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Key ion channels in mechanical stress-induced cardiac remodeling: from mechanotransduction to therapeutic targets

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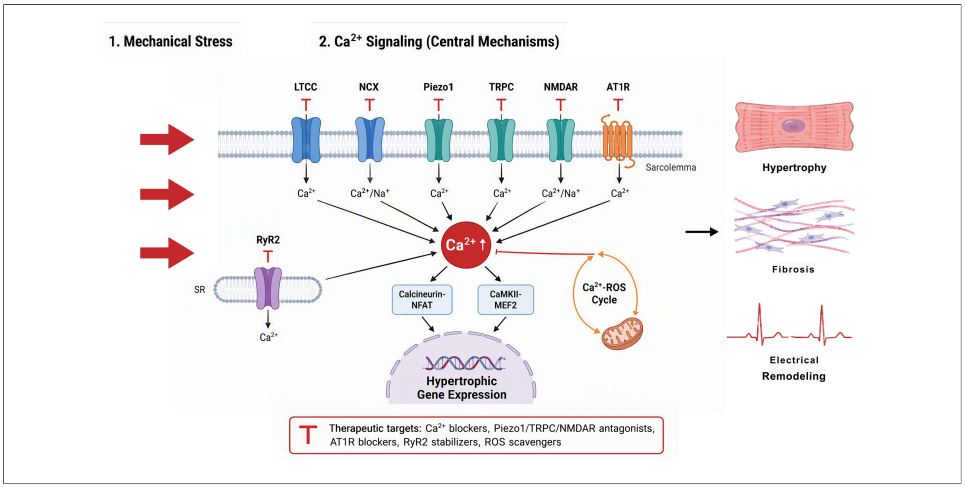

Abstract

Mechanical stress—including pressure overload and volume overload—is a core pathophysiological stimulus driving cardiac remodeling, and Ca^{2+} signaling is the central common pathway mediating this process. Traditional research has primarily focused on L-type Ca^{2+} channels (LTCC) and the renin-angiotensin-aldosterone system, whereas the synergistic contributions of mechanosensitive channels (transient receptor potential (TRP), Piezo), canonical excitation-contraction coupling channels [voltage-gated Na^+ channels, LTCC, the sarcoplasmic reticulum Ca^{2+} release channel type 2 ryanodine receptor (RyR2), and the Na^+/Ca^{2+} exchanger (NCX)], non-canonical Ca^{2+} channels (NMDAR), and the mechanosensitive angiotensin II type 1 receptor are increasingly being recognized. This review systematically integrates the mechanisms by which these distinct ion channel families transduce mechanical stimuli into intracellular Ca^{2+} signals and cooperatively regulate cardiac remodeling, with particular emphasis on their cell-type-specific distribution and function in cardiomyocytes, endothelial cells, vascular smooth muscle cells, cardiac fibroblasts, and perivascular sensory neurons and macrophages. We highlight the Ca^{2+}-Na^+-reactive oxygen species (ROS) signaling triad, which forms a self-reinforcing vicious cycle that drives cardiomyocyte hypertrophy, fibrosis, and electrical remodeling, and we elucidate how the relevant channels are differentially regulated under pressure

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overload versus volume overload. Key findings include the direct mechanosensor function of Piezo1, the multimodal sensing capacity of TRP channels, the non-canonical cardiac expression of NMDAR and its proarrhythmic effects, the paradoxical hypertrophic response triggered by reduced LTCC activity, and the pivotal role of RyR2 as a disease-modifying node. From a therapeutic perspective, we review classical calcium channel blockers and emerging strategies—including mechanosensitive channel modulators, NMDAR antagonists, RyR2 stabilizers, NCX modulation, and ROS-targeted interventions—stratified by disease context and level of evidence. This integrated mechano-calcium signaling framework provides a new theoretical basis and potential therapeutic targets for cardiac remodeling-related diseases.

