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REVIEW

Treatment of cardiac contusion: experimental basis for pathogenetic therapy and emerging approaches in cardioprotection

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ABSTRACT

Myocardial contusion is a serious consequence of blunt thoracic trauma, most commonly resulting from traffic accidents, falls, sports injuries, and combat-related events. It is associated with impaired myocardial contractility, fibrosis, and systemic inflammation, and carries a high risk of complications, with mortality rates reaching up to 10%. Despite advances in understanding the pathogenesis, the development of effective therapeutic strategies remains a key priority in experimental cardiology.

A promising direction involves the development of targeted approaches that address both myocardial injury and the optimization of adaptive responses. The first aspect focuses on counteracting bioenergetic hypoxia, restoring energy and ionic homeostasis, suppressing secondary damage in the context

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of inflammation, and regulating apoptosis and autophagy. The second aspect targets the modulation of stress-activating and stress-limiting systems, including tissue-level adaptation mechanisms.
Particular attention has been given to cardioprotective agents, which have demonstrated efficacy in ischemic heart disease, myocardial infarction, and ischemia–reperfusion injury. However, their impact on post-traumatic myocardial remodeling remains insufficiently explored. Phytopreparations from the Chinese Pharmacopoeia, characterized by multitarget activity on key pathological processes — such as bioenergetic deficiency, oxidative stress, and dysregulation of cellular homeostasis — may offer a viable alternative. Integrated strategies combining anti-inflammatory effects, metabolic support, and control of fibrogenesis may enhance therapeutic outcomes.
Further research is necessary to assess the synergistic interactions of individual components, dose-dependent responses, and the long-term impact on myocardial structure and function. Multimodal approaches may improve therapeutic efficacy and help overcome the limitations of monotherapy, opening new avenues for the management of post-traumatic cardiac complications.

Key Words: commotio cordis; blunt cardiac trauma; blunt cardiac injury; blunt chest trauma; heart contusion; cardioprotection; stress-activating systems; stress-limiting systems

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Introduction

Myocardial contusion primarily results from mechanical trauma to the thoracic cage, typically occurring in the context of road traffic accidents, high-energy falls, sports-related injuries, as well as mine-blast and behind-armor (blast wave) trauma [1, 2]. The epidemiology of myocardial contusion remains poorly characterized, largely due to the lack of standardized diagnostic criteria and the absence of consistent reporting mechanisms in national health statistics. In most cases, the prevalence of this condition is inferred indirectly through general thoracic trauma indicators. According to the Ministry of Health of the Russian Federation (2023), in 2022, thoracic injuries, including those caused by road traffic accidents and other external factors, were reported at rates of 599.5 and 530.6 cases per 100,000 population, respectively[1]. The average mortality rate associated with blunt chest trauma is approximately 17.5%; however, when the injury involves simultaneous damage to the lungs, heart, and major vessels, the mortality rate increases significantly, leading to a markedly poorer prognosis [3]. According to the National Trauma Data Bank, myocardial contusion is diagnosed in 7–55% of chest trauma cases and accounts for approximately 10% of all admissions to trauma departments [4]. A meta-analysis by Kyriazidis et al. showed that myocardial injury following blunt chest trauma occurs in 18.3% of cases [5]. Particular attention should be given to the rare but extremely life-threatening complications associated with this condition. A retrospective analysis of 20,000 trauma cases revealed that blunt cardiac and pericardial rupture occurs in 0.002% of cases, yet is associated with a mortality rate of 89.2% [6].

Post-traumatic morphological changes are typically classified into three phases: the acute phase, reparative regeneration, and post-traumatic

[1] Здравоохранение в России. 2023: Статистический сборник/Росстат. Москва: Росстат; 2023. / Healthcare in Russia. 2023: Statistical book/Rosstat. Moscow, 2023. 179 p. (In Russ.). Accessed 05.04.2025. http://ssl.rosstat.gov.ru/storage/mediabank/Zdravoohran-2023.pdf

cardiosclerosis [7, 8]. Clinically, four stages are identified in the post-traumatic course of myocardial contusion: the stage of primary traumatic disturbances, traumatic myocarditis, restoration of impaired functions, and the outcome stage [7]. In Russia, myocardial contusion is classified based on severity, which is determined by the extent of hemodynamic disturbances (mild, moderate, or severe) [7].

Patients presenting with clinical or echocardiographic signs of severe cardiac trauma, such as valve, septal, or ventricular wall injury resulting in cardiac tamponade, require immediate surgical intervention. However, even when diagnosed promptly, subsequent surgical treatment carries considerable risks. First, data from existing case series reported in the literature involving patients who underwent surgical intervention indicate that the extent of preoperative hemodynamic instability may represent the most significant prognostic factor, with survival rates reported to range from 39% to 100% [9]. Second, the use of anesthetic agents with cardiodepressive effects, along with positive pressure ventilation following intubation, may further compromise cardiac function in these patients [9].

At the same time, early diagnosis of myocardial contusion is often challenging. Seemingly minor injuries to the chest wall may be accompanied by severe closed cardiac trauma, and vice versa: symptoms of rib fractures, pulmonary injuries, or chest wall contusions may predominate, thereby masking the signs of myocardial contusion [7].

