ACCSCIENCE PUBLISHING

Eurasian Journal of Medicine and Oncology

REVIEW ARTICLE

Mechanosensitive cardiac responses to repeated low-level blast exposure: Mechanisms and cardiovascular consequences

Vadim Mitrokhin[1], Anastasia Rodina[1], Stanislav Schileyko[1], Maria Morozova[1], Andre Kamkin[1], and Mitko Mladenov[1,2]*

[1]Department of Fundamental and Applied Physiology, Russian State Medical University, Moscow, Russia

[2]Institute of Biology, Faculty of Natural Sciences and Mathematics, Ss. Cyril and Methodius University, Skopje, North Macedonia

Abstract

Introduction: Repeated low-level blast (rLLB) exposures, commonly encountered by military personnel during training and by industrial workers, pose an underrecognized risk for cardiovascular pathology. Unlike high-intensity blasts, which result in trauma, rLLB may induce cumulative subclinical myocardial injuries that gradually alter cardiac structure and function. **Objective:** This review combines available information on the biophysical properties of blast waves, the mechanics of their transmission to the heart, and mechanosensitive ion channels, which emerge as central mediators connecting mechanical inputs to electrophysiological and structural changes in the heart. **Results:** Channels such as transient receptor potential canonical 6, transient receptor potential melastatin 7, Piezo1, and two-pore domain potassium families are involved in ion fluxes and downstream signaling cascades that acutely trigger arrhythmias and myocardial stunning and chronically drive fibrosis, maladaptive remodeling, and diastolic dysfunction, leading to heart failure with preserved ejection fraction. rLLB affects cardiomyocytes and titin filaments, damages costameres, and disrupts mechano-electrical coupling, ultimately leading to chronic pathological outcomes. Furthermore, there are vascular effects driven by the activation of endothelial mechanosensors, microvascular rarefaction, and impaired vasoregulation. Potential therapeutic approaches currently being explored include counteracting mechanosensitive ion channel dysregulation, activating antifibrotic and antioxidant pathways, and modulating downstream signaling cascades, as well as developing preconditioning strategies aimed at strengthening mechanosensory resilience. However, certain research gaps persist, such as the lack of standardization of rLLB models, longitudinal human studies, and reliable early detection biomarkers. **Conclusion:** Addressing these knowledge gaps demands a multidisciplinary, concerted research effort combining blast biophysics, cardiac mechanobiology, *in vivo* imaging, and clinical science to mitigate the cardiovascular effects of rLLB exposures and inform precision diagnostics and treatments.

Keywords: Repeated low-level blast exposure; Mechanosensitive ion channels; Mechanosensitivity; Heart; Cardiovascular injuries

***Corresponding author:**
Mitko Mladenov
(mitkom@pmf.ukim.mk)

Citation: Mitrokhin V, Rodina A, Schileyko S, Morozova M, Kamkin A, Mladenov M. Mechanosensitive cardiac responses to repeated low-level blast exposure: Mechanisms and cardiovascular consequences. *Eurasian J Med Oncol.* doi: 10.36922/EJMO025430444

Received: October 22, 2025

Revised: January 26, 2026

Accepted: February 3, 2026

Published online: November 16, 2026

Copyright: © 2026 Author(s). This is an Open-Access article distributed under the terms of the Creative Commons Attribution License, permitting distribution, and reproduction in any medium, provided the original work is properly cited.

Publisher's Note: AccScience Publishing remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

1. Introduction

Explosions have emerged as a common threat to both military and civilian populations. Soldiers in active combat and bomb disposal unit members on explosive breaching missions encounter a range of blast wave intensities, from potentially fatal detonations generating shock waves with very high peak pressures to exposures of lower amplitude during training scenarios or day-to-day work activities.[1-3] High-intensity blasts, such as acute explosive events, can cause severe polytrauma, including pulmonary barotrauma and traumatic brain injury; however, an increasing body of evidence suggests that repeated lower-level blast exposures may also be dangerous, particularly by affecting the cardiovascular system (presenting a potential "silent" progressive risk).[4-6]

Research on blast injury has focused primarily on the brain and lung regions that can be acutely injured by overpressure, since they manifest structural damage immediately following exposure.[7,8] In contrast, the impact of blast waves on the heart has been relatively underexamined, which is paradoxical since the myocardium is in direct contact with mechanical forces propagated through the thoracic cage.[8,9] Recent animal experiments have indicated that overpressure from blasts may produce shock waves through the chest wall, leading to myocardial deformation and shear stress in cardiac tissue. These studies suggest that even low-level exposure may be associated with myocardial injury, arrhythmias, and impaired left ventricular (LV) function in animal models, demonstrating the heart's sensitivity to repetitive mechanical strain.[10-12] These processes may manifest as adaptations that remain clinically silent, potentially not emerging for months or years before manifesting as diastolic dysfunction, arrhythmias, or maladaptive ventricular remodeling.[13]

The mechanosensitivity of the heart has been recognized as a key element in these pathological processes. The myocardium operates in an active mechanical environment, adjusting to both preload and afterload as well as wall stress, mainly via volume and compliance regulation.[14] At the cellular level, mechanosensitive ion channels (MSCs) transduce mechanical force into spatially restricted ion fluxes that activate defined intracellular signaling modules, including Ca^{2+}/calcineurin/nuclear factor of activated T-cells (NFAT), Hippo–Yes-associated protein (YAP)/transcriptional coactivator with PDZ-binding motif (TAZ), calcium/calmodulin-dependent protein kinase II (CaMKII), and redox-dependent pathways. These MSCs belong to several channel families, such as transient receptor potential (TRP) canonical (TRPC) channels, Piezo1/2 channels, two-pore domain potassium (K2P) channels, including TREK-1 and TRAAK, and TRP melastatin (TRPM) channels, such as TRPM4 and TRPM7.[15-18] Physiologically, such channels are involved in maintaining electrical homeostasis,[19,20] which drives systemic adaptive responses to mechanical stress.[21] However, upon deleterious stimuli, such as blast waves, MSCs can become dysfunctional and result in abnormal levels of Ca^{2+} influx and depolarizing currents through profibrotic or hypertrophic mechanisms.[22-24] These observations implicate channels such as TRPC6 and Piezo1 in fibrotic remodeling during chronic stress,[25] whereas modified K2P channel function may offer a compensatory mechanism to mitigate increased depolarization.[26,27]

Despite all the presented findings, the particular effects of multiple low-level blast exposures on cardiac function remain elusive. While the effects of a single high-intensity blast on acute cardiac injury are well-documented, the long-term consequences of repetitive low-level blast (rLLB) exposures on cardiomyocyte electrophysiology, ion channel expression, and structural remodeling are not well understood.[28] This evidence gap is especially relevant in light of the hypothesis that accumulated subclinical micro-injuries may promote arrhythmogenesis and diastolic dysfunction, leading to heart failure with preserved ejection fraction (HFpEF) following blast injury.[29,30]

Hence, this review aims to: (i) summarize existing knowledge on blast-induced cardiac injury (BICI); (ii) discuss and classify MSCs as potential transducers of blast effects on the heart; and (iii) evaluate whether rLLB exposure could have long-term cardiovascular implications. We examine the intersection of blast biophysics, cardiac mechanobiology, and ion channel physiology to establish a mechanistic basis for blast-induced cardiac dysfunction and identify potential targets for intervention.

This work is organized around a conceptual model ranging from (i) the biophysical nature of low-level blast exposure, through to the (ii) cellular and molecular mechanisms of mechanotransduction, and ultimately to the potential (iii) cardiovascular implications and translational relevance. However, it is important to note that a significant portion of the mechanistic data described in this article is derived from animal models or *in vitro* studies. Despite its biological relevance for human cardiovascular risk, the available *in vivo* clinical data from exposed humans are insufficient. Therefore, mechanistic interpretations throughout the study should be considered hypothesis-generating rather than definitive, and we note that several major gaps remain in the available human data.

To facilitate discussion of this complex topic, an integrative schematic outlining the proposed cascade from repeated low-level blast exposure to mechanotransduction,

ion channel activation, and subsequent cardiac and vascular pathology is presented in Figure 1.

2. Methods

This review was conducted in accordance with established methodological guidelines regarding transparent reporting of literature-based reviews, informed by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement where applicable.

2.1. Search strategy

A literature search was conducted using electronic databases, including PubMed/MEDLINE, Scopus, and Web of Science Core Collection. The last search was performed in March 2025. To avoid missing relevant studies, we also manually screened the reference lists of key articles and relevant reviews.

The search strategy used both controlled vocabulary terms (Medical Subject Headings) and free text words, including "blast exposure," "cardiac," and "mechanotransduction." The search terms were connected using Boolean operators and included the following key terms: "blast injury (low-level)" OR "blast overpressure" OR "repeated blast exposure" AND "heart" OR "cardiac" OR "cardiomyocyte" OR "vascular" OR "endothelium" AND "mechanosensitive ion channels" OR "mechanotransduction" OR "stretch-activated channels" OR "Piezo" OR "TRP channel" OR "mechano-electric coupling" AND "fibrosis" OR "remodeling" OR "arrhythmia" OR "heart failure" OR "HFpEF."

