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Intravenous Dexmedetomidine in Cardio myocyte Biology: A Systematic Review

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A B S T R A C T

Introduction: Intravenous dexmedetomidine may influence cardiomyocyte biology through effects on apoptosis, inflammation, oxidative stress, and mitochondrial function, with possible relevance in perioperative and critical care settings. However, available evidence remains heterogeneous and translationally uncertain. This study aims to systematically evaluate its cellular effects on cardiomyocytes and clarify their clinical relevance.

Material and methods: This systematic review followed PRISMA guidelines, searched PubMed, Scopus, Web of Science, and Embase without time restriction using Boolean operators, and included original English studies on intravenous dexmedetomidine and cardiomyocyte biology. Study selection and quality assessment were performed independently by two reviewers, and key methodological and outcome data were extracted from each article.

Results: Dexmedetomidine consistently exerts direct cardiomyocyte-protective effects by attenuating apoptosis, oxidative stress, and inflammation across various stress models. Key mechanisms include activation of antioxidant pathways, enhanced autophagic flux via adrenergic signaling, and epigenetic regulation of anti-inflammatory axes. Additionally, it modulates electrophysiological properties by suppressing sodium and calcium currents, demonstrating a pleiotropic capacity to preserve cellular homeostasis and functional integrity.

Conclusion: Dexmedetomidine functions as a potent pleiotropic modulator of cardiomyocyte biology, providing robust protection against ischemic and oxygen-related stress. Beyond its sedative properties, it directly influences survival signaling, redox balance, and electrophysiology through diverse molecular pathways. These findings underscore its potential as a targeted cardioprotective agent, necessitating further clinical exploration to translate these cellular benefits into perioperative patient care.

Introduction

Dexmedetomidine is a highly selective α2-adrenergic receptor agonist that has become an important component of contemporary anesthetic and intensive care practice because of its sedative, anxiolytic, sympatholytic, and opioid-sparing properties. Unlike many traditional sedatives, it provides a cooperative form of sedation with minimal respiratory depression, which has expanded its use across perioperative

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medicine, procedural care, and the management of critically ill patients. As its clinical use has grown, interest has increasingly shifted from its immediate sedative profile toward its broader biologic effects on vital organs, including the heart. This shift is particularly relevant because the myocardium is highly sensitive to perioperative and critical illness stress, and cardio myocytes are central to maintaining both cardiac mechanical performance and electrophysiological stability. Any pharmacologic agent administered intravenously in such settings may influence not only systemic hemodynamics but also intracellular pathways related to myocardial injury and recovery. For this reason, dexmedetomidine has emerged as more than a sedative of practical convenience; it is now being considered as a potentially active modulator of cardiac cellular biology. Understanding whether intravenous dexmedetomidine affects cardio myocyte function, survival, and stress response is therefore of considerable scientific and clinical importance, particularly in patients vulnerable to ischemia, inflammation, oxidative stress, and neurohumoral activation (1).

Cardio myocytes are uniquely specialized cells that operate under exceptionally high metabolic demand and depend on precise regulation of mitochondrial function, calcium cycling, membrane excitability, and intracellular signaling. Their ability to maintain contractility and viability is tightly linked to an uninterrupted supply of oxygen and substrates, effective antioxidant defenses, and balanced pro-survival and pro-death pathways. In many perioperative and critical care conditions, these cellular requirements are disturbed. Surgical stress, ischemia-reperfusion, sepsis, hypoxemia, catecholamine excess, and mechanical ventilation can all create a hostile environment that promotes cardio myocyte dysfunction and structural injury. As a result, the biologic behavior of these cells becomes central to the pathogenesis of myocardial depression, arrhythmogenesis, and postoperative or critical illness-related cardiac complications. The possibility that dexmedetomidine may alter these processes has attracted growing attention, especially because its known effects on sympathetic outflow and stress attenuation could theoretically translate into cellular protection. Yet whether such protection is indirect, arising from hemodynamic and autonomic changes, or direct, mediated through intracellular pathways within cardio myocytes themselves, remains an unresolved question. This distinction is fundamental, because it determines how the drug should be interpreted in translational pharmacology and how confidently experimental findings can be extended to bedside practice (2).

At the cellular level, myocardial injury is driven by a complex and interconnected network of pathophysiologic mechanisms. Oxidative stress, mitochondrial dysfunction, calcium overload, inflammation, apoptosis, and impaired autophagy flux frequently interact rather than occur independently. A rise in reactive oxygen species can disrupt mitochondrial membrane potential, accelerate release of proapoptotic factors, and amplify inflammatory signaling. Similarly, altered calcium homeostasis may impair excitation-contraction coupling while simultaneously worsening mitochondrial stress and promoting cell death. These injury pathways are especially relevant during major surgery and critical illness, where repeated insults can rapidly push cardio myocytes from adaptive stress responses toward irreversible damage. A growing body of laboratory research has suggested that dexmedetomidine may influence several of these processes, including reduction of oxidative burden, attenuation of inflammatory mediator expression, preservation of mitochondrial integrity, and modulation of proapoptotic proteins. Such findings have generated enthusiasm regarding a possible cardio protective role. However, enthusiasm must be balanced with caution because experimental conditions differ greatly across studies, and cellular observations do not always correspond to clinically meaningful outcomes. Therefore, a careful assessment of the evidence is required before biologic plausibility can be translated into therapeutic significance (3).