INTRODUCTION

Mechanical stress (including pressure overload and volume overload) is a core pathophysiological stimulus driving the initiation and progression of cardiac remodeling[1-3], and Ca^{2+} signaling is the central common pathway mediating the transduction of mechanical stress into cardiac remodeling, playing an indispensable regulatory role in processes such as cardiomyocyte hypertrophy, fibrosis, and electrical remodeling. For a long time, traditional research in this field has primarily focused on excitation-contraction coupling (ECC) mediated by L-type Ca^{2+} channels (LTCC)[4,5] and the indirect regulation of calcium signaling by the renin-angiotensin-aldosterone system (RAAS), establishing the classical regulatory theory of cardiac remodeling centered on LTCC and RAAS[6]. However, the synergistic effects of different types of ion channels in cardiac remodeling have been severely underestimated[7-9]. Mechanosensitive channels (transient receptor potential (TRP), Piezo), voltage/excitation-related channels (LTCC, Na^+ channels), and non-canonical Ca^{2+} channels (NMDAR) do not act independently; rather, they form complex signaling networks under mechanical stress to jointly regulate Ca^{2+} homeostasis and the progression of cardiac remodeling. The traditional single-pathway research perspective cannot fully elucidate the underlying pathological mechanisms. On this basis, this review aims to systematically integrate the mechanistic roles of different types of ion channels under mechanical stress, clarify the synergistic regulatory network of these channels in cardiac remodeling, and provide a new theoretical basis and potential therapeutic targets for the treatment of cardiac remodeling-related diseases (such as hypertensive heart disease and heart failure).

MECHANICAL STRESS AND ION CHANNELS: FROM MECHANICAL FORCE TO ELECTROCHEMICAL SIGNALS

Mechanical stress and mechanical stress-mediated cardiac remodeling

Mechanical stress is one of the most fundamental physiological and pathological stimuli for cardiomyocytes and a key driver of cardiac remodeling initiation and progression. According to its mode of action on the ventricular wall, mechanical stress can be divided into pressure overload and volume overload, which differ significantly in their pathophysiological characteristics and ion channel activation patterns. The two activate ion channels through distinct modes of mechanosensing, converting mechanical signals into electrochemical signals and ultimately regulating the process of cardiac remodeling[10,11].

Pressure overload refers to sustained mechanical stimulation caused by elevated ventricular afterload, which is commonly seen in conditions such as hypertension, aortic valve stenosis, and pulmonary hypertension. Its core mechanical feature is increased ventricular wall stress; cardiomyocytes are mainly subjected to the combined effects of radial compression and circumferential stretch, inducing concentric cardiac hypertrophy, myocardial fibrosis, and electrical remodeling[10,11]. Under pressure overload, mechanosensitive ion channels (such as Piezo1 and TRPC1/6), acting as the primary mechanosensors, can directly sense changes in membrane tension and become rapidly activated, mediating Ca^{2+} influx[1,2]. Meanwhile, voltage-gated ion channels (such as LTCC and Na^+ channels) amplify calcium signals through ECC and cooperate with mechanosensitive channels to drive the activation of hypertrophic signaling pathways[12,13]. Traditional

research has focused mainly on LTCC and the RAAS, whereas the critical role of mechanosensitive channels—including stretch-activated ion channels and the mechanosensitive angiotensin II type 1 receptor (AGTR1)—in the sensing of pressure overload has only gradually been recognized in recent years[1,14].

Volume overload refers to sustained stretch stimulation caused by elevated ventricular preload, which is commonly seen in conditions such as aortic regurgitation, mitral regurgitation, and arteriovenous fistula. Its core mechanical feature is excessive ventricular wall stretch; cardiomyocytes are mainly subjected to axial stretch, inducing eccentric cardiac hypertrophy, ventricular dilation, and wall thinning[10,11]. Under volume overload, mechanosensitive channels such as TRPV4 are considered to play important roles; among them, TRPV4 can directly sense stretch stress and mediate non-canonical Ca^{2+} influx[15]. Some scholars have also proposed that NMDAR may participate in volume overload-related Ca^{2+} signaling regulation, but there is currently no experimental evidence that volume overload directly activates NMDAR; traditional LTCC play a relatively minor role in this context[9,16].