The search covered the period from January 1990

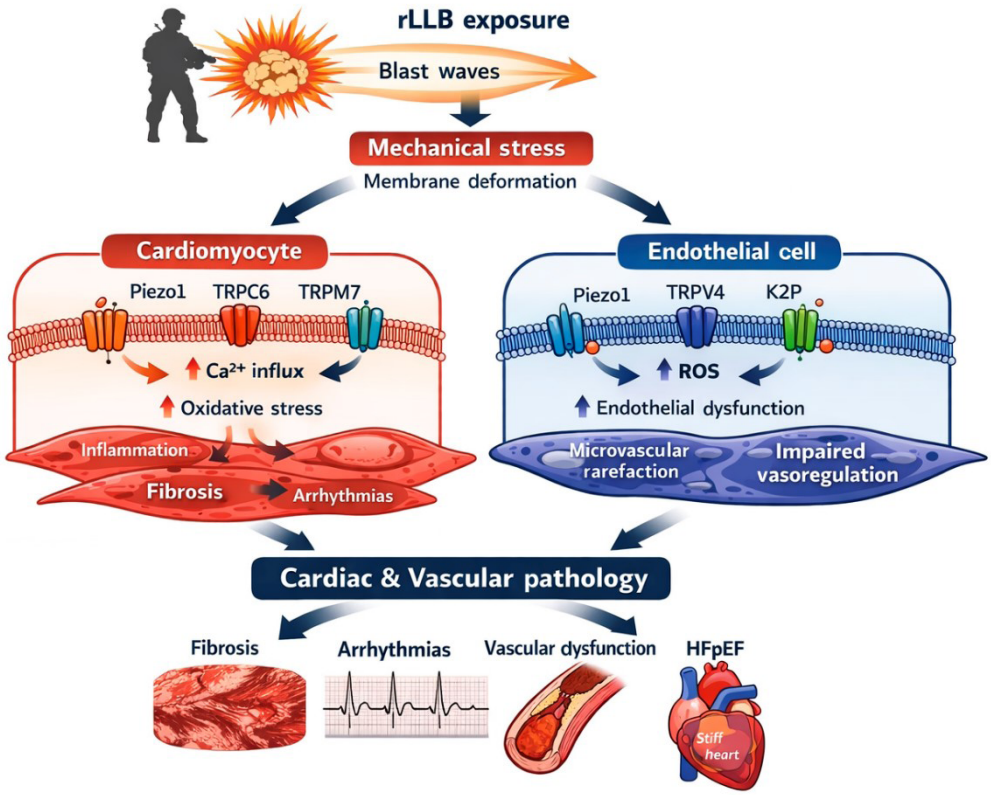


Figure 1. Integrative schematic of the proposed mechanistic cascade linking rLLB exposure to cardiac and vascular pathology. rLLB exposure generates blast waves that impose mechanical stress on cardiovascular tissues, resulting in membrane deformation and activation of mechanosensitive signaling pathways. In cardiomyocytes, activation of mechanosensitive ion channels (e.g., Piezo1, TRPC6, TRPM7) promotes Ca^{2+} influx, oxidative stress, and inflammatory signaling, contributing to maladaptive remodeling, fibrosis, and arrhythmogenesis. In endothelial cells, activation of channels such as Piezo1, TRPV4, and K2P channels induces ROS generation, endothelial dysfunction, impaired vasoregulation, and microvascular rarefaction. These convergent cellular mechanisms drive progressive cardiac and vascular pathology, ultimately manifesting as fibrosis, arrhythmias, vascular dysfunction, and HFpEF-like phenotypes. Figure is an original figure created using Adobe Illustrator.
Abbreviations: HFpEF: Heart failure with preserved ejection fraction; K2P: Two-pore domain potassium; rLLB: Repeated low-level blast; ROS: Reactive oxygen species; TRPC6: Transient receptor potential canonical 6; TRPM7: Transient receptor potential melastatin 7; TRPV4: Transient receptor potential vanilloid 4.

to March 2025 and incorporated both fundamental mechanobiology work and current advances in blast-related cardiovascular pathophysiology.

2.2. Eligibility criteria

The inclusion and exclusion criteria were established prior to the selection of articles. The inclusion criteria are as follows:

(i) Primary experimental research (e.g., *in vitro*, *ex vivo*, and *in vivo*) or clinical studies on the cardiovascular effects of blast exposure.
(ii) Research focusing on mechanotransduction, MSCs, or biomechanical signaling in cardiac or vascular tissue.
(iii) Research into molecular, cellular, electrophysiological, structural, and/or functional aspects of cardiac injury or remodeling.
(iv) Review papers with clear conceptual or translational relevance.
(v) Peer-reviewed articles published in the English language.

Exclusion criteria include:

(i) Studies of cardiovascular tissue or function unrelated to blast exposure.
(ii) Studies consisting purely of physical (e.g., ballistic, computer) models without a biological context.
(iii) Conference abstracts without available full text.
(iv) Editorials, opinion pieces, or perspectives lacking original data (unless providing critical conceptual context).

2.3. Study selection and data synthesis

Relevant articles for inclusion were identified after screening titles and abstracts, followed by a full-text review of potentially eligible studies. Studies were qualitatively reviewed and synthesized using a narrative integrative approach, given the heterogeneity of experimental models, methods, and outcomes in the field.

Rather than conducting a quantitative meta-analysis, evidence was evaluated critically to identify common mechanistic themes, areas of uncertainty, and translational considerations. This approach was chosen to provide a synthesis of molecular, cellular, physiological, and clinical findings to form a coherent conceptual model.

3. Biophysics of blast exposure and cardiac loading

3.1. Blast wave characteristics

The biophysical nature of blast exposure has been thoroughly defined in traumatic injury studies, and the Friedlander waveform is often employed as the idealized free-field blast model[31] (Table 1). This waveform consists of an initial near-instantaneous pressure rise within a few microseconds, followed by an exponential decay that may last from tens to several hundred microseconds and, in some cases, the development of a rarefaction phase associated with reflected negative pressure.[32] Low-level blasts have durations typically in the range of 1–5 milliseconds, depending on the explosive charge and environmental conditions.[33] Blast waves >5–10 bar in magnitude are typically lethal, leading to catastrophic tissue rupture;[33] low-level blast exposures (<1–2 bar) are more commonly encountered in military training explosions, law enforcement breaching operations, and industrial accidents (e.g., mine- and tunnel-clearing)[34,35] (Table 1). Although sublethal, such low-level events may still cause cumulative micro-lesions in solid internal organs, particularly the heart.[36]

3.2. Energy transmission to the heart

Although well-established acute cardiac responses to individual high-intensity blast exposures exist—including bradycardia, hypotension, and arrhythmias in animal models[37]—a significant discrepancy is the lack of published studies that have specifically addressed the presence or absence of histologic or ultrastructural myocardial injury following rLLB exposure (Table 1). Most data come from combined-injury models, including blast with hemorrhagic shock or burn-blast models, which have shown edema, degeneration, and ultrastructural damage to the myocardium.[37,38]

Conversely, rLLB in rodent and swine models has provided compelling evidence of ultrastructural vascular injury and endothelial glycocalyx disruption both in the brain and in the systemic circulation.[39,40] In addition, in exposed human subjects, these injuries were coupled with hematologic biomarker alterations consistent with endothelial stress.[29] These findings provide biological plausibility that rLLB loading of the chest could result in cumulative micro-injury to the myocardium, thereby enhancing susceptibility to arrhythmias and fibrotic remodeling (Table 1). However, direct evidence of rLLB-induced myocardial injury remains a significant gap that warrants investigation in future studies.

3.3. Mechanical effects on cardiomyocytes

At the cellular level, sudden mechanical stretch of the myocardial wall rapidly deforms cardiomyocytes (Table 1). This deformation includes sarcolemmal stretching, Z-line displacement, and elongation of sarcomeric titin molecules.[41-43] Titin, the giant sarcomeric protein, functions as a molecular spring and is a key determinant of passive

Table 1. Multiscale mechanistic framework linking repeated low-level blast exposure to cardiac injury

Biological level	Blast-related input	Immediate biophysical effect	Cellular/molecular consequences	Predicted functional outcome	Strength of evidence
Physical environment	Repeated low-level blast overpressure (<1–2 bar, 1–5 ms duration)	Rapid pressure transients, thoracic wall acceleration, tissue shear stress	-	Repetitive mechanical loading of the heart, even without macroscopic trauma	Well established (biophysics)
Thorax–heart coupling	Transmission of blast energy through the chest wall	Myocardial compression, deformation, and pressure gradients within the ventricular wall	Local strain heterogeneity across the endocardium–epicardium	Regional vulnerability to electrical and mechanical dysfunction	Moderate (animal models)
Myocardial tissue architecture	Repetitive micro-strain	Sarcomere stretch, titin elongation, and extracellular matrix perturbation	Altered titin stiffness, activation of stretch-sensitive signaling pathways	Increased passive stiffness, predisposition to diastolic dysfunction	Strong (mechanobiology literature)
Cardiomyocyte ultrastructure	Sub-injurious cyclic deformation	Costamere disruption, cytoskeletal remodeling	Altered integrin signaling, focal adhesion remodeling, and altered channel anchoring	Progressive mechano-sensitization of cardiomyocytes	Moderate–strong (experimental models)
Ion channel mechanotransduction	Membrane tension and cytoskeletal force transfer	Gating of mechanosensitive channels (TRPC6, TRPM7, Piezo1, TRPV2, K2P)	Ca2+ influx, depolarizing currents, activation of CaMKII, calcineurin–NFAT, YAP/TAZ pathways	Electrical instability, profibrotic gene activation, altered excitation–contraction coupling	Strong (cardiac mechanobiology)
Acute electrophysiology	Transient channel hyperactivation	Mechano-electric feedback	Premature depolarizations, conduction slowing, and altered repolarization	Increased arrhythmia susceptibility after exposure	Moderate (animal blast studies)
Chronic remodeling	Persistent low-level signaling	Sustained Ca^{2+} dysregulation, oxidative stress, and fibroblast activation	Collagen deposition, titin hypophosphorylation, ventricular stiffening	Progressive diastolic dysfunction, HFpEF-like phenotype	Mechanistically strong, clinically inferential
Vascular compartment	Endothelial exposure to blast-induced shear and pressure	Endothelial deformation	Piezo1/TRPV4 activation, nitric oxide imbalance, inflammation, microvascular rarefaction	Impaired perfusion reserve, contribution to fibrosis and stiffness	Moderate (animal + mechanistic)
Clinical translation (hypothesis)	Cumulative subclinical injury	No overt early symptoms	Subclinical fibrosis, silent arrhythmias, impaired strain	Long-term risk of HFpEF, atrial cardiomyopathy, and exercise intolerance	