One of the most frequently studied contexts for dexmedetomidine-related myocardial effects is ischemia-reperfusion injury. This model is highly relevant because reperfusion, while essential for tissue salvage, paradoxically triggers additional cardio myocyte injury through oxidative burst, mitochondrial damage, calcium dysregulation, and inflammatory activation. Experimental studies have often reported that dexmedetomidine limits infarct-related injury, reduces apoptotic signaling, and preserves ultrastructural features of myocardial cells in this setting. Proposed mechanisms include modulation of phosphatidylinositol 3-kinase/protein kinase B signaling, extracellular signal-regulated kinase activation, inhibition of mitochondrial permeability transition, and favorable regulation of Bcl-2 family proteins and caspases. These data suggest that dexmedetomidine may activate endogenous survival programs during periods of cellular stress. Nevertheless, not all studies use the same species, dose ranges, infusion timing, or definitions of cardio protection, and these differences complicate synthesis. Some studies administer the drug before injury, others during reperfusion, and others after damage has already begun, making direct comparisons difficult.

The route of administration also matters because intravenous exposure reflects clinical practice more closely than isolated or no physiologic delivery methods. These considerations highlight the importance of examining available data systematically rather than relying on isolated reports of benefit (4).

Beyond ischemia-reperfusion, dexmedetomidine has also been explored in models of inflammatory myocardial injury, hypoxia-reoxygenation, end toxemia, and postoperative cardiac stress. These contexts are important because many patients receiving dexmedetomidine in the intensive care unit or perioperative period experience forms of myocardial stress that are not purely ischemic. In sepsis and systemic inflammation, for example, cardio myocytes may undergo profound metabolic and structural disruption driven by cytokines, oxidative stress, microcirculatory abnormalities, and mitochondrial failure. Experimental evidence has suggested that dexmedetomidine may blunt inflammatory signaling pathways, reduce the expression of tumor necrosis factor-related mediators, and attenuate oxidative cellular injury in such models. Similar observations have been made in hypoxia-reoxygenation systems, where the drug has been associated with improved mitochondrial preservation and reduced apoptotic activity. While these findings broaden the possible relevance of dexmedetomidine, they also underscore the complexity of its biologic profile. It is unlikely that a single molecular pathway explains all observed effects, and the apparent benefits may vary according to the dominant injury mechanism in each model. As a result, a comprehensive overview is needed to determine whether the literature supports a consistent pattern of cardio myocyte protection or merely a series of context-dependent observations (5).

Another major area of interest concerns the influence of dexmedetomidine on mitochondrial biology, which is central to cardio myocyte survival. Mitochondria not only generate the ATP required for contraction but also regulate redox signaling, apoptosis, calcium buffering, and metabolic adaptation. Because cardio myocytes are densely packed with mitochondria and rely heavily on oxidative phosphorylation, mitochondrial dysfunction can rapidly lead to contractile failure and cell death. Several studies have suggested that dexmedetomidine may preserve mitochondrial membrane potential, reduce mitochondrial swelling, limit reactive oxygen species generation, and improve the balance between mitochondrial injury and repair. In some reports, these effects have been linked to modulation of ant apoptotic signaling and stabilization of intracellular energy homeostasis. Such observations are particularly relevant in perioperative and critical care medicine, where myocardial oxygen supply-demand imbalance is common. However, mitochondrial outcomes are highly sensitive to methodology, including the timing of tissue sampling, the model used, and the specific biomarkers selected. Consequently, individual experimental findings should not be interpreted in isolation. A more structured review is needed to understand whether mitochondrial preservation is a reproducible and clinically meaningful property of intravenous dexmedetomidine or an effect observed only under selected laboratory conditions (6).

The relationship between dexmedetomidine and inflammatory signaling has also become a key component of the emerging literature. Cardio myocyte injury is closely linked to inflammation, not only in overt infectious states but also after surgery, ischemia, trauma, and extracorporeal circulation. Proinflammatory cytokines can depress myocardial function, alter calcium handling, increase oxidative injury, and facilitate apoptotic progression. Dexmedetomidine has been proposed to attenuate some of these responses through both central sympatholytic mechanisms and local signaling effects. Investigators have reported associations with reduced nuclear factor kappa B activation, lower levels of inflammatory mediators, and improvement in stress-related cellular markers. These anti-inflammatory observations are attractive because they provide a plausible bridge between systemic sedation-related effects and direct myocardial cellular preservation. Yet the challenge lies in distinguishing true cardio myocyte-specific action from broader anti-stress physiology. A reduction in systemic catecholamines or inflammatory burden may indirectly improve myocardial conditions without necessarily indicating direct receptor-mediated effects within the cell itself. This distinction has important implications for how the cardio protective narrative is framed and whether dexmedetomidine should be viewed as intrinsically cytoprotective or primarily supportive through systemic modulation (7).