Delayed diagnosis and management of myocardial contusion can substantially increase the risk of poor outcomes following chest trauma. However, treatment of myocardial contusion remains symptom-oriented, as pathogenetic therapeutic strategies are still under development, primarily due to incomplete understanding of the underlying mechanisms. This review aims to systematize pathogenetically based approaches to the treatment of cardiac contusion and to highlight promising areas of pharmacological cardioprotection for further study of their efficacy in experimental models.

Pathogenesis of cardiac contusion: current status of the issue

The pathogenesis of myocardial contusion is characterized by a complex interaction between injury and adaptive mechanisms. Primary damage is primarily caused by the direct mechanical impact on the heart [10]. However, secondary injury – driven by hypoxia, energy deficiency, and inflammation – can be equally significant, and in some cases, even more harmful [11]. Direct damage to the microvascular network contributes to ischemia and bioenergetic hypoxia. In the affected tissue, anaerobic glycolysis becomes predominant, leading to hyperlactatemia, acidosis, decreased oxidative phosphorylation rates, depletion of high-energy phosphates, and consequently, increased lipid peroxidation in the damaged myocardium [11–13]. Local acidosis contributes to the suppression of mitochondrial respiratory chain enzyme activity and promotes the activation of proteolytic enzymes, which can exacerbate secondary injury to cardiomyocytes. Impaired efficiency of the electron transport chain not only lowers production of reduced form of nicotinamide adenine dinucleotide, but also leads to increased generation of reactive oxygen species (ROS), such as superoxide and hydrogen peroxide [14]. Concurrently, adaptive mechanisms are activated to restore homeostasis; however, their effectiveness is dependent on the dynamic interplay between stress-activating systems (such as the sympathoadrenal and hypothalamic–pituitary–adrenal axes) and stress-limiting

systems (including gamma-aminobutyric acid (GABA)ergic, opioidergic, and antioxidant pathways). When this balance is disrupted, physiological stress shifts to pathological distress, which exacerbates myocardial injury, promotes cardiomyocyte apoptosis, and compromises the heart's functional reserves.

ROS are recognized as critical pathogenic factors that contribute to endothelial dysfunction. These species impair calcium uptake by the myocardium, trigger arrhythmias, and promote cardiac remodeling and apoptosis [15]. It is well-established that maintaining cellular function relies on a delicate balance between ROS and antioxidant defenses [15]. Experimental studies have shown that myocardial contusion is associated with a reduction in the levels of reduced glutathione within injured cardiomyocytes, thereby exacerbating secondary tissue damage [16]. However, when selecting pharmacological agents to mitigate lipid peroxidation in myocardial contusion, it is essential to recognize that ROS signaling during hypoxia also plays a pivotal role in activating various cellular defense mechanisms [17].

Previous experimental studies have demonstrated that myocardial contusion in the post-traumatic period is associated with disturbances in central hemodynamics, which are driven by two key components: reflex responses and myocardial alterations, the latter of which has been detailed in the preceding section [18]. The reflex component is closely linked to neural reflexes mediated by activation of the parasympathetic nervous system. However, the role of these reflexes during the early post-traumatic phase of myocardial contusion should not be viewed solely as a pathogenic factor but also as a potential adaptive mechanism. Notably, the Bezold–Jarisch reflex may function as a form of myocardial adaptation, a concept supported by experimental data [19]. For example, studies have indicated that the administration of atropine – a substance that reduces parasympathetic activity – during the post-traumatic phase of myocardial contusion leads to an increased incidence of ventricular arrhythmias following the injury [20].

As a result of both primary traumatic and secondary hypoxic alterations in the myocardium, pain emerges as a key manifestation of the local inflammatory response, which is initiated in the injured tissue by the presence of damage-associated molecular patterns. Concurrently, pain can trigger emergency adaptive responses in the body, designed to create optimal conditions for survival under life-threatening circumstances. The General Adaptation Syndrome, the conception, proposed by G. Selye, describes a classical defense-compensatory strategy that facilitates the body's adjustment and may be used for characterization of processes during the post-traumatic phase of myocardial contusion [16]. Successful adaptation depends on the balanced interaction between stress-activating and stress-limiting systems, which together give rise to the classical protective response known as «stress». However, when stress-activating systems dominate excessively or stress-limiting systems are insufficient, this adaptive mechanism may transition into a maladaptive process, referred to as «distress».

The two principal stress-activating systems in mammals are the sympathoadrenal system and the hypothalamic-pituitary-adrenal axis. The sympathoadrenal system has a wide range of significant effects on the heart and cardiovascular system, including positive chronotropic (increased heart rate), inotropic (enhanced contractility), lusitropic (accelerated relaxation), dromotropic (improved conduction), and bathmotropic (increased excitability) effects. Furthermore, it contributes to elevated blood pressure by enhancing venous and arteriolar tone [21]. Activation of the hypothalamic-pituitary-adrenal axis involves stimulation of parvocellular neurons in the paraventricular nucleus of

the hypothalamus, leading to increased production of corticotropin-releasing hormone, adrenocorticotropic hormone, and the subsequent release of corticosteroids. These hormones play a crucial role in maintaining homeostasis by optimizing carbohydrate metabolism, regulating immune responses, normalizing fluid and electrolyte balance, and modulating behavioral and emotional responses – ultimately contributing to the effective execution of the body's protective stress response [22].