Abbreviations: CamKII: Calcium/calmodulin-dependent protein kinase II; HFpEF: Heart failure with preserved ejection fraction; K2P: Two-pore domain potassium; NFAT: Nuclear factor of activated T-cells; rLLB: Repeated low-level blast; ROS: Reactive oxygen species; TAZ: Transcriptional coactivator with PDZ-binding motif; TRPC6: Transient receptor potential canonical 6; TRPM7: Transient receptor potential melastatin 7; TRPV4: Transient receptor potential vanilloid 4; YAP: Yes-associated protein.

stiffness in cardiomyocytes.[44] Sustained alterations in titin-based passive stiffness can promote profibrotic signaling and a pathological phenotype switch by enhancing myocyte stiffness and exacerbating mechanosensitive signaling mediated through stretch-activated channels (SACs) (Table 1).[45,46]

Sub-injurious micro-strain events, when repeated, induce cytoskeletal remodeling and disruption of costameres (Table 1)—the integrin-based complexes that anchor sarcomeres to the extracellular matrix (ECM).[47] Over time, such chronic structural stress on the cytoskeleton may sensitize MSCs by shifting gating thresholds and augmenting mechano-electrical coupling.[19] Dysregulated mechanotransduction, in turn, provides a plausible substrate for arrhythmogenesis, myocardial

fibrosis, and maladaptive ventricular remodeling, thereby linking acute mechanical stress to long-term cardiac pathophysiology (Table 1).[18,48]

In summary, blast waves interact with cardiac tissue through a cascade of events—from thoracic wall loading to myocardial deformation and subcellular strain. The nature of this mechanical environment critically shapes mechanosensitive signaling, with MSCs serving as central mediators of the myocardial response to blast exposure.

3.4. Molecular mechanisms of mechanosensitive ion channel activation and downstream signaling

When cardiomyocytes are deformed, this alters the lipid bilayer and cytoskeletal structure of the cells, which in turn modulates the activation of MSCs through changes in membrane tension and coupling to the cytoskeleton. Such deformation can induce conformational unfolding and channel opening, allowing Ca^{2+} influx through channels such as TRPC6, whereas mechanical stimuli can directly activate Piezo1. Stretch-activated phospholipase C signaling links Ca^{2+} influx to increased intracellular diacylglycerol levels.

The local Ca^{2+} entry through MSCs generates localized Ca^{2+} microdomains, which in turn activate downstream effectors such as calmodulin, calcineurin, and CaMKII. Activation of calcineurin facilitates the translocation of NFAT transcription factors to the nucleus, resulting in upregulation of profibrotic genes, including collagen types I/III and connective tissue growth factor. Additionally, concomitant Piezo1-dependent YAP/TAZ nuclear translocation, via suppression of Hippo pathway kinase activity, further augments fibroblast activation and ECM accumulation.

Furthermore, MSC activation exhibits crosstalk with redox signaling pathways. Mechanical stretch stimulates mitochondrial reactive oxygen species production via stretch-induced reactive oxygen species signaling, which then activates redox-sensitive channels such as TRPM7 and TRP vanilloid (TRPV)-2 to establish a positive feedback loop that enhances Ca^{2+} influx and promotes maladaptive remodeling. The sustained activation of these pathways leads to cytoskeletal remodeling, titin hypophosphorylation, impaired relaxation, and increased structural stiffness of the myocardium. Collectively, the molecular cascades outlined here serve as a mechanistic link between acute mechanical stress and both acute cardiac remodeling and chronic cardiomyopathy.

4. Cardiovascular consequences of repeated low-level blast exposure

Repeated low-level blast exposure, which is frequently overlooked in the clinical setting, may potentially impact the cardiovascular system, based primarily on preclinical evidence (Figure 2). While acute high-intensity blasts have the potential to cause structural injury, rLLB exposures (<1–2 bar) can induce subtle myocardial dysfunction that accumulates over time. These effects have been proposed to occur in distinct temporal phases, starting with micro-injury, followed by intermediate maladaptive responses and chronic remodeling, including atrial phenotypical changes (Figure 2), that collectively influence the blast-associated evolution of cardiovascular disease.[11,35]

4.1. Immediate (acute) effects

The typical features of BICI are electrophysiological derangements and temporary mechanical myocardial dysfunction, in combination with altered serum biomarkers of myocardial injury. Cation-nonselective SACs (SAC_{NS}), such as TRPC1 and TRPC6, further exacerbate acute events by conducting depolarizing inward currents that interfere with normal action potential propagation and promote ventricular arrhythmias (Figure 1).[49,50]

In animal models of blast exposure, disrupted mechano-electrical coupling during and following exposure has the potential to produce arrhythmias, as evidenced by premature ventricular contractions,[10] atrioventricular conduction delays (first-degree atrioventricular block and PR prolongation),[51] and, in extreme cases, ventricular fibrillation.[10,51]

Experimental work has also demonstrated reversible myocardial stunning following blast, which is consistent with transient LV dysfunction. This represents transient abnormalities of excitation–contraction coupling due to acute Ca^{2+} overload, oxidative stress, and reversible sarcomeric alterations.[52,53] These changes may lead to a temporary decrease in LV ejection fraction and deformation profiles, which generally recover within a few days to a week, but may render the myocardium susceptible to further stretch-induced endocardial and epicardial responses.[54]

Elevated cardiac troponin (cTn) levels are a sensitive indicator of subclinical myocardial injury due to blast exposure. In two independent animal studies—in rodents and swine—serum cardiac troponins cTnT and cTnI were found to be elevated after rLLB exposure, even in the absence of overt myocardial rupture (Figure 2).[55,56] These findings indicate that membrane disruption—possibly facilitated by TRPV2 channel activation—occurs and consequently allows cytosolic troponins to be released into the coronary circulation, thereby acting as an early biomarker for myocardial micro-injury.[57]

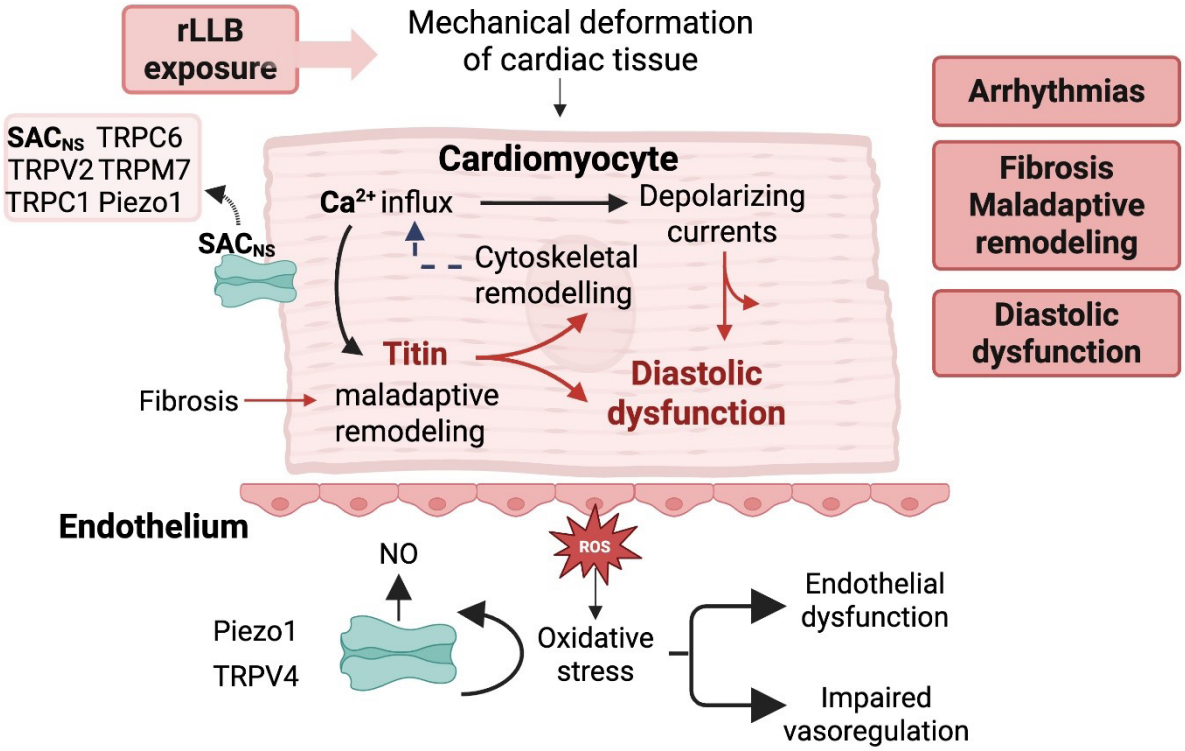


Figure 2. Mechanosensitive channel activation generates spatially restricted Ca^{2+} microdomains, which activate calcineurin–NFAT signaling, YAP/TAZ nuclear translocation, CaMKII activation, and redox-sensitive X-ROS pathways. These events link mechanical deformation to transcriptional reprogramming, fibrosis, electrophysiological instability, and maladaptive remodeling. Created in BioRender. M, V. (2026) https://BioRender.com/2x5zinn. Abbreviations: CamKII: Calcium/calmodulin-dependent protein kinase II; NFAT: Nuclear factor of activated T-cells; NO: Nitric oxide; rLLB: Repeated low-level blast; ROS: Reactive oxygen species; SACNS: Cation-nonselective stretch-activated channel; TAZ: Transcriptional coactivator with PDZ-binding motif; TRPC: Transient receptor potential canonical; TRPM7: Transient receptor potential melastatin; TRPV4: Transient receptor potential vanilloid; YAP: Yes-associated protein; X-ROS: Stretch-induced reactive oxygen species. Created in BioRender. M, V. (2026) https://BioRender.com/2x5zinn.

