bachschmid, M.M.; Balschi, J.A.; et al. Decreased ATP production and myocardial contractile reserve in metabolic heart disease. *J. Mol. Cell Cardiol.* **2018**, *116*, 106–114. [CrossRef] [PubMed] [PubMed Central]
141. Lu, X.; Kwong, J.Q.; Molkentin, J.D.; Bers, D.M. Individual cardiac mitochondria undergo rare transient permeability transition pore openings. *Circ. Res.* **2015**, *118*, 834–841. [CrossRef] [PubMed]
142. Saotome, M.; Katoh, H.; Yaguchi, Y.; Tanaka, T.; Urushida, T.; Satoh, H.; Hayashi, H. Transient opening of mitochondrial permeability transition pore by reactive oxygen species protects myocardium from ischemia-reperfusion injury. *Am. J. Physiol. Heart Circ. Physiol.* **2009**, *296*, H1125–H1132. [CrossRef] [PubMed]
143. Leung, C.H.; Wang, L.; Fu, Y.Y.; Yuen, W.; Caldarone, C.A. Transient mitochondrial permeability transition pore opening after neonatal cardioplegic arrest. *J. Thorac. Cardiovasc. Surg.* **2011**, *141*, 975–982. [CrossRef] [PubMed]
144. Szeto, H.H.; Liu, S.; Soong, Y.; Wu, D.; Darrah, S.F.; Cheng, F.Y.; Zhao, Z.; Ganger, M.; Tow, C.Y.; Seshan, S.V. Mitochondria-Targeted peptide accelerates ATP recovery and reduces ischemic kidney injury. *J. Am. Soc. Nephrol.* **2011**, *22*, 1041–1052. [CrossRef] [PubMed]
145. Matteucci, M.; Ronco, D.; Kowalewski, M.; Massimi, G.; De Bonis, M.; Formica, F.; Jiritano, F.; Folliguet, T.; Bonaros, N.; Sponga, S.; et al. Long-term survival after surgical treatment for post-infarction mechanical complications: Results from the Caution study. *Eur. Heart J. Qual. Care Clin. Outcomes* **2024**, *10*, 737–749. [CrossRef] [PubMed]
146. Sittitrai, P.; Ruenmarkkaew, D.; Klibngern, H.; Ariyanon, T.; Hanprasertpong, N.; Boonyaprapa, S.; Sreesawat, M. Perioperative versus postoperative calcium and vitamin D supplementation to prevent symptomatic hypocalcemia after total thyroidectomy: A randomized placebo controlled trial. *Int. J. Surg.* **2023**, *109*, 13–20. [CrossRef] [PubMed] [PubMed Central]
147. Arganbright, J.M.; Tracy, M.; Feldt, M.; Narayanan, S.; Mahadev, A.; Noel-MacDonnell, J. Postoperative Hypocalcemia following Non-Cardiac Surgical Procedures in Children with 22q11.2 Deletion Syndrome. *Genes.* **2022**, *13*, 1905. [CrossRef] [PubMed] [PubMed Central]
148. Ștef, A.; Bodolea, C.; Bocșan, I.C.; Achim, A.; Tintiuc, N.; Pop, R.M.; Solomonean, A.G.; Manea, A.; Buzoianu, A.D. Perioperative Modulation of Left Ventricular Systolic Performance: A Retrospective Study on Ionized Calcium and Vitamin D in Cardiac Surgery Patients. *J. Pers. Med.* **2024**, *14*, 850. [CrossRef] [PubMed] [PubMed Central]
149. Cao, J.L.; Adaniya, S.M.; Cypress, M.W.; Suzuki, Y.; Kusakari, Y.; Jhun, B.S.; O-Uchi, J. Role of mitochondrial Ca2+ homeostasis in cardiac muscles. *Arch. Biochem. Biophys.* **2019**, *663*, 276–287. [CrossRef] [PubMed]
150. Borbolis, F.; Ploumi, C.; Palikaras, K. Calcium-mediated regulation of mitophagy: Implications in neurodegenerative diseases. *npj Metab. Health Dis.* **2025**, *3*, 4. [CrossRef] [PubMed]
151. Zhao, Y.; Wu, C.; Liang, X.; Yang, M. Cell-free mitochondrial DNA as a pro-inflammatory agent in blood circulation: Mechanisms, therapeutic implications, and clinical challenges in immune dysregulation. *Front. Immunol.* **2025**, *16*, 1640748. [CrossRef] [PubMed]