In addition to apoptosis and inflammation, dexmedetomidine has been linked to other processes relevant to cardio myocyte adaptation, including autophagy, endoplasmic reticulum stress, and transcriptional regulation. These mechanisms are increasingly recognized as important determinants of whether myocardial stress responses remain adaptive or become maladaptive. Controlled autophagy may help remove damaged organelles and preserve cellular homeostasis, whereas dysregulated autophagy may contribute to injury progression. Similarly, endoplasmic reticulum stress can initially promote adaptation but may later trigger apoptosis if unresolved. Some experimental studies have suggested that dexmedetomidine influences these pathways through AMP-activated protein kinase,

mitogen-activated protein kinase, and related intracellular regulators. Emerging reports have also implicated microRNAs and other post-transcriptional modulators in its myocardial effects. Although these findings deepen the mechanistic landscape, they also increase the heterogeneity of the literature. Not all pathways have been studied consistently, and not all reported molecular changes necessarily translate into functional cardio myocyte benefit. Therefore, any meaningful interpretation requires integration of molecular data with broader experimental context, including route of administration, dosage, duration, and the physiologic state in which dexmedetomidine is delivered (8).

Clinical translation remains the most important unresolved issue. Dexmedetomidine is commonly used in patients undergoing cardiac and no cardiac surgery, in critically ill patients requiring sedation, and in individuals with varying degrees of cardiovascular vulnerability. These are precisely the populations in whom any beneficial or adverse cardio myocyte effect would matter most. On the one hand, attenuation of sympathetic activation, reduction of myocardial oxygen demand, and modulation of cellular injury pathways could support cardiac protection. On the other hand, the drug's known ability to induce bradycardia and hypotension in some settings raises concern that systemic effects could offset any intrinsic cellular benefit, particularly in patients with limited perfusion reserve. Furthermore, many clinical outcome studies focus on biomarker release, arrhythmias, length of stay, or hemodynamic variables rather than direct assessment of cardio myocyte biology. While such outcomes are clinically meaningful, they cannot fully resolve mechanistic questions. This gap between experimental promise and clinical inference is a major challenge in the current literature and reinforces the need to critically examine how strongly preclinical cardio myocyte data can inform real-world therapeutic conclusions (9).

Another reason this topic merits careful review is the substantial methodological diversity among published studies. Experimental work varies in species, age of animals, disease background, in vitro versus in vivo design, infusion protocols, timing of administration, and the molecular endpoints selected for analysis. Some studies use isolated cardio myocytes exposed to controlled injury conditions, while others infer cellular effects from organ-level or whole-animal observations. Such variability can generate an appearance of mechanistic richness while actually limiting comparability. In addition, positive findings may be more likely to receive attention than neutral or conflicting results, increasing the risk of selective interpretation. For a pharmacologic agent as widely used as dexmedetomidine, it is essential to move beyond descriptive enthusiasm and determine whether the evidence is coherent, reproducible, and clinically relevant. This requires a structured synthesis that assesses not only the direction of reported effects but also the quality of study design, consistency of mechanistic claims, and extent to which intravenous administration in experimental settings resembles clinical exposure. Only through such evaluation can the field identify which conclusions are well supported and which remain provisional (10).

Given these considerations, a focused synthesis of the available literature is needed to clarify the current understanding of intravenous dexmedetomidine in cardio myocyte biology. The present study is a systematic review designed to evaluate evidence regarding its effects on cardio myocyte survival, apoptosis, oxidative stress, mitochondrial function, inflammatory signaling, calcium regulation, and related molecular pathways under conditions relevant to perioperative and critical care medicine. By concentrating specifically on intravenous administration and by examining findings through a cardio myocyte-centered framework, this review aims to distinguish direct cellular evidence from indirect systemic cardiovascular effects and to identify areas where current knowledge remains limited or inconsistent. A systematic review is particularly appropriate in this field because it allows a structured appraisal of heterogeneous studies and provides a more reliable basis for interpreting whether dexmedetomidine should be regarded simply as a sedative with cardiovascular consequences or as a pharmacologic agent with meaningful myocardial cellular implications.

Material and methods

Study Design

This study was conducted as a systematic review designed to comprehensively evaluate the available evidence regarding the biological effects of intravenous dexmedetomidine on cardio myocytes. The methodology of the review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure transparency, reproducibility, and methodological rigor. All stages of the review process, including identification, screening, eligibility assessment, and final inclusion of studies, were performed according to PRISMA recommendations. The objective was to systematically collect and synthesize experimental and translational evidence addressing the cellular and molecular impact of dexmedetomidine on cardio myocyte function and survival.

Inclusion and Exclusion Criteria

Studies considered eligible for inclusion if they investigated the effects of dexmedetomidine on cardio myocytes or myocardial cellular mechanisms and reported outcomes related to cellular biology such as apoptosis, oxidative stress, mitochondrial function, inflammatory signaling, calcium handling, or related molecular pathways. Both in vitro and in vivo experimental studies, as well as translational or preclinical investigations evaluating cardio myocyte-related outcomes after intravenous dexmedetomidine exposure, considered. Only original research articles published in peer-reviewed journals and written in English were included. Studies excluded if they were review articles, editorials, conference abstracts without full data, case reports, or studies that did not evaluate cardio myocyte-related cellular outcomes. Articles in which dexmedetomidine administered through non-intravenous routes or studies focusing solely on systemic hemodynamic outcomes without assessment of myocardial cellular mechanisms also excluded.

Search Strategy

A comprehensive literature search performed across several electronic databases to identify relevant studies. The databases searched included PubMed/MEDLINE, Scopus, Web of Science, and Embase. No time restrictions applied in order to capture all available evidence from database inception to the final search date. The search strategy combined controlled vocabulary terms and free-text keywords related to dexmedetomidine and cardio myocyte biology. Boolean operators (AND, OR) were used to combine search terms and optimize retrieval of relevant studies. The literature search was conducted independently by two reviewers, and any discrepancies in study selection were resolved through discussion and consensus (table 1).