4.2. Long-term (chronic) effects

An emerging body of evidence indicates that the chronic stage of cardiac pathology resulting from rLLB is characterized by progressive fibrosis, maladaptive ventricular remodeling, and diastolic dysfunction, fueled by persistent alterations in mechanosensitive signaling cascades and dysfunctional repair (Figure 2).

Fibrosis and structural remodeling represent the cornerstone of chronic injury. Prolonged TRPC6-dependent Ca^{2+} influx induces calcineurin/NFAT pathway activation, whereas Piezo1-induced YAP/TAZ nuclear translocation via Hippo pathway inactivation, together drive fibroblast activation and ECM deposition.[22,25] The resulting increase in myocardial stiffness, aberrant collagen cross-linking, and chamber wall dilatation is similar to the pathological remodeling observed in pressure overload hypertrophy.[50] A significant consequence of such remodeling is the loss of diastolic reserve. Increased ECM deposition and altered expression of α-myosin heavy chain (MYH6), together with titin hypophosphorylation, result in decreased myocardial compliance with consequent impaired myocardial relaxation and increased LV filling pressures.[45,46] Crucially, these diastolic abnormalities are frequently subclinical and can only be detected with sophisticated imaging modalities or invasive hemodynamics; however, they may form the basis for the gradual onset of HFpEF (Figure 2).[58]

One theoretical long-term consequence of rLLB exposure is a possible contribution to HFpEF development. However, this hypothesis is currently supported mainly by mechanistic overlap with known HFpEF pathways rather than by direct clinical evidence in blast-exposed populations. This hypothesis is further supported by the observation that blast-mediated microvascular rarefaction, combined with sustained systemic inflammation and profibrotic signaling, is consistent with current models of HFpEF etiology.[30,59]

4.3. Vascular consequences

Blast forces not only cause myocardial damage but also disrupt coronary vasomotion and lead to endothelial dysfunction and microvascular impairment. Under physiological conditions, endothelial mechanosensors (e.g., Piezo1 and TRPV4) mediate nitric oxide release and vasorelaxant signaling in response to shear- and pressure-mediated stimuli that underpin flow-dependent vascular responses (Figure 1).[60,61]

Sustained dysregulation of these channels leads to endothelial inflammation, oxidative stress, and arterial stiffness, mechanisms that contribute to vascular dysfunction and systemic hypertension.[62,63] Clinical findings also indicate that coronary microcirculatory dysfunction may link blast exposure to ischemia-like symptoms. Impairment of normal endothelium-dependent vasodilation and microvascular rarefaction further diminishes myocardial perfusion reserve, especially during hyperemic conditions, resulting in chronic ischemia and ultimately progressive interstitial fibrosis (Figure 2).[59,64,65]

5. Potential therapeutic strategies

Signaling pathway-focused therapeutic strategies targeting maladaptive MSC-mediated remodeling represent conceptual opportunities emerging from preclinical studies, rather than established treatments. At present, all such approaches remain experimental, and no therapies have been validated for clinical use in rLLB-related cardiovascular injury (Table 2). There is a growing body of evidence supporting the involvement of MSCs in acute electrophysiological changes and long-term structural alterations following blast injury. Possible interventions could include modulation of channel function, inhibition of profibrotic signaling, enhancement of myocardial resistance to injury, or interruption of downstream maladaptive pathways, with the aim of preventing the transition into irreversible chronic failure (Table 2).

5.1. Mechanosensitive ion channel modulation

One theoretically promising approach, supported exclusively by *in vitro* **a**nd animal studies, is direct modulation of MSCs as an experimental therapeutic concept. Small-molecule inhibitors, such as the spider venom peptide GsMTx4, that block relatively specific cationic SACs and other SAC_{NS} channel classes have been identified (Table 2).[66] In preclinical studies, GsMTx4 attenuates stretch-induced depolarization, Ca^{2+} overload, and arrhythmogenesis.[67,68] Derivatives of streptomycin have also been found to reduce electrical instability, at least in part by blocking SAC_{NS} and Ca^{2+} entry, which limits mechanically driven ionic currents.[69]

Inhibitors of TRP channels represent another therapeutic class. Inhibition of aberrant Ca^{2+} flux through TRPC channels has been demonstrated to reduce calcineurin–NFAT-mediated hypertrophy and reverse deleterious remodeling in pressure overload and neuroendocrine-stimulated animal models.[22,50] Similarly, TRPV channel antagonists may attenuate depletion of the intracellular Ca^{2+} stores and cell death signaling resulting from sarcolemmal injury-related activation of TRPV2, thereby decreasing Ca^{2+}-induced toxicity (Table 2).[70]

Piezo1 modulators, while in early experimental development, currently represent mechanistic research tools rather than clinically viable therapies, and their translational applicability in rLLB remains highly speculative. Recently, small molecules that rapidly inhibit Piezo1 activity have been reported to reduce shear stress-induced endothelial activation and mitigate proinflammatory signaling and maladaptive fibroblast responses (Table 2).[62,71] Although such agents provide valuable mechanistic insight, their systemic use raises substantial safety concerns as Piezo1 and TRP channels are widely expressed in the cardiovascular system, nervous system, kidney, and immune cells. Therefore, any clinical application would carry a significant risk of off-target effects, including vascular dysregulation, altered baroreflex function, and impaired physiological mechanoadaptation.

5.1.1. Mechanosensitive ion channel-related antifibrotic and antioxidant strategies

In addition to targeting ion channel activity, antifibrotic measures are expected to counteract the TRPC6–Piezo1–YAP/TAZ pathway and reduce ECM deposition and myocardial stiffening. Renin–angiotensin–aldosterone system inhibitors, such as angiotensin-converting enzyme inhibitors and mineralocorticoid receptor antagonists, are known to be potent modulators of antifibrotic pathways and have been consistently shown to ameliorate myocardial remodeling following a range of cardiac insults (Table 2).[72,73] To date, however, no studies have evaluated whether these agents modify outcomes specifically in blast-related myocardial injury, and any extrapolation to rLLB must therefore be considered theoretical.

Nuclear factor erythroid 2-related factor 2 has been proposed as a potential therapeutic target for antioxidants. Bardoxolone methyl and other agents upregulate antioxidant gene expression, downregulate proinflammatory signaling, and create a favorable myocardial environment for mitigating oxidative stress.[74] Notably, oxidative stress directly affects the properties of MSCs by sensitizing TRP and Piezo channels, thereby enhancing maladaptive signaling cascades (Table 2).[75]

Table 2. Mechanistically informed therapeutic and preventive strategies for repeated low-level blast–induced cardiac injury

Intervention category	Primary target level	Mechanistic rationale	Expected benefit	Key limitations/ risks	Translational readiness	Future research priority
Direct MSC inhibition	MSCs (e.g., TRPC6, TRPV2, Piezo1, SAC_{NS})	Limits pathological Ca^{2+} influx and depolarizing currents during excessive mechanical stimulation	Reduction of acute arrhythmogenesis and downstream profibrotic signaling	High off-target risk; channels essential in vasculature, kidney, central nervous system; poor tissue specificity	Preclinical only	Develop cardiac-targeted delivery systems (e.g., nanoparticle or antibody-guided blockers) and test in rLLB-specific models
TRP channel modulation	TRPC6/TRPM7-mediated Ca^{2+} signaling	Reduces calcineurin–NFAT-driven hypertrophy and fibroblast activation	Attenuation of chronic remodeling and fibrosis	TRP channels involved in physiological adaptation; risk of impaired mechanoadaptation	Preclinical only	Dose–response studies under physiological vs. pathological mechanical stress
Piezo1 pathway modulation	Piezo1–YAP/TAZ axis (cardiomyocytes + fibroblasts + endothelium)	Reduces mechanotransduction-driven fibroblast activation and ECM deposition	Limits myocardial stiffening and HFpEF-like progression	Piezo1 is required for vascular homeostasis; systemic blockade is likely unsafe	Preliminary experimental	Cell-specific Piezo1 manipulation (e.g., fibroblast-selective knockout models)
Antifibrotic pharmacology	TGF-β signaling, RAAS axis, fibroblast activation	Suppresses ECM deposition downstream of mechanotransduction	Limits progression toward diastolic dysfunction	Hypotension, renal effects; not tested in blast-specific models	Clinically available (indirect evidence)	Randomized intervention in rLLB animal models with fibrosis endpoints
Antioxidant/ redox modulation	ROS-sensitive MSCs (TRPM7, TRPV2), mitochondrial signaling	Breaks X-ROS amplification loop that sensitizes mechanosensitive channels	Reduces channel hyperactivation and remodeling	Nrf2 overactivation carries cardiovascular risk; context-dependent	Preclinical–early clinical	Identify redox-sensitive biomarkers predictive of therapeutic response
Targeting downstream signaling	Calcineurin–NFAT, MAPK, YAP/TAZ	Blocks pathological transcriptional programs driving fibrosis/hypertrophy	Prevents chronic remodeling despite persistent mechanical stress	Interferes with repair and regeneration; systemic toxicity possible	Preclinical	Develop transient or inducible inhibition protocols instead of chronic blockade
Exercise-based preconditioning	System-level mechanoadaptation	Improves adaptive mechanotransduction, antioxidant capacity, vascular compliance	Increased resilience to mechanical insult; cardioprotection	Inter-individual variability; compliance challenges in high-risk occupations	Clinically feasible	Controlled trials in military trainees with mechanobiology biomarkers
Mechanical conditioning protocols	MSC sensitivity calibration	Low-level cyclic mechanical stimulation may normalize channel-gating thresholds	Reduced susceptibility to pathological hyperactivation	Dose-response unknown; may exacerbate injury if improperly applied	Conceptual/ experimental	Define a safe amplitude/frequency window in animal models
Multimodal strategy	Channels + fibrosis + oxidative stress	Addresses both acute electrophysiology and chronic remodeling	Synergistic protection across disease phases	Complex trial design; polypharmacy risks	Future direction	Sequential therapy studies (acute channel modulation + chronic antifibrotic phase)

Abbreviations: ECM: Extracellular matrix; HFpEF: Heart failure with preserved ejection fraction; MAPK: Mitogen-activated protein kinase; MSC: Mechanosensitive ion channel; NFAT: Nuclear factor of activated T-cells; Nrf2: Nuclear factor erythroid 2-related factor 2; rLLB: Repeated low-level blast; RAAS: Renin–angiotensin–aldosterone system; ROS: Reactive oxygen species; SACNS: Cation-nonselective stretch-activated channel; TAZ: Transcriptional coactivator with PDZ-binding motif; TGF-β: Transforming growth factor β; TRP: Transient receptor potential; TRPC: Transient receptor potential canonical; TRPM: Transient receptor potential melastatin; TRPV: Transient receptor potential vanilloid; YAP: Yes-associated protein; X-ROS: Stretch-induced reactive oxygen species.