152. Kong, C.; Song, W.; Fu, T. Systemic inflammatory response syndrome is triggered by mitochondrial damage (Review). *Mol. Med. Rep.* **2022**, *25*, 147. [CrossRef] [PubMed] [PubMed Central]
153. Jovanović, A. Cardioprotective signaling: Outline and future directions. *Biomedicines* **2025**, *13*, 2973. [CrossRef] [PubMed]
154. Hausenloy, D.J.; Lecour, S.; Yellon, D.M. Reperfusion injury salvage kinase and survivor activating factor enhancement prosurvival signaling pathways in ischemic postconditioning: Two sides of the same coin. *Antioxid. Redox Signal* **2011**, *14*, 893–907. [CrossRef] [PubMed]
155. Pagliaro, P.; Alloatti, G.; Penna, C. Cardioprotection Reloaded: Reflections on 40 years of research. *Antioxidants* **2025**, *14*, 889. [CrossRef] [PubMed]
156. Chiari, P.; Fellahi, J.L. Myocardial protection in cardiac surgery: A comprehensive review of current therapies and future cardioprotective strategies. *Front. Med.* **2024**, *11*, 1424188. [CrossRef] [PubMed]
157. Slagsvold, K.H.; Rognmo, Ø.; Høydal, M.; Wisløff, U.; Wahba, A. Remote ischemic preconditioning preserves mitochondrial function and influences myocardial MicroRNA expression in atrial myocardium during coronary bypass surgery. *Circ. Res.* **2013**, *114*, 851–859. [CrossRef] [PubMed]
158. Leistner, M.; Sommer, S.; Kanofsky, P.; Leyh, R.; Sommer, S. Ischemia time impacts on respiratory chain functions and Ca^{2+}-handling of cardiac subsarcolemmal mitochondria subjected to ischemia reperfusion injury. *J. Cardiothorac. Surg.* **2019**, *14*, 92. [CrossRef] [PubMed]
159. Bertero, E.; Popoiu, T.A.; Maack, C. Mitochondrial calcium in cardiac ischemia/reperfusion injury and cardioprotection. *Basic. Res. Cardiol.* **2024**, *119*, 569–585. [CrossRef] [PubMed]
160. Sandler, N.; Kaczmarek, E.; Itagaki, K.; Zheng, Y.; Otterbein, L.; Khabbaz, K.; Liu, D.; Senthilnathan, V.; Gruen, R.L.; Hauser, C.J. Mitochondrial DAMPs Are Released During Cardiopulmonary Bypass Surgery and Are Associated with Postoperative Atrial Fibrillation. *Heart Lung Circ.* **2018**, *27*, 122–129. [CrossRef] [PubMed]
161. Hyslop, K.; Ki, K.K.; Naidoo, R.; O'Brien, D.; Prabhu, A.; Gill, D.; Anstey, C.; Rapchuk, I.L.; McDonald, C.I.; Marshall, L.; et al. Cell-free mitochondrial DNA may predict the risk of post-operative complications and outcomes in surgical aortic valve replacement patients. *Sci. Rep.* **2025**, *15*, 15857. [CrossRef] [PubMed]
162. Montaigne, D.; Marechal, X.; Lefebvre, P.; Modine, T.; Fayad, G.; Dehondt, H.; Hurt, C.; Coisne, A.; Koussa, M.; Remy-Jouet, I.; et al. Mitochondrial dysfunction as an arrhythmogenic substrate: A translational proof-of-concept study in patients with metabolic syndrome in whom post-operative atrial fibrillation develops. *J. Am. Coll. Cardiol.* **2013**, *62*, 1466–1473. [CrossRef] [PubMed]
163. Deng, Y.; Wu, Y. Postoperative atrial fibrillation following coronary artery bypass grafting surgery: Role of IL-6 from structural to electrical remodeling. *Interdiscip. Nurs. Res.* **2024**, *3*, 57–61. [CrossRef]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.