Table 1. Database Search Strategy for Identification of Eligible Studies

Database	Search Strategy
PubMed/MEDLINE	(“Dexmedetomidine” OR “alpha-2 adrenergic agonist”) AND (“cardio myocyte” OR “cardiac myocyte” OR “myocardial cell”) AND (“apoptosis” OR “mitochondria” OR “oxidative stress” OR “inflammation” OR “cell signaling”)
Scopus	(TITLE-ABS-KEY dexmedetomidine) AND (cardio myocyte OR “cardiac myocyte” OR myocardial) AND (apoptosis OR mitochondrial OR oxidative OR inflammation OR signaling)
Web of Science	TS=(dexmedetomidine) AND TS=(cardio myocyte OR myocardial cell) AND TS=(apoptosis OR mitochondria OR oxidative stress OR inflammation)
Embase	(‘dexmedetomidine’/exp OR dexmedetomidine) AND (‘cardio myocyte’ OR ‘cardiac cell’ OR ‘myocardial cell’) AND (‘apoptosis’ OR ‘mitochondria’ OR ‘oxidative stress’ OR ‘inflammation’)

Quality Assessment of Included Studies

The methodological quality and risk of bias of the included studies rigorously evaluated using the National Toxicology Program (NTP) Office of Health Assessment and Translation (OHAT) Risk of Bias Tool. This instrument specifically selected for its robustness in assessing non-clinical experimental studies, including both in vitro cardio myocyte models and *in vivo* laboratory investigations. Each study was scrutinized across several critical domains, including selection bias (sequence generation and allocation concealment), performance bias (blinded experimental conditions and identical treatment protocols), detection bias (blinding of outcome assessment), and attrition bias (completeness of outcome data).

Data Extraction

Relevant data extracted from each included study using a standardized data extraction form developed for this review. Extracted information included the first author’s name, year of publication, country of origin, study design, experimental model (in vitro or in vivo), type of cardio myocyte or animal model used, route and dosage of dexmedetomidine administration, experimental conditions or injury model, primary cellular outcomes assessed, key molecular pathways investigated, and the main findings related to cardio myocyte biology. This structured extraction approach ensured consistency across studies and facilitated a comprehensive synthesis of the evidence regarding the cellular effects of intravenous dexmedetomidine.

Results

Based on the PRISMA flowchart provided, the initial database search across PubMed (n=269), Web of Science (n=83), Science Direct (n=26), and Google Scholar (n=144) yielded 529 unique records. Following the preliminary screening phase, 88 records excluded, leaving 441 full-text articles to assess for eligibility. After a rigorous evaluation of these papers, 436 were excluded with specific reasons, ultimately

resulting in the inclusion of 5 studies in the final qualitative synthesis (figure 1).

Across the included studies, intravenous dexmedetomidine consistently demonstrated direct cardio myocyte-protective effects, although the dominant mechanisms varied according to the experimental model and type of cellular stress. In ischemic, hypoxic, and oxygen-stress conditions, dexmedetomidine generally attenuated apoptosis, reduced inflammatory and oxidative signaling, and improved cellular viability or functional preservation. Cai et al. showed that these effects linked to activation of the JAK2/STAT3/catalase pathway, with consequent suppression of oxidative stress, endoplasmic reticulum stress, and apoptotic signaling. Xiao et al. further demonstrated that dexmedetomidine enhanced autophagy flux and reduced myocardial injury through an α2-adrenergic receptor-dependent AMPK-mediated mechanism. In contrast, Li Yan et al. identified a distinct electrophysiological action, reporting that dexmedetomidine directly suppressed sodium and L-type calcium currents and prolonged action potential duration in human iPSC-derived cardio myocytes, apparently independent of classical adrenergic receptor pathways. Li Wang et al. extended the mechanistic spectrum by showing that dexmedetomidine also exerted epigenetic and anti-inflammatory effects via the TET1/Sirt1/NF-κB axis, thereby limiting apoptosis and inflammatory mediator production in both in vitro and in vivo ischemia/reperfusion models. Finally, Borger et al. demonstrated that under both hypoxic and hyperoxic oxygen stress, dexmedetomidine modulated proliferation-related, apoptotic, autophagy, oxidative stress, extracellular remodeling, and Hippo pathway-associated markers, suggesting a broader role in preserving cardio myocyte homeostasis under disturbed oxygen environments. Taken together, these findings indicate that dexmedetomidine acts not merely as a sedative with indirect hemodynamic consequences, but as a pleiotropic cellular modulator capable of influencing survival signaling, redox balance, autophagy, electrophysiology, inflammation, and stress-responsive transcriptional programs in cardio myocytes (table 2).