Critically, therapeutic approaches using antifibrotic and antioxidant treatments have important limitations. Long-term renin–angiotensin–aldosterone system blockade is accompanied by hypotension, electrolyte abnormalities, renal insufficiency, and poor tolerability in some patient groups. Nuclear factor erythroid 2-related factor 2 activators, such as bardoxolone methyl, have been associated with safety concerns in clinical trials, including an increased risk of cardiovascular events in high-risk individuals. Even biologically plausible therapies can be risky and should be carefully evaluated before being used in blast-exposed individuals.

5.2. Preconditioning approaches

Regulated physical training involving mechanical stimuli could be beneficial for cardioprotection against blast-induced injury. For example, chronic exercise training improves adaptive mechanotransduction pathways, increases both myocardial and vascular antioxidant defenses, and promotes vascular and ventricular compliance.[76,77] Similarly, training protocols that utilize whole-body vibration, which provides low-amplitude cyclic mechanical stimulation, may positively influence MSC signaling and reduce channel susceptibility to hyperactivation, thereby reducing vulnerability to acute myocardial insults (Table 2).[78]

However, implementing structured preconditioning programs in real-world military or occupational settings presents significant logistical, ethical, and compliance challenges, particularly given variability in exposure risk, individual fitness level, and comorbidities.

5.3. Targeting downstream pathways

In addition to direct channel modulation, several downstream signaling cascades have emerged as potential targets for therapeutic intervention. Although YAP/TAZ inhibitors could theoretically ameliorate fibroblast activation,[79,80] these pathways are also essential for tissue repair, regeneration, and cellular survival, raising concern that chronic inhibition could impair physiological healing responses and result in unintended adverse effects (Table 2).

Similarly, targeting mitogen-activated protein kinase (MAPK) signaling using extracellular signal-regulated kinase 1/2 and p38 inhibitors may represent a potential strategy to prevent pro-hypertrophic transcription and fibrotic gene expression driving adverse remodeling following sustained MSC stimulation (Table 2).[81]

Furthermore, preclinical studies suggest potential benefits of suppressing the calcineurin–NFAT axis. Calcineurin inhibitors, including cyclosporine and tacrolimus (FK506) analogs, have been shown to suppress pathological hypertrophy and abnormal heart geometry in mouse models of dilated cardiomyopathy (Table 2).[82] However, toxicity limits the long-term use of broad immunosuppressive agents. Accordingly, next-generation drugs designed to selectively inhibit calcineurin–NFAT interactions may offer a safer approach to preventing maladaptive remodeling. Moreover, broad inhibition of pathways such as calcineurin–NFAT or MAPK carries a well-recognized risk of immunosuppression, impaired stress adaptation, and systemic toxicity, further complicating their potential long-term use in otherwise healthy blast-exposed individuals.

5.4. Integrated therapeutic strategy

Combining these therapeutic strategies could induce synergistic effects. Ion channel blockers primarily attenuate acute electrophysiological aberrations, whereas antifibrotic and downstream signaling inhibitors target chronic remodeling following rLLB exposure. Overall, these intervention strategies illustrate potential mechanistically informed directions for future therapeutic development but currently lack validation in rLLB-specific experimental models or human clinical trials. Similarly, introducing preconditioning strategies among at-risk populations (e.g., military and first-responder personnel) may theoretically enhance baseline mechanosensory resilience; however, the feasibility, safety, adherence, and long-term effectiveness of such preventive strategies in real-world high-risk populations remain unknown (Table 2).[83-86]

5.5. Translational challenges and limitations of targeting mechanosensitive ion channels

The increasing attention toward MSCs as potential therapeutic targets faces substantial translational challenges. Most of the channels implicated in rLLB-induced cardiovascular pathology—including Piezo1, TRP channels, and members of the K2P family—are broadly expressed across multiple cell types and organ systems and constitute integral components of normal cardiovascular, neurological, and systemic physiology. Therefore, systemic pharmacological intervention carries a considerable risk of off-target effects and disruption of physiological mechanoadaptation.

Moreover, the functional role of mechanosensitive channels is likely to be context-specific, with a given channel able to mediate adaptive responses under physiological loading but maladaptive signaling during chronic or pathological mechanical loading. This duality complicates the definition of safe therapeutic windows. Accordingly, tissue-specific interventions and context-dependent or selective modulation of downstream signaling nodes may be

preferable to universal channel blockade. Further advances in targeted drug delivery and precision modulation may be required before mechanosensitive signaling pathways can be translated into safe clinical interventions for blast-related cardiovascular injury.

These challenges collectively emphasize that targeting mechanosensitive signaling pathways in rLLB remains a long-term research priority rather than an imminent clinical strategy.

6. Research gaps and future directions

While it is now clear that blast causes injury to the cardiovascular system, substantial uncertainty remains regarding the specific mechanisms of damage, clinical course, and long-term effects. Addressing these gaps is essential to advance the diagnosis, monitoring, and management of repeated sub-threshold blast overpressure exposure in military and industrial personnel.

6.1. Lack of standardized models

The challenge lies not only in the lack of standardized models but also in the absence of consensus on which exposure parameters are biologically relevant to cardiovascular damage. For instance, mechanisms of damage and repair vary depending on how the inter-blast interval, cumulative exposure dose, thoracic orientation, or recovery time post-exposure are manipulated. However, few studies explicitly control these variables, which strongly influence tissue responses. Future studies should therefore include: (i) reproducible pressure–time waveforms with validated shock-tube calibration; (ii) clinically relevant repetition paradigms over days to weeks rather than short single-day exposures; and (iii) cardiovascular-specific outcomes such as myocardial strain, fibrosis burden, and electrophysiological remodeling.

In the absence of standardized protocols, cross-study comparability and translational relevance will be limited (Table 3). A practical next step could involve a multicenter methodological initiative to define a "cardiovascular rLLB core protocol" with harmonized pressure–time waveforms, standardized exposure frequency and recovery intervals, and a minimum required set of cardiovascular outcomes (e.g., electrocardiogram, echocardiography/strain imaging, fibrotic markers) to enable reproducible cross-laboratory validation.

6.2. Limited human studies

Little is known about the long-term effects of blast exposure on the human myocardium. Despite multiple cellular and molecular mechanisms demonstrated in animal models, available human data remain largely limited to cross-sectional observations in veterans or occupational cohorts. These studies, however, cannot capture dynamic changes in myocardial structure and function.[87,88] For example, only a small number of longitudinal studies have been initiated (e.g., ACTRN12613000764774).

The main limitation of existing human evidence is not only the small number of studies but also the insufficient depth of cardiovascular phenotyping. Most cohorts rely heavily on self-reported exposure histories and broad clinical characterization, whereas few incorporate detailed cardiac assessments such as strain echocardiography, cardiac magnetic resonance with tissue characterization, ambulatory rhythm monitoring, and biomarker profiling. Future studies should therefore adopt longitudinal designs with accurate quantification of exposure dose, pre-specified cardiac imaging protocols, and comprehensive electrophysiological and molecular assessments. Such an approach would also allow the determination of whether subclinical cardiac alterations precede overt disease in blast-exposed individuals.

A logical next step is the development of prospective surveillance cohorts in well-defined high-risk populations (e.g., military breachers, explosive ordnance disposal personnel, and miners). These cohorts should ideally include baseline cardiovascular assessment prior to exposure, followed by repeated longitudinal evaluations (e.g., at 6 months, 1 year, and ≥5 years). Monitoring strategies may include wearable exposure and physiological sensors, multimodal cardiac imaging, and serial blood-based biomarker analyses, enabling precise characterization of exposure–response relationships and early disease trajectories.