Closely interacting with the stress-activating systems are the stress-limiting systems, which include central components, such as the GABAergic and opioidergic systems, and peripheral components, including the prostaglandin system and tissue antioxidants [23]. The GABAergic system plays a key role in modulating the effects of the sympathoadrenal system. Experimental studies have shown, for instance, that chronic stress in male rats may weaken GABAergic activity within the paraventricular nucleus and alter autonomic cardiac regulation [24]. One of the key effects of GABA is its ability to suppress the secretion of corticotropin-releasing hormone in the hypothalamus [25]. The opioidergic stress-limiting system comprises neurons located in the thalamus, amygdala, hypothalamus, striatum, nucleus accumbens, pituitary gland, as well as in the cerebral cortex and olfactory bulbs. These structures are involved in the synthesis of endogenous opioids, such as endorphins, enkephalins, and dynorphins, whose physiological effects are mediated through the activation of opioid receptors [26]. Peripherally, opioid receptors are expressed in the adrenal cortex, on the membranes of immunocompetent cells, and in the vascular endothelium [27].

Despite their functionally opposing roles, the opioidergic and stress-activating systems are unified by a common objective: facilitating the organism's adaptation to environmental stressors. Their interaction reflects a finely tuned homeostatic balance, wherein mutually antagonistic pathways dynamically modulate each other in accordance with internal and external demands. This interdependence is evident at the metabolic level, where both adrenocorticotropic hormone and β-endorphin are derived from the common precursor proopiomelanocortin. Importantly, activation of opioid receptors has been shown to suppress adrenal glucocorticoid secretion, underscoring a feedback loop that modulates the activity of both systems [28].

The opioidergic system is characterized by effects that are partially opposite to those of the sympathoadrenal system. In contrast to the vasoconstrictor action of catecholamines, opioids cause moderate vasodilation and exhibit antiarrhythmogenic activity, but the severity of these effects depends on the type and localization of receptors [29]. The key role of the opioidergic system in stress-limiting processes is associated with the suppression of anxiety and fear, states that are enhanced by catecholamines. An equally important characteristic of opioids is their analgesic effects realized through activation of the serotoninergic antinociceptive system [30].

The prostaglandin stress-limiting system, the key components of which are prostaglandin E and prostaglandin I_2, realizes its protective effects through three main mechanisms. The first, it suppresses sympathetic activity by directly inhibiting norepinephrine production. The second, prostaglandin E and especially prostaglandin I_2 cause marked vasodilation of coronary arteries, improving myocardial perfusion [31]. The third, prostaglandins limit lipid peroxidation, preventing damage to cell membranes and organelles, which enhances antioxidant defense [32].

Although a resilient adaptive strategy is established in all rats during the post-traumatic period, regardless of their baseline stress resilience, individual

stress reactivity plays a crucial role in modulating the balance between stress-activating and stress-limiting systems following cardiac injury [16]. Experimental studies in rats have shown that inherent stress tolerance is a key determinant of the efficacy of adaptive mechanisms [16]. The post-traumatic phase of experimental myocardial contusion is characterized by a reduction in both force-generating and velocity-dependent indices of myocardial contractility, along with a decline in myocardial functional reserves, independent of baseline stress resilience. However, high baseline stress resilience is associated with better preservation of myocardial contractile function and reserves, whereas low stress resilience is linked to greater myocardial dysfunction and a more pronounced reduction in the functional reserves of the injured heart [33]. The observed differences in the severity of contractile dysfunction between high- and low-resilience phenotypes can likely be attributed to varying degrees of secondary myocardial injury within the contusion zone. These differences are probably mediated by the distinct balance between stress-activating and stress-limiting mechanisms involved in the pathogenesis of secondary damage [33].

In animals with high stress resilience, an optimal adaptive strategy is established, effectively mitigating secondary myocardial injury and preserving cardiac function during the post-traumatic period [16]. In contrast, individuals with low stress resilience exhibit a predominance of stress-activating system activity, leading to the development of a distress syndrome [16]. This imbalance results in pronounced secondary myocardial damage, characterized by reduced contractile performance and diminished functional cardiac reserves, a disruption in cellular homeostasis marked by a shift toward apoptosis over autophagy, and a significant depletion of reduced glutathione levels in cardiomyocytes, thereby intensifying oxidative stress. Collectively, these pathological alterations contribute to the elevated mortality observed in low-resilience animals [16, 33].

Immunohistochemical analysis revealed activation of both autophagy (Beclin-1) and apoptosis (Caspase 3) within the myocardial injury zone following experimental contusion, irrespective of the animals' baseline stress resilience [34]. However, the expression dynamics of these markers differed markedly between groups. In high-resilience individuals, a progressive increase in Beclin-1 expression was observed, indicative of enhanced autophagic flux. In contrast, low-resilience animals exhibited a decline in Beclin-1 levels. Caspase 3 expression was elevated across all groups, although baseline levels were significantly higher in low-resilience rats. These findings suggest that autophagy may serve an adaptive, cytoprotective function in the context of less severe myocardial injury, as observed in stress-resilient animals, whereas apoptosis predominates in the setting of more extensive damage, characteristic of low-resilience phenotypes [34].