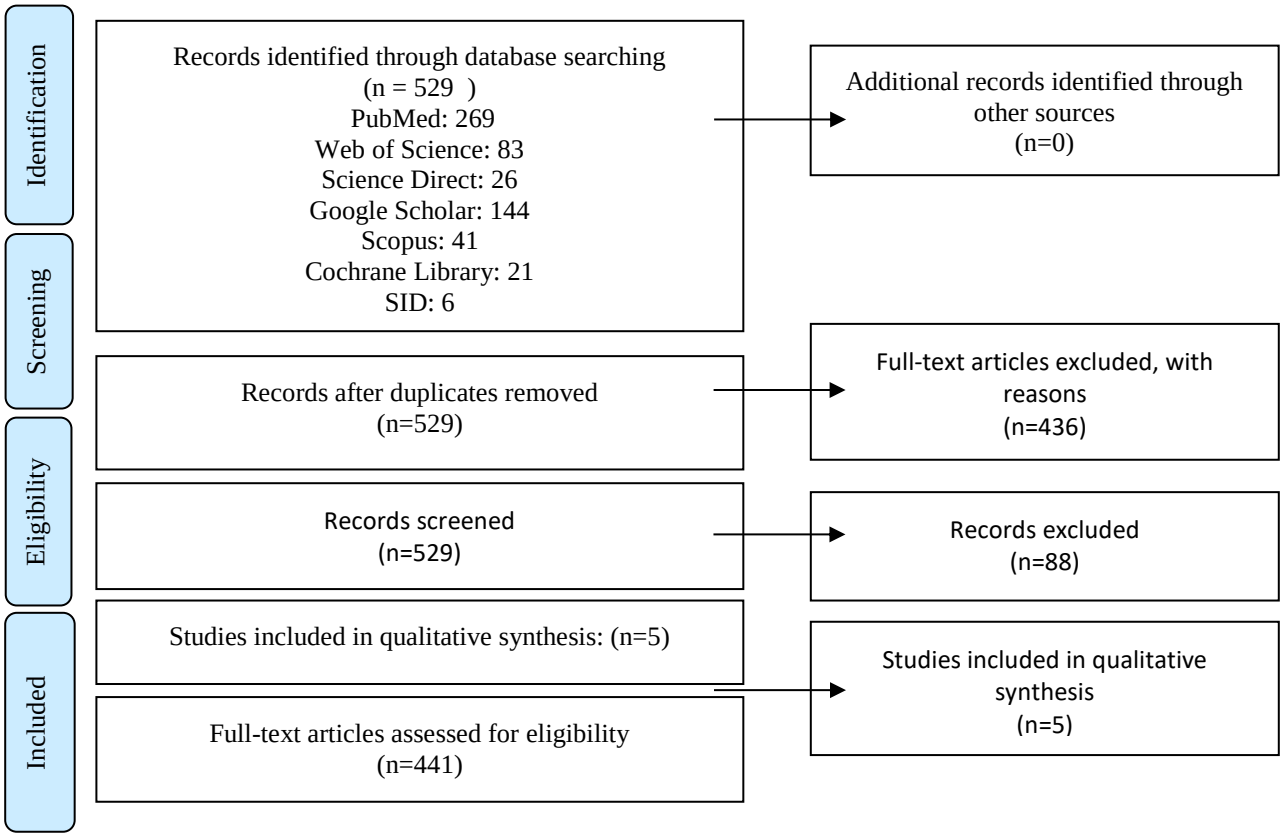

Figure 1. Flowchart depicting the selection process and stepwise inclusion and exclusion of studies in the present systematic review and meta-analysis2020

Table 2. Summary of Included Studies on the Effects and Mechanisms of Dexmedetomidine in Cardio myocyte Models

Study (Author, Year)	Experimental Model(s)	Key Molecular / Cellular / Functional Findings	Identified Signaling Pathways / Mechanisms
Cai et al. (2021) (11)	Rat H9c2 cardio myocytes subjected to hypoxia/reoxygenation (H/R) injury	Dexmedetomidine increased cell viability and reduced LDH release, ROS accumulation, and MDA levels. It also suppressed inflammatory cytokines, enhanced antioxidant defenses, and inhibited apoptosis through increased Bcl-2 and decreased Bax and cleaved caspase-3.	Cardio protection was mediated through activation of the JAK2/STAT3/catalase pathway, attenuating oxidative stress, ER stress, inflammation, and apoptosis.
Xiao et al. (2021) (12)	Human heart tissue from TOF patients and human iPSC-derived cardio myocytes	Dexmedetomidine reduced TUNEL-positive cells and cleaved caspase-3 expression, while enhancing autophagy flux, evidenced by increased LC3-II and p62 degradation. These effects were abolished by yohimbine and 3-MA.	Dexmedetomidine acted through an α2-adrenergic receptor-dependent AMPK/autophagy pathway, promoting autophagy clearance and reducing cardio myocyte injury.
Li Yan et al. (2021) (13)	Human iPSC-derived cardiomyocytes (predominantly ventricular-like hiPSC-CMs) assessed by patch-clamp electrophysiology	Dexmedetomidine dose-dependently reduced spontaneous action potential frequency, prolonged APD90, and inhibited INa and ICa amplitudes without substantial effects on If, IK1, or IKr. It also altered sodium and calcium channel kinetics.	Dexmedetomidine directly modulated cardio myocyte electrophysiological activity by suppressing sodium and L-type calcium currents, apparently independent of α2-adrenoceptor, imidazoline receptor, and α1-adrenoceptor signaling.
Li Wang et al. (2022) (14)	Human cardio myocyte cell lines (HCM and AC16) subjected to OGD/R injury, plus rat myocardial ischemia/reperfusion model	Dexmedetomidine dose-dependently improved viability and proliferation, reduced apoptosis-related proteins, increased Bcl-2, and decreased inflammatory mediators in OGD/R-treated cells. In vivo, it also reduced histopathological damage, apoptosis, and inflammatory cytokine expression in rat myocardium after I/R.	Dexmedetomidine exerted cardio protection through the TET1/Sirt1/NF-κB axis by increasing TET1, reducing DNA methylation, demethylating the Sirt1 promoter, enhancing Sirt1 expression, and suppressing NF-κB activation.
Moritz Borger et al. (2023) (15)	Rat H9c2 cardio myoblasts and primary neonatal rat cardio myocytes (NRCMs) exposed to hypoxia (5% O2), normoxia (21% O2), or hyperopia (80% O2)	Dexmedetomidine partially restored proliferation under oxygen stress, increased CycD2 expression, reduced apoptotic markers (Casp3, Casp8, and in H9c2 also AIF), modulated autophagy-related genes (Atg5, Atg12), attenuated oxidative stress response markers (GCLC, Nrf2, Hif1α), reduced extracellular matrix/remodeling-associated markers (Timp1, Timp2), and influenced structural injury marker Tnnt2 under hyperoxic conditions. It also counteracted oxygen stress–associated alterations in cell-cycle and growth behavior, although effects on LDH release and viability were limited or model-dependent.	Dexmedetomidine appeared to protect cardio myocytes against oxygen stress induced injury through multi-target modulation of apoptosis, autophagy, oxidative stress signaling, and Hippo pathway-associated regulators. Proposed mechanisms included restoration of Cul7, suppression of Lats2, enhancement of Tead1, and normalization of YAP1, suggesting involvement of Hippo signaling in addition to anti-apoptotic and anti-oxidative actions.