6.3. New biomarker discovery

It is widely acknowledged that current biomarkers for early diagnosis of rLLB-induced myocardial damage are inadequate. Although cardiac troponins indicate sarcolemmal injury, they do not capture subclinical or chronic damage. Moreover, biomarker development remains underdeveloped, not only in number but also in conceptual approach. Most studies rely on general injury markers (e.g., troponins, C-reactive protein) that lack specificity for mechanotransduction-driven pathology. A more focused approach should prioritize biomarkers specific to MSC dysregulation and mechanical stress signaling, such as circulating mechanosensitive microRNAs (e.g., miR-21, miR-29, and miR-133), extracellular vesicle cargo reflecting fibroblast activation, or plasma markers of titin degradation and ECM remodeling.[89,90]

Furthermore, biomarker identification should be combined with controlled exposure paradigms to

Table 3. Research gaps and prioritized roadmap for advancing the field of repeated low-level blast–induced cardiovascular injury

Priority area	Current limitation	Rationale for barrier	Proposed strategy	Expected outcome
Standardization of experimental models	Large variability in pressure profiles, repetition paradigms, recovery intervals, and outcome measures across laboratories	Prevents reproducibility, limits cross-study comparison, and weakens translational relevance	Establish a multicenter consensus "cardiovascular rLLB core protocol" defining standardized waveforms, exposure frequency, recovery windows, and mandatory cardiovascular endpoints (e.g., ECG, strain echocardiography, fibrosis markers)	Enables reproducible mechanistic studies and robust preclinical validation
Lack of longitudinal human data	Human evidence is mostly cross-sectional and lacks detailed cardiovascular phenotyping	Unable to determine whether subclinical abnormalities precede clinical disease	Establish prospective surveillance cohorts in high-risk populations (e.g., breachers, EOD personnel) with baseline cardiac MRI, strain echocardiography, Holter monitoring, and blood biomarkers, followed for ≥5 years longitudinally with precise exposure dosimetry	Enables causal inference and identification of early predictors of long-term disease
Inadequate biomarker strategies	Reliance on nonspecific markers (e.g., troponin, C-reactive protein) not linked to mechanotransduction biology	Limits sensitivity for subclinical injury and provides little mechanistic insight	Prioritize mechanotransduction-linked biomarkers (e.g., miR-21, miR-29, titin fragments, extracellular vesicle cargo) and validate them in dose–response rLLB animal models before testing in longitudinal human cohorts	Facilitates the development of mechanism-based early detection tools
Fragmented imaging and electrophysiology approaches	Imaging, electrophysiology, and biomarkers are often studied in isolation	Fails to capture the opportunity to define integrated disease signatures and trajectories	Implement standardized multimodal phenotyping protocols (strain echocardiography + MRI + Holter) in both experimental and clinical studies to identify early subclinical signatures predictive of later disease	Enables discovery of composite diagnostic signatures and risk stratification
Weak translational integration	Disconnect between blast biophysics, mechanobiology, and clinical cardiology	Slows translation from mechanism to clinical relevance	Establish multidisciplinary consortia linking blast engineers, mechanobiologists, cardiologists, and imaging experts to design integrated studies and shared datasets	Accelerates translation and supports precision-medicine approaches
Lack of validated interventional strategies	Most therapeutic concepts remain theoretical or extrapolated from other disease models	No evidence base to support prevention or treatment in exposed populations	Embed interventional arms (e.g., exercise conditioning, antifibrotic agents, biomarker-guided surveillance) into rLLB-specific animal models and subsequently into high-risk human cohorts	Opens pathway toward evidence-based prevention and early intervention

Abbreviations: ECG: Electrocardiogram; EOD: Explosive ordnance disposal; MRI: Magnetic resonance imaging; rLLB: Repeated low-level blast.

elucidate dose–response relationships, rather than relying on cross-sectional associations. For instance, controlled preclinical paradigms should evaluate whether candidate biomarkers (e.g., miR-21, titin fragments, extracellular vesicle-derived fibroblast signatures) exhibit graded dose–response relationships across increasing rLLB exposure intensity, thereby facilitating the identification of markers most suitable for clinical translation. Parallel advances in imaging biomarkers—such as T1/T2 mapping by cardiac magnetic resonance and emerging positron emission tomography tracers targeting fibroblast activation—could provide noninvasive indicators of dynamic myocardial changes over serial time points (Table 3).

6.4. Advanced imaging and electrophysiology

Advanced imaging and electrophysiologic modalities provide a noninvasive window to detect blast-induced myocardial injury before traditional clinical presentation. Sophisticated echocardiographic methods, such as strain imaging or speckle-tracking echocardiography, can unmask subtle dysfunction in myocardial deformation.[58] In parallel, three-dimensional electroanatomic and optical mapping in animal hearts can reveal arrhythmogenic tissue substrates, whereas high-resolution cardiac magnetic resonance imaging can identify microstructural remodeling and fibrosis.[91]

Concrete next steps include adopting multimodal cardiovascular phenotyping protocols in both animal models and exposed human populations. For instance, combining strain echocardiography, cardiac magnetic resonance imaging (T1/T2 mapping), and prolonged rhythm monitoring into a single longitudinal study would enable the correlation of structural, electrical, and molecular changes over time. Such harmonized protocols could also assess whether early mechanistic changes (i.e., subclinical fibrosis, atrial strain abnormalities, silent arrhythmias) predict subsequent clinical sequelae.

7. Conclusion

At present, available data indicate that rLLB-induced cardiac changes are primarily mediated by MSC-dependent processes, according to previous experimental and preclinical studies. Channels such as TRPC6, TRPV2, Piezo1, and TRPM7 transduce mechanical stress into intracellular signals following blast exposure by rapidly converting mechanical energy into ionic fluxes. These fluxes ultimately initiate intracellular biochemical cascades that influence cardiomyocyte function and survival. While short-term activation of these mechanisms may be adaptive and potentially beneficial in acute settings (e.g., electrical stabilization, reparative signaling), chronic or repetitive activation drives maladaptive remodeling, resulting in fibrosis, diastolic dysfunction, and arrhythmogenesis, thereby increasing vulnerability to HFpEF.

The clinical implications are profound but remain speculative, highlighting the need for robust longitudinal human evidence. At present, these therapeutic concepts should be regarded as preclinical or hypothesis-generating, and none can be recommended for clinical implementation in blast-exposed populations. Despite the biological plausibility of MSCs and their downstream mechanisms, their ubiquitous physiological expression, context-dependent behavior, and potential for systemic side effects markedly complicate clinical translation. Accordingly, while these pathways offer important mechanistic insight and promising directions for future research, extreme caution is warranted when considering therapeutic targeting. Emerging approaches under investigation include ion channel blockers, Piezo1 modulators, antifibrotic agents, and inhibitors targeting Hippo–YAP/TAZ, MAPK, and calcineurin–NFAT signaling pathways. In addition, preconditioning strategies, such as controlled mechanical conditioning, may enhance mechanosensory resilience in high-risk individuals.

In view of the severity of this health risk, a comprehensive management strategy is needed for the prevention and treatment of BICI. Integrating blast biophysics with cardiac mechanobiology, multimodal imaging, and longitudinal clinical investigation will be essential to elucidate the trajectory from subclinical injury to overt disease. Such interdisciplinary collaboration could address critical knowledge gaps and accelerate the development of precision diagnostics and targeted therapeutic strategies to preserve cardiovascular health in populations exposed to blast.

Future progress in this field will require not only continued mechanistic discovery but also coordinated efforts to establish standardized experimental paradigms, prospective human cohorts, and mechanistically grounded biomarker strategies. Together, these elements are necessary to achieve meaningful translational advances.

Acknowledgments

None.

Funding

The work was supported by Russian Science Foundation grant No. 25-25-20036.

Conflict of interest

The authors declare they have no competing interests.

Author contributions

Conceptualization: Vadim Mitrokhin, Mitko Mladenov
Investigation: Anastasija Rodina, Stanislav Schileyko, Maria Morozova
Methodology: Maria Morozova, Anastasija Rodina
Visualization: Vadim Mitrokhin, Stanislav Schileyko, Maria Morozova
Writing–original draft: Mitko Mladenov, Andre Kamkin
Writing–review & editing: Vadim Mitrokhin, Mitko Mladenov

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

References

1. Cernak I. The importance of systemic response in the pathobiology of blast-induced neurotrauma. *Front Neurol.* 2010;1:151.

doi: 10.3389/fneur.2010.00151

2. Elsayed NM. Toxicology of blast overpressure. *Toxicology*. 1997;121(1):1-15.

doi: 10.1016/S0300-483X(97)03651-2

3. Rafaels K, Bass CRD, Salzar RS, *et al*. Survival risk assessment for primary blast exposures to the head. *J Neurotrauma*. 2011;28(12):2319-2328.

doi: 10.1089/neu.2009.1207

4. de Lanerolle NC, Bandak F, Kang D, *et al*. Characteristics of an explosive blast-induced brain injury in an experimental model. *J Neuropathol Exp Neurol*. 2011;70(11):1046-1057.

doi: 10.1097/NEN.0b013e318235bef2

5. Elder GA, Mitsis EM, Ahlers ST, *et al*. Blast-induced mild traumatic brain injury. *Psychiatr Clin North Am*. 2010;33(4):757-781.

doi: 10.1016/j.psc.2010.08.001

6. Belding JN, Englert RM, Fitzmaurice S, *et al*. Potential health and performance effects of high-level and low-level blast: A scoping review of two decades of research. *Front Neurol*. 2021;12:628782.

doi: 10.3389/fneur.2021.628782

7. Cernak I. Understanding blast-induced neurotrauma: How far have we come? *Concussion*. 2017;2(3):CNC42.

doi: 10.2217/cnc-2017-0006

8. Cernak I, Noble-Haeusslein LJ. Traumatic brain injury: An overview of pathobiology with emphasis on military populations. *J Cereb Blood Flow Metab*. 2010;30(2):255-266.

doi: 10.1038/jcbfm.2009.203

9. Chavko M, Koller WA, Prusaczyk WK, *et al*. Measurement of blast wave by a miniature fiber optic pressure transducer in the rat brain. *J Neurosci Methods*. 2007;159(2):277-281.

doi: 10.1016/j.jneumeth.2006.07.018

10. Irwin RJ, Lerner MR, Bealer JF, *et al*. Cardiopulmonary physiology of primary blast injury. *J Trauma*. 1997;43(4):650-655.

doi: 10.1097/00005373-199710000-00015

11. Guy RJ, Watkins PE, Edmondstone WM. Electrocardiographic changes following primary blast injury to the thorax. *J R Nav Med Serv*. 2000;86(3):125-133.