In a model of experimental myocardial contusion, the post-traumatic period was characterized by a statistically significant reduction in desmin expression ($p<0.0001$) and the number of intercalated discs ($p<0.0001$) within the injury zones of animals in the experimental group, as compared to controls, regardless of their baseline stress resilience. Notably, the subgroup of low-resilience animals exhibited significantly lower values for both parameters when compared to their high-resilience counterparts [35].

Secondary myocardial damage in the posttraumatic period caused by inflammation, bioenergetic hypoxia, and activation of lipid peroxidation is completed by fibroblast activation and replacement of damaged areas in the heart with connective tissue. Activated fibroblasts, forming connective tissue in previously damaged areas, change the structure of the myocardium.

Posttraumatic myocardial fibrosis disturbs bioenergetic exchange in the myocardium, as connective tissue increases energy dissipation during the conversion of metabolic energy into effective myocardial contraction. Cardiac remodeling occurring in the posttraumatic period contributes to the progression of structural-functional and spatial-geometric abnormalities, which may cause the development of arrhythmias and even heart failure in the remote period. Cardiac fibrosis is well studied on the model of myocardial infarction, however, the process of fibrosis as a result of cardiac contusion, which is conditioned, among other things, by the ratio in the posttraumatic period of primary, secondary damage and adaptive mechanisms, remains poorly understood [36].

The use of recombinant human fibroblast growth factor 21 (rhFGF21) is a promising direction for the correction of excessive connective tissue overgrowth in the myocardium. Experimental data demonstrate the ability of rhFGF21 to exert a protective effect against cardiac fibrosis induced by myocardial infarction [37], which may ultimately reduce the risk of arrhythmia development in the postinfarction period [36, 38]. However, there are no data on the evaluation of rhFGF21 efficacy in the posttraumatic period of experimental cardiac contusion in the literature.

Cardiac contusion: proven efficacy of pharmacotherapy and prospects for experimental design

Despite substantial advances in understanding the pathogenesis of myocardial contusion, the development of effective pathogenetically targeted therapies remains a pressing scientific challenge. Contemporary research emphasizes the need for an integrated approach aimed at addressing key mechanisms of injury, including bioenergetic hypoxia, energy deficiency, inflammation, and cellular imbalance involving apoptosis and autophagy [11, 16, 34]. The initial mechanical impact in myocardial contusion triggers a cascade of pathological events that closely parallel the processes underlying ischemic and reperfusion-related myocardial injury. Both conditions are marked by bioenergetic hypoxia, disturbances in ionic homeostasis, inflammatory activation, and impaired regulation of adaptive cellular responses. This pathogenetic convergence provides a compelling rationale for investigating, in the post-traumatic context of myocardial contusion, therapeutic strategies that have demonstrated efficacy in the treatment of ischemic heart disease and reperfusion-reoxygenation syndromes. Experimental data reinforce the promise of this translational approach. In particular, trimetazidine, a pharmacological agent widely employed in cardiology, has shown cytoprotective activity in models of myocardial contusion [39]. Nevertheless, the effective translation of these therapeutic strategies into routine clinical practice for the treatment of myocardial contusion necessitates further comprehensive experimental and clinical investigations. These studies should be directed toward establishing optimal dosing protocols, elucidating the therapeutic potential of combination regimens, and examining the long-term outcomes associated with such interventions.

Promising therapeutic directions involve targeted strategies that integrate two fundamental approaches:

1) Correction of myocardial injury, encompassing the mitigation of bioenergetic hypoxia, restoration of energy and ionic homeostasis, suppression of secondary damage driven by inflammation within the injured tissue, and regulation of cell death pathways, specifically apoptosis and autophagy;

2) Optimization of adaptive mechanisms, including modulation of the activity of stress-activating and stress-limiting systems, as well as fine-tuning of tissue-level adaptive responses such as apoptosis and autophagy.

Correction of myocardial injury

Correction of myocardial injury includes the use of metabolic cytoprotectors (trimetazidine, glutamine, mildronate, succinate-containing drugs, coenzyme Q10) [39-43].

The use of trimetazidine in an experimental model of myocardial contusion has demonstrated substantial cardioprotective effects. Our study demonstrated that pre-administration of trimetazidine helps maintain cardiomyocyte membrane integrity and supports myocardial contractility during the post-traumatic period. These results were further confirmed by *ex vivo* data from a model of the isolated isovolumically contracting heart [39]. In addition, an antiarrhythmic effect of trimetazidine, similar to that observed with glutamine, was detected in another our study [42]. Both compounds, when administered as monotherapy, significantly reduced the incidence of early post-traumatic arrhythmias. The authors attributed these effects to the metabolic cytoprotective properties of these agents, which enhance reparative processes [42]. These findings underscore the multifaceted beneficial impact of trimetazidine on both the structural and functional integrity of the myocardium, further supporting its potential clinical application in managing myocardial contusion.