Fundamental modes of mechanotransduction

Mechanotransduction is the core process by which cells sense and respond to extracellular mechanical stimuli. Its fundamental mode relies on key nodes such as changes in cell membrane tension, cytoskeletal rearrangement, and activation of mechanosensitive channels, efficiently converting physical signals into intracellular biochemical signals and participating in the regulation of diverse biological functions, including cell proliferation, differentiation, migration, and the maintenance of tissue homeostasis[16,17].

The cell membrane is the first interface for sensing mechanical stimuli, and changes in lipid bilayer tension constitute the initial step of mechanotransduction. External forces such as blood flow-induced shear stress and extracellular matrix traction can directly alter cell membrane tension and curvature. Such physical changes can either directly regulate membrane protein conformation through the lipid tension model or trigger downstream signaling cascades by altering membrane fluidity, thereby laying the foundation for subsequent signal transduction[18]. Studies have shown that cell membrane tension can serve as a physical bridge connecting extracellular mechanical stimuli to intracellular signaling pathways, occupying a central position in mechanical signal sensing[19].

The cytoskeleton is mainly composed of actin filaments, microtubules, and intermediate filaments, and is connected to the cell membrane through structures such as focal adhesions and integrins. The cell membrane rapidly transmits mechanical signals to the cytoskeleton via membrane-localized focal adhesions and integrins, triggering rapid rearrangement of cytoskeletal components. Tension signals are transmitted through the actin-myosin system, activating the Rho/ROCK pathway and promoting stress fiber formation. Meanwhile, focal adhesion complexes (such as FAK and talin) bind integrins outward to engage the extracellular matrix and connect to the cytoskeleton inward. Through their own deformation, they transmit mechanical stretch signals from the extracellular space to the cytoskeleton and further inward to the nucleus, achieving signal transmission across compartments[20]. Previous studies have systematically elucidated the three-tiered regulatory mechanism of the cytoskeleton in mechanotransduction, encompassing focal adhesion assembly, stress fiber formation, and nucleoskeletal signal transduction, and have confirmed that the cytoskeleton can participate in the activation of mechanosensitive channels through the tether model, thereby solidifying the structural basis of mechanical signal transmission[21]. For example, Viola *et al.*[22] reported that LTCC are coupled to mitochondria via the cytoskeleton (F-actin and β-tubulin)[22].

Mechanosensitive G protein-coupled receptor: the AGTR1

In addition to ion channels, G protein-coupled receptors (GPCRs) can also serve as mechanosensors, particularly the AGTR1 within the RAAS[14,23]. Using cardiomyocytes from angiotensinogen-knockout mice, Zou *et al.*[14] demonstrated that even in the complete absence of angiotensin II, mechanical stretch can still

activate AGTR1 and initiate downstream ERK and hypertrophic signaling, establishing AGTR1 as a bona fide mechanosensor[14]. Subsequent biophysical analyses revealed that membrane stretch can stabilize an active conformation of AGTR1, causing it to preferentially couple to β-arrestin-biased signaling, indicating that mechanical force is an allosteric modulator of AGTR1 signaling bias[23].

These findings have two important implications. First, they provide a molecular basis for the observation that "mechanical overload can locally activate RAAS-dependent hypertrophic programs without requiring systemic angiotensin II generation." Second, they offer a mechanistic explanation for the efficacy of angiotensin receptor blockers (ARBs) with inverse agonist properties under pressure overload conditions: by stabilizing the inactive conformation of AGTR1, these drugs can simultaneously block both ligand-dependent and mechanically evoked receptor activation[14,23]. Mechanosensitive AGTR1 signaling converges with multiple pathways activated by mechanosensitive ion channels (including Ca^{2+} mobilization, reactive oxygen species (ROS) generation, and calcineurin/nuclear factor of activated T cells (NFAT) activation), highlighting the close interplay between receptor- and channel-mediated mechanotransduction in cardiac remodeling[24,25].