doi: 10.1136/jrnms-86-125

12. Kalbitz M, Amann EM, Bosch B, *et al*. Experimental blunt chest trauma-induced myocardial inflammation and alteration of gap-junction protein connexin 43. *PLoS One*. 2017;12(11):e0187270.

doi: 10.1371/journal.pone.0187270

13. Kiriu N, Saitoh D, Sekine Y, *et al*. Shock wave damage from the ventral side in primary blast injury: An experimental study in pigs. *Injury*. 2024;55(12):111982.

doi: 10.1016/j.injury.2024.111982

14. Tsuda T. Clinical assessment of ventricular wall stress in understanding compensatory hypertrophic response and maladaptive ventricular remodeling. *J Cardiovasc Dev Dis*. 2021;8(10):122.

doi: 10.3390/jcdd8100122

15. Ranade SS, Syeda R, Patapoutian A. Mechanically activated ion channels. *Neuron*. 2015;87(6):1162-1179.

doi: 10.1016/j.neuron.2015.08.032

16. Coste B, Mathur J, Schmidt M, *et al*. Piezo1 and Piezo2 are essential components of distinct mechanically activated cation channels. *Science*. 2010;330(6000):55-60.

doi: 10.1126/science.1193270

17. Sorum B, Docter T, Panico V, *et al*. Tension activation of mechanosensitive two-pore domain K+ channels TRAAK, TREK-1, and TREK-2. *Nat Commun*. 2024;15:3142.

doi: 10.1038/s41467-024-47208-5

18. Peyronnet R, Nerbonne JM, Kohl P. Cardiac mechano-gated ion channels and arrhythmias. *Circ Res*. 2016;118(2):311-329.

doi: 10.1161/CIRCRESAHA.115.305043

19. Quinn TA, Kohl P. Cardiac mechano-electric coupling: Acute effects of mechanical stimulation on heart rate and rhythm. *Physiol Rev*. 2021;101(1):37-92.

doi: 10.1152/physrev.00036.2019

20. Herrera-Pérez S, Campos-Ríos A, Rueda-Ruzafa L, *et al*. Contribution of K2P potassium channels to cardiac physiology and pathophysiology. *Int J Mol Sci*. 2021;22(12):6635.

doi: 10.3390/ijms22126635

21. Ranade S, Qiu Z, Woo SH, *et al*. Piezo1, a mechanically activated ion channel, is required for vascular development in mice. *Proc Natl Acad Sci USA*. 2014;111(28):10347-10352.

doi: 10.1073/pnas.1409233111

22. Onohara N, Nishida M, Inoue R, *et al*. TRPC3 and TRPC6 are essential for angiotensin II-induced cardiac hypertrophy. *EMBO J*. 2006;25(22):5305-5316.

doi: 10.1038/sj.emboj.7601417

23. Guo Y, Yu ZY, Wu J, *et al*. The Ca2+-activated cation channel TRPM4 is a positive regulator of pressure overload-induced cardiac hypertrophy. *eLife*. 2021;10:e66582.

doi: 10.7554/eLife.66582

24. Du J, Xie J, Zhang Z, *et al*. TRPM7-mediated Ca2+ signals confer fibrogenesis in human atrial fibrillation. *Circ Res*. 2010;106(5):992-1003.

doi: 10.1161/CIRCRESAHA.109.206771

25. Blythe NM, Muraki K, Ludlow MJ, *et al*. Mechanically

activated Piezo1 channels of cardiac fibroblasts stimulate p38 mitogen-activated protein kinase activity and interleukin-6 secretion. *J Biol Chem*. 2019;294(46):17395-17408.

doi: 10.1074/jbc.RA119.009167

26. Lengyel M, Enyedi P, Czirják G. Negative influence by the force: Mechanically induced hyperpolarization via K2P background potassium channels. *Int J Mol Sci*. 2021;22(16):9062.

doi: 10.3390/ijms22169062

27. Tan JHC, Liu W, Saint DA. Differential expression of the mechanosensitive potassium channel TREK-1 in epicardial and endocardial myocytes in rat ventricle. *Exp Physiol*. 2004;89(2):237-242.

doi: 10.1113/expphysiol.2003.027052

28. Committee on Gulf War and Health. Gulf War and Health, Volume 9: Long-Term Effects of Blast Exposures. Washington, DC, USA: National Academies Press; 2014.

doi: 10.17226/18253

29. Rhind SG, Shiu MY, Tenn C, *et al*. Repetitive low-level blast exposure alters circulating myeloperoxidase, matrix metalloproteinases, and neurovascular endothelial molecules in experienced military breachers. *Int J Mol Sci*. 2025;26(5):1808.

doi: 10.3390/ijms26051808

30. Pfeffer MA, Shah AM, Borlaug BA. Heart failure with preserved ejection fraction in perspective. *Circ Res*. 2019;124(11):1598-1617.

doi: 10.1161/CIRCRESAHA.119.313572

31. Dewey JM. The Friedlander equations. In: *Shock Wave and High Pressure Phenomena*. Springer International Publishing; 2017:37-55.

doi: 10.1007/978-3-319-70831-7_3

32. Reeder EL, Liber ML, Traubert OD, Connell CJO, Turner RC, Robson MJ. Characterization of blast waveforms produced by different driver gasses in an open-ended shock tube model. *arXiv*. Preprint posted online June 9, 2022.

doi: 10.48550/arXiv.2206.04106

33. Kundu A, Thangadurai M. A study on the interaction of shock tube-generated blast waves with a circular object at different pressure ratios. *Eur J Mech B Fluids*. 2025;109:145-161.

doi: 10.1016/j.euromechflu.2024.10.001

34. Bass CR, Rafaels KA, Salzar RS. Pulmonary injury risk assessment for short-duration blasts. *J Trauma*. 2008;65(3):604-615.

doi: 10.1097/TA.0b013e3181454ab4

35. Elder GA, Stone JR, Ahlers ST. Effects of low-level blast exposure on the nervous system: Is there really a controversy? *Front Neurol*. 2014;5:269.

doi: 10.3389/fneur.2014.00269

36. Kirkman E, Watts S, Cooper G. Blast injury research models. *Philos Trans R Soc Lond B Biol Sci*. 2011;366(1562):144-159.

doi: 10.1098/rstb.2010.0240

37. Eschbach D, Steinfeldt T, Hildebrand F, *et al*. A porcine polytrauma model with two different degrees of hemorrhagic shock: Outcome related to trauma within the first 48 h. *Eur J Med Res*. 2015;20(1):73.

doi: 10.1186/s40001-015-0162-0

38. Weng C, Yang G, Zhang S, *et al*. Baoguan baozha youfa de shaoshang fuhesun ji zhongyao qiguan sunshang de dashu moxing: guancha yanjiu [Burn-blast combined injury and important organ injury in rats induced by explosion in a closed pipe: An observation study]. *J Army Med Univ*. 2024;46(9):1323-1335. [In Chinese].

doi: 10.16016/j.2097-0927.202309061

39. Hall AA, Mendoza MI, Zhou H, *et al*. Repeated low intensity blast exposure is associated with damaged endothelial glycocalyx and downstream behavioral deficits. *Front Behav Neurosci*. 2017;11:104.

doi: 10.3389/fnbeh.2017.00104

40. Heyburn L, Abutarboush R, Goodrich S, *et al*. Repeated low-level blast overpressure leads to endovascular disruption and alterations in TDP-43 and Piezo2 in a rat model of blast TBI. *Front Neurol*. 2019;10:766.

doi: 10.3389/fneur.2019.00766

41. Linke WA, Fernandez JM. Cardiac titin: Molecular basis of elasticity and cellular contribution to elastic and viscous stiffness components in myocardium. *J Muscle Res Cell Motil*. 2002;23(5-6):483-497.

doi: 10.1023/A:1023462507254

42. LeWinter MM, Granzier HL. Cardiac titin and heart disease. *J Cardiovasc Pharmacol*. 2014;63(3):207-212.

doi: 10.1097/FJC.0000000000000007

43. Trombitás K, Granzier H. Actin removal from cardiac myocytes shows that near Z line titin attaches to actin while under tension. *Am J Physiol*. 1997;273(2):C662-C670.

doi: 10.1152/ajpcell.1997.273.2.C662

44. Granzier HL, Labeit S. The giant protein titin: A major player in myocardial mechanics, signaling, and disease. *Circ Res*. 2004;94(3):284-295.

doi: 10.1161/01.RES.0000117769.88862.F8

45. Hamdani N, Herwig M, Linke WA. Tampering with springs: Phosphorylation of titin affecting the mechanical function of cardiomyocytes. *Biophys Rev*. 2017;9(3):225-237.

doi: 10.1007/s12551-017-0263-9

46. Krüger M, Linke WA. Titin-based mechanical signalling in normal and failing myocardium. *J Mol Cell Cardiol*. 2009;46(4):490-498.

doi: 10.1016/j.yjmcc.2009.01.004

47. Samarel AM. Costameres, focal adhesions, and cardiomyocyte mechanotransduction. *Am J Physiol Heart Circ Physiol*. 2005;289:H2291-H2301.

doi: 10.1152/ajpheart.00749.2005

48. Prosser BL, Ward CW, Lederer WJ. X-ROS signaling: Rapid mechano-chemo transduction in heart. *Science*. 2011;333:1440-1445.

doi: 10.1126/science.1202768

49. Spassova MA, Hewavitharana T, Xu W, *et al*. A common mechanism underlies stretch activation and receptor activation of TRPC6 channels. *Proc Natl Acad Sci USA*. 2006;103:16586-16591.

doi: 10.1073/pnas.0606894103

50. Seo K, Rainer PP, Hahn VS, *et al*. Combined TRPC3 and TRPC6 blockade by selective small-molecule or genetic deletion inhibits pathological cardiac hypertrophy. *Proc Natl Acad Sci USA*. 2014;111:1551-1556.