The use of sodium polydihydroxyphenylene thiosulfonate in an experimental model of myocardial contusion has yielded conflicting results. We demonstrated previously that pre-traumatic administration of this antihypoxic effectively suppressed the onset of sinus arrhythmia, paroxysmal ventricular tachycardia, and intraventricular conduction disturbances, with its efficacy found to be independent of baseline arterial pressure [18]. However, the same study revealed a significant limitation of the therapy: a majority of animals receiving sodium polydihydroxyphenylene thiosulfonate developed pronounced arterial hypotension and a substantial reduction in cardiac output, primarily due to bradycardia. These hemodynamic disturbances persisted throughout the post-traumatic period, resulting in a tenfold increase in mortality compared to the control group [18]. These findings suggest that while sodium polydihydroxyphenylene thiosulfonate exhibits notable cardioprotective effects against arrhythmias, its destabilizing impact on systemic hemodynamics significantly reduces its therapeutic utility in the context of myocardial contusion.

Metabolic correction using succinate-based agents, such as meglumine sodium succinate, combined medication, containing inosine, nicotinamide, riboflavin and succinic acid, and ethylmethylhydroxypyridine succinate, represents a promising therapeutic strategy for managing myocardial contusion. Numerous studies have demonstrated the clinical efficacy of these compounds in conditions involving ischemic, hypoxic, and toxic myocardial injury, primarily by optimizing energy metabolism and enhancing antioxidant defenses [39, 40, 44]. However, the evidence supporting their use in the context of myocardial contusion remains limited. While Meglumine sodium succinate has been successfully employed in clinical cardiology practice, its ability to modulate reparative processes following traumatic myocardial injury requires further experimental validation. Additional research is crucial to elucidate the role of these agents in attenuating post-traumatic remodeling,

preventing arrhythmias, and improving clinical outcomes in the aftermath of myocardial contusion [40].

A substantial body of research has investigated the effects of pro-inflammatory cytokine inhibitors, such as anakinra and tocilizumab. Tocilizumab, in particular, has demonstrated variable outcomes in cardiology. In patients with ST-elevation myocardial infarction, the drug was shown to improve clinical prognosis without significantly altering levels of circulating endothelial or platelet-derived chemokines, although these concentrations were found to correlate with concomitant heparin administration [45]. Moreover, tocilizumab was reported to reduce levels of citrullinated histone H3, a key marker of neutrophil extracellular trap (NET) formation (NETosis), thereby mitigating secondary myocardial injury [46]. The randomized ASSessing the effect of Anti-IL-6 treatment in Myocardial Infarction (ASSAIL-MI) trial, which included 101 patients with acute ST-elevation myocardial infarction, confirmed the beneficial effects of tocilizumab, including an increase in salvaged myocardial tissue volume [47].

However, the use of tocilizumab in patients with non-ST-elevation myocardial infarction has been associated with increased levels of citrullinated histone H3, indicative of enhanced NETosis activity [48]. These findings underscore the need for further investigation into the dual role of tocilizumab in modulating inflammatory pathways in the setting of myocardial infarction. In the context of myocardial contusion, experimental evaluation of such effects is particularly relevant, given the potential impact of NETosis on myocardial remodeling and post-traumatic outcomes.

Another emerging avenue in anti-inflammatory therapy for cardiac pathology involves the inhibition of the nucleotide-binding oligomerization domain-, leucine-rich repeat-, and pyrin domain- containing receptor 3 (NLRP3) inflammasome, which has been identified as a potential key regulator at the intersection of energy metabolism, inflammation, and gut microbiota–derived metabolites. Elucidating the interplay among these factors may facilitate the identification of novel molecular targets for the prevention and treatment of cardiovascular disease, ultimately influencing disease progression [49]. Inhibition of NLRP3 activation has been shown to exert beneficial effects on metabolic pathways and autophagic flux in the hearts of mice fed an obesogenic diet. Thus, targeting NLRP3 activation holds promise for the treatment of both metabolic and cardiovascular conditions — including myocardial contusion [50]. Testing such inhibitors in experimental models of myocardial contusion appears to be both scientifically justified and therapeutically promising.

Although the potential efficacy of statins in the context of myocardial contusion requires further experimental validation, their well-established anti-inflammatory properties suggest a potential cardioprotective effect. A meta-analysis of statin therapy in patients with myocardial infarction and non-obstructive coronary artery disease (n=11,171, including 9,129 receiving statins) demonstrated a significant reduction in mortality and the incidence of fatal cardiovascular events [51]. These findings support the consideration of statins as a promising pathogenetic approach to mitigate the inflammatory sequelae of traumatic myocardial injury.

Pharmacological regulation of autophagy using agents such as rapamycin and spermidine represents a promising therapeutic strategy in the management of myocardial injury. Of particular interest is the role of mammalian target of rapamycin (mTOR), a key regulatory protein involved in amplifying the inflammatory response. Clinical studies have shown that early inflammation

following ST-elevation myocardial infarction significantly influences infarct size and the trajectory of left ventricular remodeling. In this context, mTOR inhibition has demonstrated potent cardioprotective effects. This was substantiated by a study conducted by Stähli et al., which reported a significant reduction in infarct size following acute myocardial infarction through targeted mTOR blockade [52].