Ion channels and cardiac remodeling: the Ca^{2+}-Na^{+}-ROS signaling triad

The transmembrane influx of Ca^{2+} and Na^{+} mediated by the activation of mechanosensitive ion channels, together with the generation of ROS, constitutes the core signal-integration network downstream of mechanotransduction. Through the interplay between ion homeostasis regulation and redox signaling, these signals convert mechanical signals into diverse cellular effects, playing key roles in mechanosensing and disease regulation in the cardiovascular system[24,25].

Mechanical stimulation triggers the opening of mechanosensitive channels (such as Piezo1 and TRPV4), first mediating Ca^{2+} influx, which is the most central second-messenger event downstream of mechanotransduction. Elevated intracellular Ca^{2+} concentration can directly activate calmodulin (CaM), calmodulin-dependent protein kinase (CaMK), and the calcineurin/NFAT pathway, triggering the expression of hypertrophy-related genes; meanwhile, Piezo1-mediated Ca^{2+} influx in vascular endothelial cells can further activate eNOS signaling to regulate vascular tone, whereas mechanical stretch of cardiomyocytes participates in the pathological process of cardiac hypertrophy through Ca^{2+} signaling mediated by TRPC channels. In addition, Ca^{2+} influx can also activate NADPH oxidases (NOX), providing a critical trigger signal for subsequent ROS generation.

Na^{+} signaling cooperates with Ca^{2+} signaling to indirectly regulate the activity of voltage-gated Ca^{2+} channels (VGCCs) by altering the cell membrane potential, forming a Na^{+}-Ca^{2+} signal amplification loop: Na^{+} influx mediated by mechanosensitive sodium channels (such as members of the ENaC family and the nonselective cation currents through Piezo channels) causes cell membrane depolarization, promoting VGCC opening to further increase Ca^{2+} influx; meanwhile, elevated intracellular Na^{+} concentration can activate the NCX in its reverse mode to transport Ca^{2+} into the cell, amplifying the calcium signal. This synergistic regulation is highly significant for cardiomyocyte mechanical responses and arrhythmogenesis[26,27].

ROS serve as an integration hub connecting ionic signals with redox signals in mechanotransduction and exert bidirectional regulatory effects: on the one hand, Ca^{2+} influx promotes ROS generation by activating NOX enzymes; on the other hand, ROS can enhance the sensitivity of mechanosensitive channels (such as Piezo1 and TRPV4) to mechanical stimuli through redox modification of their cysteine residues, forming a positive feedback loop. This reciprocal regulation plays a key role in vascular endothelial dysfunction and myocardial ischemia-reperfusion injury, in which ROS can amplify mechanical signals and thereby aggravate the pathological process[24,25].

Ca^{2+}, Na^{+}, and ROS signals do not exist independently but achieve functional integration through multiple feedback loops: Na^{+} influx amplifies Ca^{2+} signals through membrane potential regulation, Ca^{2+} further induces ROS generation, and ROS, in turn, regulates ion channel activity through redox modification. Together, these three components constitute the signaling network downstream of mechanotransduction, determining the direction of cellular responses to mechanical stimuli and participating in the development and progression of cardiovascular diseases.