This schematic illustrates the major effects of dexmedetomidine on cardio myocytes. Dexmedetomidine reduces apoptosis, oxidative stress, and inflammation, while promoting

protective autophagy and regulating key signaling pathways, including JAK2/STAT3, AMPK, and TET1/Sirt1/NF-kB. It also modulates sodium and calcium channel activity, indicating effects on both cardio myocyte survival and electrophysiological function. Overall, dexmedetomidine acts as a multifunctional protective regulator in cardio myocytes under stress conditions (figure 2).

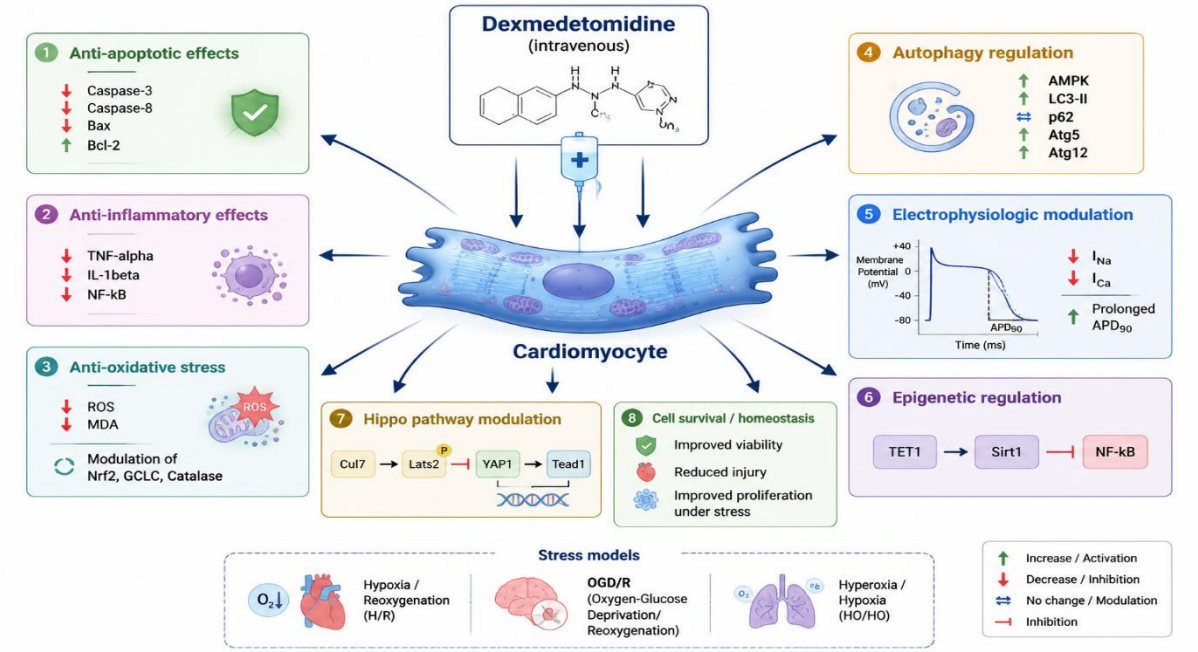

Figure 2. Effects of dexmedetomidine on cardio myocytes

Discussion

The findings synthesized in this systematic review suggest that intravenous dexmedetomidine exerts direct and biologically meaningful effects on cardio myocytes that extend beyond its established sedative, analgesic, and sympatholytic properties. Across the included experimental studies, dexmedetomidine consistently reduced cellular injury under ischemic, hypoxic, hyperoxic, and reperfusion-related stress conditions. Despite variation in model systems and endpoints, the overall pattern was convergent: dexmedetomidine decreased apoptosis, attenuated oxidative and inflammatory stress, improved viability, and modulated signaling pathways involved in intracellular adaptation and survival. In addition, some evidence indicated direct electrophysiological effects on ion-channel behavior, further broadening the mechanistic scope of its cardio myocyte actions. Taken together, these data support the concept that dexmedetomidine is not merely a hemodynamically active sedative but a pleiotropic modulator of cardio myocyte biology with potential translational relevance in myocardial stress states (16).