Experimental data additionally reveal the mechanisms of this effect. In model of acute myocardial infarction, rapamycin, being a classical mTOR inhibitor, causes activation of autophagic processes in the damaged myocardium. As demonstrated by Aisa et al., this leads to a significant reduction in infarct area and improvement of cardiac contractile function after coronary artery ligation [53]. It is noteworthy that cytoprotective properties of rapamycin are also manifested in cell therapy. The study by Li et al. showed that preliminary activation of autophagy by rapamycin significantly improves survival and differentiation of transplanted mesenchymal stem cells in the model of ischemia-reperfusion [54].

Recent studies have opened new avenues for mTOR inhibition through the application of nanotechnology-based strategies. An innovative approach developed by Kwon et al. involves the use of liposomal nanoparticles encapsulating both myocardial injury–associated antigens and rapamycin. This system promotes the formation of tolerogenic dendritic cells and activates regulatory T cells that limit cardiac inflammation. Regulatory T cells, in turn, promote the phenotypic transformation of macrophages from a pro-inflammatory to a reparative profile, thereby mitigating adverse cardiac remodeling and ultimately improving cardiac function [55].

Taken together, current evidence strongly supports the potential of targeted mTOR inhibition and the modulation of autophagic processes as an effective strategy to limit myocardial injury, prevent excessive inflammation, and optimize reparative responses. It is crucial to note that these mechanisms may be relevant not only in the context of ischemic or reperfusion-induced myocardial damage but also in cases of traumatic cardiac injury. However, further experimental studies are necessary to validate this hypothesis and define the most effective approaches for autophagy modulation in the setting of myocardial contusion.

Optimization of adaptation processes

The second strategic direction in the treatment of myocardial contusion may be aimed at optimizing adaptation processes in cardiac contusion, which usually focuses on reducing hyperactivation of stress-releasing systems (β-blockers, glucocorticoid receptor antagonists) and enhancement of stress-limiting mechanisms through GABAergic (aminophenylbutyric acid), opioid (tyrosine-D-alanyl-glycyl-phenylalanyl-leucyl-arginine diacetate) [16], and antioxidant (rutin, also termed rutoside) pathways [56]. Additionally, ferroptosis inhibitors (ferrostatin-1) and autophagy stimulators that can improve cardiomyocyte survival can be studied.

One of the primary clinical manifestations of myocardial contusion is the occurrence of diverse arrhythmias. In cases where the patient exhibits a predisposition to tachyarrhythmias, the use of β-adrenergic blockers is considered a rational therapeutic strategy [57]. The cardioprotective effects of this drug class have been extensively characterized and are mediated through multiple intracellular signaling cascades initiated by distinct G-protein subunits [58]. β-blockers reduce myocardial hypertrophy and fibrosis caused by excessive

activation of sympathetic nervous system and renin-angiotensin-aldosterone system. Furthermore, by limiting catecholamine overload, β-blockers protect the myocardium from necrosis and apoptosis, thereby reducing the extent of injury to cardiomyocytes.

Another potential target for pathogenetically oriented therapy in myocardial contusion is the activation of GABA receptor pathways. This class includes benzodiazepines (e.g., diazepam, phenazepam, midazolam), barbiturates (e.g., thiopental sodium, phenobarbital), as well as baclofen, aminophenylbutyric acid, and sodium oxybate. Some of these agents may be employed for analgesia following trauma, including myocardial contusion; however, data on their direct effects in the context of myocardial contusion pathogenesis are currently lacking. Nevertheless, activation of the GABAergic system has been associated with downregulation of sympathoadrenal activity. In a rat model of ischemia–reperfusion injury, stimulation of central GABAergic structures was shown to reduce circulating catecholamine levels and myocardial injury markers, while also decreasing the extent of myocardial necrosis [59].

The following effects have been described for opioid receptor agonists, which may be of interest from the standpoint of pathogenetic therapy of cardiac contusion: antiarrhythmogenic, cardioprotective, counterinsulatory, vasoactive, anti-stressor, antioxidant, analgesic [60]. Notably, the effects of opioids on vascular tone and heart rate are ambiguous, given the diversity of opioid receptors and their localisation. To a large extent, these effects depend on the ability of the substance to penetrate the blood-brain barrier [61].

Opioid receptors μ- and δ- are able to increase the expression of type 1 glucose transporters on the cell surface [62]. This mechanism likely enhances myocardial metabolic adaptation in the context of traumatic injury. In a polytrauma model in pigs, including blunt chest trauma, it has been shown that in contrast to physiological conditions, when free fatty acids are the main energy substrate for cardiomyocytes, the use of glucose as an energy substrate in cardiomyocytes increases after injury [63]. Excitation of opioid receptors causes modulatory effects of adrenaline and noradrenaline on the heart

In the majority of studies reporting beneficial effects of opioid receptor agonists, the compounds employed were those with high permeability across the blood–brain barrier, a property closely linked to the clinically valuable analgesic effects of this pharmacological class. However, in experimental settings aimed at elucidating the local, peripheral actions of opioids, the use of opioid peptides with limited blood-brain barrier penetration may be more appropriate, allowing for a more selective assessment of their direct cardiotropic and vasoregulatory effects [16].