doi: 10.1073/pnas.1308963111

51. Simovic MO, Yang Z, Jordan BS, *et al*. Immunopathological alterations after blast injury and hemorrhage in a swine model of prolonged damage control resuscitation. *Int J Mol Sci*. 2023;24:7494.

doi: 10.3390/ijms24087494

52. Bolli R, Marbán E. Molecular and cellular mechanisms of myocardial stunning. *Physiol Rev*. 1999;79:609-634.

doi: 10.1152/physrev.1999.79.2.609

53. Kloner RA, Jennings RB. Consequences of brief ischemia: Stunning, preconditioning, and their clinical implications: Part 2. *Circulation*. 2001;104:3158-3167.

doi: 10.1161/hc5001.100039

54. Ako J, Sudhir K, Farouque HMO, *et al*. Transient left ventricular dysfunction under severe stress: Brain–heart relationship revisited. *Am J Med*. 2006;119:10-17.

doi: 10.1016/j.amjmed.2005.08.022

55. Chavko M, Prusaczyk WK, McCarron RM. Lung injury and recovery after exposure to blast overpressure. *J Trauma*. 2006;61:933-942.

doi: 10.1097/01.ta.0000233742.75450.47

56. Senthil K, Ranganathan A, Piel S, *et al*. Elevated serum neurologic biomarker profiles after cardiac arrest in a porcine model. *Resusc Plus*. 2024;19:100726.

doi: 10.1016/j.resplu.2024.100726

57. Iwata Y, Katanosaka Y, Arai Y, *et al*. A novel mechanism of myocyte degeneration involving the Ca2+-permeable growth factor-regulated channel. *J Cell Biol*. 2003;161:957-967.

doi: 10.1083/jcb.200301101

58. Shah AM, Solomon SD. Myocardial deformation imaging: Current status and future directions. *Circulation*. 2012;125(2):e244-e248.

doi: 10.1161/CIRCULATIONAHA.111.086348

59. Paulus WJ, Tschöpe C. A novel paradigm for heart failure with preserved ejection fraction: Comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. *J Am Coll Cardiol*. 2013;62:263-271.

doi: 10.1016/j.jacc.2013.02.092

60. Li J, Hou B, Tumova S, *et al*. Piezo1 integration of vascular architecture with physiological force. *Nature*. 2014;515:279-282.

doi: 10.1038/nature13701

61. Mendoza SA, Fang J, Gutterman DD, *et al*. TRPV4-mediated endothelial Ca2+ influx and vasodilation in response to shear stress. *Am J Physiol Heart Circ Physiol*. 2009;298:H466-H476.

doi: 10.1152/ajpheart.00854.2009

62. Coste B, Delmas P. PIEZO ion channels in cardiovascular functions and diseases. *Circ Res*. 2024;134:572-591.

doi: 10.1161/CIRCRESAHA.123.322798

63. Thodeti CK, Matthews B, Ravi A, *et al*. TRPV4 channels mediate cyclic strain-induced endothelial cell reorientation through integrin-to-integrin signaling. *Circ Res*. 2009;104:1123-1130.

doi: 10.1161/CIRCRESAHA.108.192930

64. Taqueti VR, Di Carli MF. Coronary microvascular disease: Pathogenic mechanisms and therapeutic options. *J Am Coll Cardiol*. 2018;72:2625-2641.

doi: 10.1016/j.jacc.2018.09.042

65. Gama Sosa MA, De Gasperi R, Pryor D, *et al*. Low-level blast exposure induces chronic vascular remodeling, perivascular astrocytic degeneration and vascular-associated neuroinflammation. *Acta Neuropathol Commun*. 2021;9:167.

doi: 10.1186/s40478-021-01269-5

66. Bowman CL, Gottlieb PA, Suchyna TM, *et al*. Mechanosensitive ion channels and the peptide inhibitor GsMTx-4: History, properties, mechanisms and pharmacology. *Toxicon*. 2007;49:249-270.

doi: 10.1016/j.toxicon.2006.09.030

67. Bode F, Sachs F, Franz MR. Tarantula peptide inhibits atrial fibrillation. *Nature*. 2001;409:35-36.

doi: 10.1038/35051165

68. Yeung EW, Whitehead NP, Suchyna TM, *et al*. Effects of stretch-activated channel blockers on [Ca2+]i and muscle damage in the mdx mouse. *J Physiol*. 2005;562:367-380.

doi: 10.1113/jphysiol.2004.075275

69. Hamill OP, Martinac B. Molecular basis of mechanotransduction in living cells. *Physiol Rev*. 2001;81:685-740.

doi: 10.1152/physrev.2001.81.2.685

70. Perálvarez-Marín A, Solé M, Serrano J, *et al*. Evidence for the involvement of TRPV2 channels in the modulation of vascular tone in the mouse aorta. *Life Sci*. 2024;336:122286.

doi: 10.1016/j.lfs.2023.122286

71. Evans EL, Cuthbertson K, Endesh N, *et al*. Yoda1 analogue (Dooku1) which antagonizes Yoda1-evoked activation of Piezo1 and aortic relaxation. *Br J Pharmacol*. 2018;175:1744-1759.

doi: 10.1111/bph.14188

72. Pitt B, Zannad F, Remme WJ, *et al*. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med*. 1999;341:709-717.

doi: 10.1056/NEJM199909023411001

73. McMurray JJV, Packer M, Desai AS, *et al*. Angiotensin–neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371:993-1004.

doi: 10.1056/NEJMoa1409077

74. de Zeeuw D, Akizawa T, Audhya P, *et al*. Bardoxolone methyl in type 2 diabetes and stage 4 chronic kidney disease. *N Engl J Med*. 2013;369:2492-2503.

doi: 10.1056/NEJMoa1306033

75. Zong B, Yu F, Zhang X, *et al*. Mechanosensitive Piezo1 channel in physiology and pathophysiology of the central nervous system. *Ageing Res Rev*. 2023;90:102026.

doi: 10.1016/j.arr.2023.102026

76. Laughlin MH, Bowles DK, Duncker DJ. The coronary circulation in exercise training. *Am J Physiol Heart Circ Physiol*. 2012;302(1):H10-H23.

doi: 10.1152/ajpheart.00574.2011

77. Morris JH, Chen L. Exercise training and heart failure: A review of the literature. *Card Fail Rev*. 2019;5:57-61.

doi: 10.15420/cfr.2018.31.1

78. Ma Y, Kuang Y, Bo W, *et al*. Exercise training alleviates cardiac fibrosis through increasing fibroblast growth factor 21 and regulating TGF-β1–Smad2/3–MMP2/9 signaling in mice with myocardial infarction. *Int J Mol Sci*. 2021;22:12341.

doi: 10.3390/ijms222212341

79. Liu S, Martin JF. The regulation and function of the Hippo pathway in heart regeneration. *Wiley Interdiscip Rev Dev Biol*. 2019;8:e335.

doi: 10.1002/wdev.335

80. Mia MM, Cibi DM, Abdul Ghani SAB, *et al*. YAP/TAZ deficiency reprograms macrophage phenotype and improves infarct healing and cardiac function after myocardial infarction. *PLoS Biol*. 2020;18:e3000941.

doi: 10.1371/journal.pbio.3000941

81. Bueno OF, De Windt LJ, Tymitz KM, *et al*. The MEK1–ERK1/2 signaling pathway promotes compensated cardiac hypertrophy in transgenic mice. *EMBO J*. 2000;19:6341-6350.

doi: 10.1093/emboj/19.23.6341

82. Molkentin JD, Lu JR, Antos CL, *et al*. A calcineurin-dependent transcriptional pathway for cardiac hypertrophy. *Cell*. 1998;93:215-228.

doi: 10.1016/S0092-8674(00)81573-1

83. Rainer PP, Kass DA. Old dog, new tricks: Novel cardiac targets and stress regulation by protein kinase G. *Cardiovasc Res*. 2016;111:154-162.

doi: 10.1093/cvr/cvw107

84. McMurray JJV, Solomon SD, Inzucchi SE, *et al*. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2019;381:1995-2008.

doi: 10.1056/NEJMoa1911303

85. Marber MS, Latchman DS, Walker JM, *et al*. Cardiac stress protein elevation 24 hours after brief ischemia or heat stress is associated with resistance to myocardial infarction. *Circulation*. 1993;88:1264-1272.

doi: 10.1161/01.cir.88.3.1264

86. Chowdhury MA, Sholl HK, Sharrett MS, *et al*. Exercise and cardioprotection: A natural defense against lethal myocardial ischemia–reperfusion injury and potential guide to cardiovascular prophylaxis. *J Cardiovasc Pharmacol Ther*. 2018;24:18-30.

doi: 10.1177/1074248418788575

87. Martindale SL, Kolaja CA, Belding JN, *et al*. Blast exposure and long-term diagnoses among veterans: A Millennium Cohort Study investigation of high-level blast and low-level blast. *Front Neurol*. 2025;16:1599351.

doi: 10.3389/fneur.2025.1599351

88. Sajja VSSS, Statz JK, Walker PB, *et al*. Pulmonary injury risk curves and behavioral changes from blast overpressure exposures of varying frequency and intensity in rats. *Sci Rep*. 2020;10:16644.

doi: 10.1038/s41598-020-73643-7

89. Li M, Zhang J. Circulating microRNAs: Potential and emerging biomarkers for diagnosis of cardiovascular and

cerebrovascular diseases. *Biomed Res Int*. 2015;2015:730535. doi: 10.1155/2015/730535

90. Barile L, Moccetti T, Marbán E, *et al*. Roles of exosomes in cardioprotection. *Eur Heart J*. 2017;38:1372-1379. doi: 10.1093/eurheartj/ehw304

91. Chitiboi T, Axel L. Magnetic resonance imaging of myocardial strain: A review of current approaches. *J Magn Reson Imaging*. 2017;46:1263-1280. doi: 10.1002/jmri.25718