A brief overview of the included articles reinforces this interpretation. In one ischemia/reperfusion-related model, dexmedetomidine activated the JAK2/STAT3/catalase pathway and suppressed oxidative stress, endoplasmic reticulum stress, and apoptosis, suggesting an antioxidant-centered mechanism of cytoprotection (17). In a hypoxia/reoxygenation setting, dexmedetomidine enhanced autophagy flux and reduced myocardial injury through an α2-adrenergic receptor-dependent AMPK-mediated process, indicating that regulated autophagy is an important component of its protective profile (18). In human induced pluripotent stem cell-derived cardio myocytes, dexmedetomidine directly suppressed sodium and L-type calcium currents and prolonged action potential duration, apparently in a receptor-independent manner, thereby revealing a distinct electrophysiological mode of action (19). In both cellular and animal ischemia/reperfusion models, dexmedetomidine also showed epigenetic and anti-inflammatory effects via the TET1/Sirt1/NF-κB axis, reducing inflammatory mediator production and apoptosis (20). Finally, under disturbed oxygen environments, dexmedetomidine modulated proliferation-related, apoptotic, autophagy, oxidative stress, extracellular remodeling, and Hippo pathway-associated markers, pointing to a broader role in preserving cardio myocyte homeostasis under environmental stress (21).

One of the most consistent themes across these studies is the anti-apoptotic action of dexmedetomidine. Cardio myocyte loss during ischemia, hypoxia, and reperfusion driven not only by necrotic damage but also by tightly regulated apoptotic pathways triggered by mitochondrial dysfunction, reactive oxygen species generation, calcium overload, and inflammatory signaling. The observed reductions in TUNEL-positive cells, cleaved caspases, and pro-apoptotic proteins,

together with increases in anti-apoptotic regulators, suggest that dexmedetomidine interferes with this injury cascade at several levels. Mechanistically, this effect is plausible because preservation of mitochondrial integrity and reduction of oxidative burden can blunt cytochrome c release, caspase activation, and downstream execution of apoptosis. In this sense, dexmedetomidine appears to shift the balance from programmed cell death toward survival, which may represent a final common pathway underlying many of the reported benefits across otherwise heterogeneous experimental models (22).

Oxidative stress reduction also appears to be a central mechanism by which dexmedetomidine confers cardio myocyte protection. The myocardium is particularly vulnerable to fluctuations in oxygen availability because cardio myocytes depend heavily on oxidative metabolism and possess a high density of mitochondria. During ischemia/reperfusion and hypoxia/reoxygenation, abrupt restoration of oxygen supply can generate excessive reactive oxygen species, overwhelming endogenous defenses and promoting lipid peroxidation, protein misfolding, DNA damage, and apoptotic signaling. The reported activation of JAK2/STAT3/catalase signaling provides a coherent explanation for how dexmedetomidine may counter these events. Catalase detoxifies hydrogen peroxide, whereas STAT3 has well-established roles in mitochondrial stabilization, antioxidant defense, and cell survival. Therefore, enhancement of this axis may reduce oxidative injury at both the cytosolic and mitochondrial levels, ultimately preserving cardio myocyte viability and limiting stress-induced dysfunction (23).

The interaction between dexmedetomidine and autophagy offers an additional mechanistic layer that is particularly relevant to stressed cardio myocytes. Autophagy is a tightly regulated homeostatic process responsible for degrading damaged proteins and organelles, especially dysfunctional mitochondria. In the setting of ischemic or hypoxic stress, appropriately activated autophagy can be beneficial because it removes injured subcellular components and supports energy balance. However, excessive or ineffective autophagy may become maladaptive. The reviewed evidence suggests that dexmedetomidine does not simply increase autophagy indiscriminately; rather, it improves autophagy flux in a coordinated and protective fashion. The involvement of α2-adrenergic receptor signaling and AMPK is mechanistically important because AMPK functions as a cellular energy sensor that activated during ATP depletion and metabolic stress. By engaging AMPK-dependent pathways, dexmedetomidine may promote adaptive intracellular recycling, preserve energetic homeostasis, and reduce the accumulation of toxic cellular debris, thereby enhancing resistance to reperfusion-related injury (24).

Inflammation is another major contributor to cardio myocyte injury, particularly in ischemia/reperfusion contexts, and the included data suggest that dexmedetomidine attenuates inflammatory responses through both signaling and epigenetic mechanisms. The reported suppression of NF-κB activity, accompanied by reductions in inflammatory cytokines such as TNF-α and IL-1β, supports a model in which dexmedetomidine restrains the amplification phase of cellular stress. The accompanying increase in TET1 expression and demethylation of the Sirt1 promoter are especially noteworthy because they suggest that dexmedetomidine may influence not only acute molecular signaling but also the transcriptional architecture of stress adaptation. Sirt1 is a key regulator of mitochondrial homeostasis, oxidative defense, and inflammatory restraint, and its upregulation may partly explain the broad protective phenotype observed in these models. Thus, the TET1/Sirt1/NF-κB axis provides a compelling framework through which dexmedetomidine may integrate anti-inflammatory, anti-apoptotic, and cytoprotective responses at both epigenetic and post-transcriptional levels (25).