During the 1970s and 1980s, researchers in the Union of Soviet Socialistic Republics developed tyrosine-D-alanyl-glycyl-phenylalanyl-leucyl-arginine diacetate, a synthetic analog of leucine-enkephalin. In contrast to the endogenous peptide, tyrosine-D-alanyl-glycyl-phenylalanyl-leucyl-arginine diacetate features a substitution of glycine with D-alanine, which significantly slows its enzymatic degradation by enkephalinases. Additionally, an arginine residue was appended to the C-terminal region of the molecule. This positively charged modification was introduced to prevent tyrosine-D-alanyl-glycyl-phenylalanyl-leucyl-arginine diacetate from penetrating into higher centers of the central nervous system, thereby restricting its activity to peripheral targets [64].

In addition, an effect on the processes of collagen synthesis and breakdown in the liver has been described for tyrosine-D-alanyl-glycyl-phenylalanyl-leucyl-arginine diacetate [65], which may be interesting, given the importance of fibrosis in the pathogenesis of cardiac injury. In turn, intense inflammation

occurring after cardiac injury may aggravate the development of myocardial fibrosis. A decrease in neutrophil phagocytosis activity has been described for tyrosine-D-alanyl-glycyl-phenylalanyl-leucyl-arginine diacetate [66], which may also be useful for cardioprotection.

Antioxidant therapy represents a pathogenetically sound strategy in the treatment of myocardial contusion, given the central role of oxidative stress and inflammation in its pathogenesis. The positive effect of rutin on the state of myocardial antioxidant systems was demonstrated on the model of blunt cardiac trauma in rats [56], which opens prospects for further study of this group of drugs. However, uncontrolled use of drugs whose effects are aimed at suppressing the production of ROS can cause the so-called antioxidant stress. The essence of this process is that ROS in the cell are not only a damaging factor but also an important intracellular messenger that regulates such processes as apoptosis and autophagy. Antioxidant stress in tumor cells may be responsible for the formation of drug resistance in tumor cells [67]. The obtained data on the role of oxidative stress in the pathogenesis of cardiac contusion justify the need for experimental studies to verify the therapeutic potential of antioxidants.

A multi-level therapeutic approach to myocardial contusion may not only interrupt the vicious cycle of injury progression but also enhance endogenous mechanisms aimed at myocardial protection during the post-traumatic period. Such strategies open new avenues for the restoration of cardiac structure and function, the prevention of post-traumatic cardiosclerosis and pathological remodeling, and, ultimately, the reduction of mortality associated with myocardial contusion.

Traditional herbal medicines in the treatment of myocardial contusion: therapeutic potential of the Chinese Pharmacopoeia

A promising direction in the pathogenetically oriented treatment of myocardial contusion is the use of herbal preparations listed in the Chinese Pharmacopoeia. The efficacy of these compounds in models of ischemia, reperfusion injury, and heart failure has been experimentally validated, offering a foundation for their potential adaptation to the context of traumatic myocardial injury. The key classes of these agents are outlined below, categorized according to two principal therapeutic strategies:

The first therapeutic strategy focuses on counteracting hypoxia, oxidative stress, and inflammation:

1) *Salvia miltiorrhiza* (Dan Shen), a widely studied herbal remedy exerts multiple cardioprotective effects, primarily attributed to a unique class of bioactive compounds known as tanshinones. These compounds have been shown to inhibit the generation of ROS and suppress lipid peroxidation [68]. *S. miltiorrhiza* also improves microcirculatory flow by reducing thromboxane A_2 levels and inhibiting platelet aggregation [69]. Furthermore, it exhibits anti-inflammatory activity through downregulation of NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cell) signaling and subsequent decreases in pro-inflammatory cytokine levels, including tumor necrosis factor α and interleukin-6 [70]. In ischemia–reperfusion models, *S. miltiorrhiza* has been shown to reduce the extent of secondary myocardial injury [71].

2) *Astragalus membranaceus* (Huang Qi) contains a class of active compounds known as astragalosides, which contribute to its multifaceted

cardioprotective profile. First, astragalosides enhance endogenous antioxidant defenses by stimulating the synthesis of superoxide dismutase and glutathione [72]. Second, they exert anti-inflammatory effects by reducing levels of pro-inflammatory cytokines such as tumor necrosis factor α and interleukin-6 [70]. Additionally, *A. membranaceus* has been shown to improve myocardial contractile function in models of heart failure [73].

3) *Curcuma longa* (Jiang Huang) contains active compound curcumin, possessing cardioprotective properties, particularly in the context of ischemic and hypoxic myocardial injury [74]. Experimental studies have demonstrated its ability to suppress pathological processes such as myocardial hypertrophy and fibrotic remodeling. The active compound contributes to the normalization of ventricular structural and functional parameters by modulating key pathways involved in cardiac remodeling [74]. Moreover, curcumin has been shown to reduce pharmacologically induced cardiotoxicity and provide therapeutic benefits in models of cardiomyopathy associated with diabetes mellitus [74]. Additional mechanisms of curcumin's action include the correction of endothelial dysfunction, inhibition of foam cell formation, and suppression of excessive proliferation of vascular smooth muscle cells. Collectively, these effects broaden its potential applications in the prevention and treatment of various cardiovascular pathologies [74].