At the molecular level, the feedback of ROS on ion channel activity is mediated by well-defined oxidative modifications. ROS oxidize critical methionine residues (Met281/282) of calmodulin-dependent protein kinase II (CaMKII), locking the kinase in a constitutively active state that persists even after the initial Ca^{2+} signal has subsided[28]. Oxidative modification of type 2 ryanodine receptor (RyR2) increases sarcoplasmic reticulum (SR) Ca^{2+} leak, amplifies cytosolic and mitochondrial Ca^{2+} oscillations, and further stimulates ROS generation in chronic heart failure[29]. Reactive nitrogen species can S-nitrosylate TRP channels and enhance their activity, providing direct redox gating of mechanosensitive Ca^{2+} influx[30]. In cardiomyocytes, TRPC3 forms a signaling complex with NADPH oxidase 2 (Nox2); stretch-induced TRPC3-mediated Ca^{2+} influx stabilizes Nox2 and increases ROS generation, while ROS, in turn, sustains TRPC3 activity—an amplification loop that drives adverse remodeling[31]. Finally, elevated cytosolic Na^{+} in failing cardiomyocytes reduces mitochondrial Ca^{2+} uptake, impairs NADH regeneration and antioxidant capacity, and thereby increases mitochondrial ROS formation, directly linking Na^{+} channel remodeling to oxidative stress[27].

These channel-ROS feedback mechanisms contribute differentially to the three major features of adverse remodeling. First, hypertrophic growth is primarily driven by sustained activation of Ca^{2+}-dependent calcineurin/NFAT and CaMKII/histone deacetylase (HDAC) signaling downstream of mechanosensitive Ca^{2+} influx[6,32]. Second, myocardial fibrosis arises from mechanical stress activation of mechanosensitive channels in cardiac fibroblasts (such as TRPM7, TRPV4, and Piezo1), which couple Ca^{2+} influx to profibrotic transcription, myofibroblast differentiation, and extracellular matrix deposition[33-35]. Third, electrical remodeling stems from redox- and Ca^{2+}-dependent modifications of ion channels—including increased late sodium current, oxidized RyR2-mediated SR Ca^{2+} leak, and NMDAR-mediated Nav1.5 downregulation—which together constitute the substrate for arrhythmogenesis[26,29,36]. This mechanistic stratification provides a framework for understanding how targeting different channels can modify specific aspects of the remodeling phenotype [Figure 1].

CONVENTIONAL SIGNALING PATHWAYS

The ion channels discussed in this section—such as voltage-gated Na^{+} channels, LTCC, RyR2, and the NCX—are mainly expressed in cardiomyocytes and participate in ECC. ECC is the central process that converts the action potential into mechanical contraction, and Ca^{2+}-induced Ca^{2+} release (CICR) is the fundamental mode of ECC. The transient elevation of cytosolic Ca^{2+} is the direct driving force of contraction, but extracellular Ca^{2+} influx alone is insufficient to trigger effective contraction. Signal cascade amplification must rely on Na^{+} channels, LTCC, and RyR2[4,5].

Canonical pathways

Early studies showed that cardiac hypertrophy is regulated by a series of canonical and complex intracellular signaling pathways that mediate physiological or pathological cardiac growth, depending on the nature of the stimulus. Among these, GPCRs are the core initiating elements that sense neurohumoral factors (such as angiotensin II, endothelin-1, and catecholamines) and induce pathological cardiac hypertrophy, activating multiple downstream pathways. Members of the mitogen-activated protein kinase (MAPK) family exert distinct roles: the MEK1-ERK1/2 pathway can induce compensatory hypertrophy, whereas p38 and JNK generally negatively regulate the hypertrophic response, and their activation is more closely associated with