An important and conceptually distinct aspect of the evidence is the direct electrophysiological effect of dexmedetomidine on cardio myocytes. The finding that dexmedetomidine suppresses sodium and L-type calcium currents and prolongs action potential duration, apparently independently of α2-adrenoceptor, imidazole receptor, or α1-adrenoceptor antagonism, suggests that some of its cardiac cellular actions are not mediated by canonical receptor pathways. This observation broadens the pharmacologic interpretation of dexmedetomidine and raises the possibility of direct interactions with membrane ion channels or channel-regulatory proteins. Such effects may be biologically relevant in the setting of cellular stress because limiting sodium influx and calcium entry could reduce excitability, attenuate calcium overload, and lower energy demand. Since calcium overload is a major driver of mitochondrial injury, contractile dysfunction, and arrhythmogenic instability, direct electrophysiological modulation may represent another means by which dexmedetomidine preserves cardio myocyte function under adverse conditions (26).

The broader transcriptional and signaling changes observed under hypoxic and hyperoxic conditions further support the view that dexmedetomidine acts as a global regulator of cellular stress adaptation. The reported modulation of apoptosis-related markers, autophagy-associated genes, oxidative stress regulators, extracellular matrix-related factors, and Hippo pathway components suggests that dexmedetomidine may influence multiple

interconnected programs involved in cardio myocyte resilience. This is particularly relevant because oxygen stress does not trigger a single linear pathway; rather, it induces a network response involving metabolism, redox control, structural remodeling, and fate-determining transcriptional signals. The possible involvement of Hippo-associated elements such as YAP-related signaling is intriguing, as this pathway linked to survival, mechanotransduction, and regenerative signaling in cardiac tissue. Although the functional significance of these changes requires further clarification, the data collectively imply that dexmedetomidine may help cardio myocytes maintain homeostasis by coordinating several adaptive systems simultaneously rather than targeting a single downstream injury mediator (27).

When interpreted together, the mechanistic diversity across the included studies not seen as a weakness, but rather as evidence that dexmedetomidine acts in a context-dependent manner. Cardio myocytes exposed to ischemia/reperfusion, hypoxia/reoxygenation, hyperopia, or electrophysiological stress do not respond identically, and it is therefore unsurprising that the dominant protective pathway varies by model. What remains consistent is the direction of effect: dexmedetomidine repeatedly shifts cardio myocyte responses away from oxidative injury, apoptosis, inflammatory activation, and maladaptive stress signaling, and toward survival, homeostasis, and functional preservation. In this respect, the agent appears to operate as a biologic stabilizer, with different signaling nodes recruited according to the specific stress environment. Such context sensitivity may be one reason why dexmedetomidine has shown broad experimental benefit across highly diverse cellular settings (28).

These findings may also carry important translational implications. Because dexmedetomidine is already widely administered intravenously in perioperative and critical care practice, the demonstration of direct cardio myocyte-protective effects raises the possibility that some of its clinical benefits may derive not only from reduced sympathetic tone and improved hemodynamic control, but also from intrinsic myocardial cellular actions. Nevertheless, the evidence interpreted cautiously. The included studies differ in species, cell source, oxygen protocol, drug concentration, exposure duration, and outcome measurement. Some experiments used human iPSC-derived cardio myocytes, whereas others used rat-derived cells or in vivo models, and not all tested concentrations may directly reflect clinically achieved myocardial exposure. Moreover, receptor-dependent and receptor-independent findings coexist, indicating that dexmedetomidine pharmacology at the cardio myocyte level is complex and not yet fully resolved. Accordingly, while the biological plausibility is strong, further translational and clinical studies needed to determine dose relevance, timing, and the extent to which these cellular benefits contribute to measurable protection in human cardiac stress states (29).

Overall, this systematic review supports the conclusion that intravenous dexmedetomidine functions as a multifaceted modulator of cardio myocyte biology. Its protective actions appear to arise through convergent effects on apoptosis, oxidative stress, autophagy regulation, inflammatory signaling, epigenetic control, ion-channel activity, and stress-responsive transcriptional pathways. Rather than acting through a single dominant mechanism, dexmedetomidine appears to engage a network of adaptive responses that collectively preserve cardio myocyte integrity under adverse conditions. This broad mechanistic profile strengthens the rationale for considering dexmedetomidine as more than a sedative agent and highlights its potential relevance in myocardial protection. Future investigations should focus on validating these pathways in human-relevant systems, clarifying the relative importance of receptor-mediated versus direct cellular actions, and determining how these mechanistic effects can be translated into improved cardiovascular outcomes in clinical practice (30).

Conclusion

In conclusion, this systematic review demonstrates that intravenous dexmedetomidine serves as a multi-target modulator of cardio myocyte health, offering significant protection against ischemic, hypoxic, and oxidative injuries. Its efficacy is mediated through a complex interplay of signaling cascades, including antioxidant activation, autophagy regulation, epigenetic modifications, and direct electrophysiological stabilization. These direct cellular actions distinguish dexmedetomidine from traditional sedatives, highlighting its role as a pleiotropic agent capable of preserving myocardial homeostasis. While preclinical evidence is compelling, future translational research is essential to bridge the gap between these molecular mechanisms and clinical outcomes in perioperative and critical care medicine.

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Conflicts of interest

The authors declare that they have no competing interests.

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