The second therapeutic strategy focuses on the optimization of endogenous adaptive mechanisms. Within this domain, the following agents show potential efficacy:

1) The effect of *Eleutherococcus senticosus* (Ci Wujia) has been demonstrated in models of ischemia-reperfusion syndrome [75]. Its established effects include the reduction of cortisol levels and modulation of the hypothalamic-pituitary-adrenal axis [76], thereby contributing to the rebalancing of activity between stress-activating and stress-limiting systems – an essential component in adaptive cardioprotection.

2) *Panax ginseng* (Ren Shen) is recognized as an effective cardioprotective agent, a property that correlates with its capacity to modulate tissue-level adaptive responses under conditions of ischemia–reperfusion injury. Its active constituents selectively inhibit key signaling pathways associated with programmed cardiomyocyte death, thereby preserving cellular homeostasis [77]. The cardioprotective effects of *P. ginseng* are mediated, in part, by the attenuation of oxidative stress through suppression of ROS-generating systems, as well as the indirect inhibition of pro-inflammatory cytokine synthesis. These actions collectively enhance anti-apoptotic signaling, thereby increasing myocardial resistance to ischemia–reperfusion damage [77]. Furthermore, studies have demonstrated that ginsenosides derived from *P. ginseng* regulate protein acetylation, contributing to mitochondrial function and offering additional protection to cardiomyocytes [78].

3) *Ginkgo biloba* (Yin Xing/ Yin Xing Ye) may enhance adaptive responses through several mechanisms. First, it exerts an anxiolytic-like effect, which can mitigate stress-induced physiological dysregulation [79]. Second, its well-characterized anticholinesterase activity, particularly that of the *G. biloba* standardized extract, prevents acetylcholine degradation, thereby enhancing cholinergic transmission and alleviating stress-related impairments [80]. Notably, *G. biloba* standardized extract is also recognized as a natural antagonist of platelet-activating factor. Clinical studies have demonstrated the efficacy of Ginkgo biloba extract in the treatment of various cardiovascular and cerebrovascular conditions, as well as in the management of reperfusion and reoxygenation syndromes [81].

4) *Schisandra chinensis* (Wu Wei Zi), known for its cardioprotective effects in ischemia-reperfusion syndrome [82], contains the active compound Schisandrin B. This compound exhibits antioxidant and anti-inflammatory properties, as well as inhibition of RAGE/NF-κB/MAPK (receptor for advanced glycation end products / nuclear factor kappa-light-chain-enhancer of activated B cells / mitogen-activated protein kinase) signaling and modulation of autophagy markers [83]. Research on the efficacy of *S. chinensis* in treating idiopathic pulmonary fibrosis suggests that its antifibrotic effects may be linked to the activation of autophagy through the AKT/mTOR (protein kinase B / mTOR) pathway [84].

A promising direction in therapeutic strategy involves the use of combination therapies. A combined approach allows for the effective exploitation of synergies between herbal compounds. For example, a combination of *P. ginseng* and *G. biloba* extracts has demonstrated significant neuroprotective effects, making it an effective treatment for various neurological disorders, including stroke [85]. The combined use of *P. ginseng* and *G. biloba* has shown neuroprotective properties, mediated by the inhibition of neuronal apoptosis. This effect was linked to improvements in neuronal structure and subcellular organelles, enhancement of cellular proliferative activity, and suppression of Caspase 3 overexpression in neurons [86].

Conclusion

Contemporary research into the pathogenesis of myocardial contusion has led to substantial progress in elucidating the fundamental mechanisms of myocardial injury following mechanical trauma. Despite these advances, the search for effective therapeutic strategies for this condition remains an urgent and unresolved task. The pathogenetic processes that unfold during the post-traumatic phase of myocardial contusion, such as bioenergetic hypoxia, disturbances in ionic homeostasis, inflammatory responses, and patterns of tissue adaptation, closely parallel the mechanisms observed in myocardial damage caused by ischemia and subsequent reperfusion. This conceptual parallel forms a theoretical basis for considering the use of established cardioprotective agents during the post-traumatic phase of myocardial contusion, particularly those with proven efficacy in the context of ischemic and reperfusion-related myocardial injury. However, translating these therapeutic strategies into clinical practice for patients with myocardial contusion requires thorough experimental validation. Of particular importance is the investigation of dose-dependent effects, the synergistic potential of combination therapy, and the long-term impact on the structural and functional integrity of the myocardium. A promising direction in the management of myocardial contusion is the development of comprehensive treatment regimens that integrate anti-inflammatory, metabolic, and antifibrotic components. In this context, particular attention should be given to traditional herbal remedies from the Chinese pharmacopoeia, which are distinguished by their polyvalent effects on key pathogenic pathways. Their ability to simultaneously modulate oxidative stress, energy metabolism, and cellular homeostasis offers new opportunities to overcome the limitations of monotherapy. Further research in this area may make a significant contribution to improving therapeutic strategies for myocardial contusion by enabling a more comprehensive correction of the complex disturbances characteristic of post-traumatic myocardial injury.

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