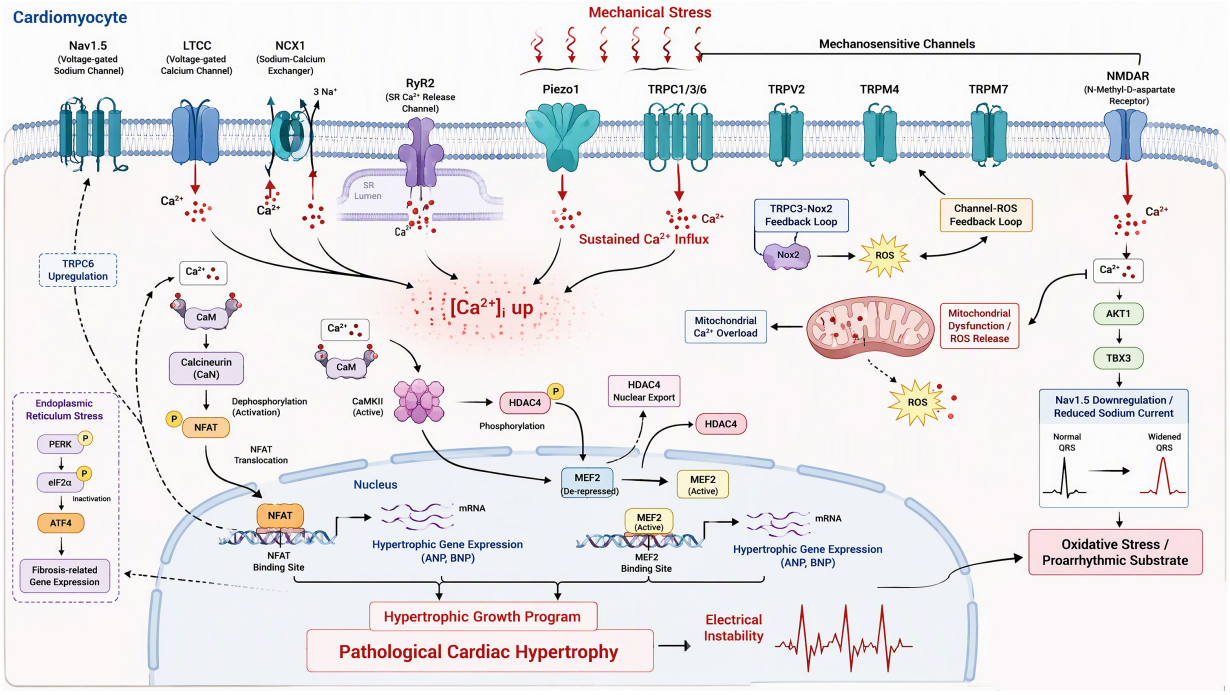

Figure 1. Cell-type-specific ion channel and receptor mechanisms of mechanical stress-induced cardiac remodeling. Mechanical stress activates mechanosensors (Piezo1, TRP channels, NMDAR, AGTR1) and dysregulates cardiomyocyte excitation-contraction coupling channels (LTCC, Nav1.5, RyR2, NCX1), driving Ca^{2+} signaling and ROS feedback that culminate in hypertrophy, fibrosis, and electrical remodeling. The figure was created with Matplotlib (Python) and Adobe Illustrator.

cardiomyopathy and cardiac dysfunction. The calcineurin-NFAT pathway is the central pathway of pathological hypertrophy: Ca^{2+}-activated calcineurin dephosphorylates NFAT, promoting its nuclear translocation and initiating hypertrophic gene expression. The IGF-I-PI3K-AKT/PKB-mTOR pathway plays a dual role in regulating physiological hypertrophy, growth, and development, in which AKT/PKB is essential for cardiac growth, but its excessive activation is deleterious. In addition, the HDAC pathway is equally critical: class I HDACs (such as HDAC1/2) promote pathological hypertrophy, whereas class II HDACs (such as HDAC5/9) suppress the expression of pathological hypertrophy genes by interacting with transcription factors such as myocyte enhancer factor-2 (MEF2). Complex interactions exist among these pathways, which together precisely regulate cardiac growth and remodeling[6].

Na^+ channels: the upstream electrical basis of ECC

The cardiac action potential, mediated by voltage-gated Na^+ channels, provides the electrical basis for subsequent LTCC activation; during the action potential plateau, LTCC activate, triggering Ca^{2+} influx. Meanwhile, Na^+ channels can influence the activity of the NCX by regulating intracellular Na^+ concentration, thereby modulating cytosolic Ca^{2+} homeostasis and synergistically enhancing the Ca^{2+} influx efficiency of LTCC, improving overall ECC performance[4,37]. Under mechanical stress or pathological conditions, Nav channels undergo remodeling, manifested as an increased late (persistent) Na^+ current (INa,L). This abnormal Na^+ influx elevates intracellular Na^+ concentration, impairs mitochondrial Ca^{2+} uptake, and increases mitochondrial ROS generation, while simultaneously promoting reverse-mode NCX activity, leading to Ca^{2+} overload, prolonged action potential duration, early afterdepolarizations, and increased susceptibility to arrhythmias, thereby exacerbating cardiac hypertrophy and heart failure[26,27]. Notably, Wan *et al.*[26] demonstrated that experimentally increasing abnormal Na^+ influx is sufficient to cause cardiomyopathy and atrial fibrillation in mice, establishing a causal role for Nav remodeling in structural heart disease[26]. Recent studies further indicate that NMDAR activation aggravates ischemic arrhythmias by

downregulating Nav1.5 through the AKT1-TBX3 axis, linking non-canonical channel signaling to Nav channel remodeling and electrical instability in the ischemic heart[36].

LTCC: the specific Ca^{2+} trigger signal of ECC

Cardiac ECC is initiated when Ca^{2+} flows inward across the plasma membrane through voltage-gated LTCC. L-type voltage-gated Ca^{2+} channels (LTCCs) are a major subfamily among the ten types of VGCCs and represent the main route of extracellular Ca^{2+} influx in ventricular myocytes. They are voltage-activated during the action potential plateau, generating an inward Ca^{2+} current that mediates the influx of a small amount of Ca^{2+} down its electrochemical gradient, serving as the dedicated trigger signal for ECC[38-40]. LTCC is a multi-subunit complex composed of the pore-forming α1 (Cav1.2) subunit together with auxiliary α2δ, β, and γ subunits: the α1 subunit contains the voltage sensor and the ion-conducting pore and provides the binding sites for most calcium channel blockers (CCBs), whereas the auxiliary subunits regulate gating properties, trafficking, and pharmacological responses, thereby influencing ECC efficiency[38,39].

Dysregulated Ca^{2+} handling is an important cause of cardiac hypertrophy, and LTCC is the main route of Ca^{2+} influx in cardiomyocytes, capable of activating downstream protein synthesis signaling pathways and thereby inducing hypertrophy. The study by Gao *et al.*[41] demonstrated that Ca^{2+} influx through LTCC and TRP channels can activate pathological hypertrophic signaling and downstream protein synthesis in cardiomyocytes[41]. Another study found that under α1-adrenergic stimulation, LTCC and CaMKII can form a positive feedback activation loop within the caveolae microdomain, promoting hypertrophy-related protein synthesis[42]. In addition, calcineurin physically and functionally interacts with cardiac LTCC; this interaction is associated with signal transduction and can upregulate protein synthesis[43]. Further studies have shown that mechanical stretch can increase LTCC stability through a polycystin-1/AKT-dependent mechanism, thereby enhancing Ca^{2+} influx and promoting hypertrophic protein synthesis in cardiomyocytes[44]. Meanwhile, LTCC opening is also regulated by depolarization stimuli and by various molecules, including Ca^{2+}, CaM, and interactions with multiple auxiliary proteins, which in turn affect protein synthesis[45]. Studies have found that the transcription factor NFATc4 cooperates with myocardin to upregulate the expression of the LTCC α1C subunit, promoting Ca^{2+} influx and enhancing cardiac hypertrophy-related protein synthesis[46]. It has been confirmed that reduced cardiac L-type Ca^{2+} channel activity can trigger neuroendocrine stress, increase SR RyR2 Ca^{2+} leak, lead to an abnormally elevated Ca^{2+} signaling gain, and activate the calcineurin/NFAT pathway, inducing spontaneous cardiac hypertrophy and accelerating heart failure[12].

However, the relationship between LTCC activity and the development of cardiac hypertrophy is not a simple direct proportion. The study by the Goonasekera team[12] demonstrated that reduced LTCC activity can induce neuroendocrine stress, accompanied by compensatory enhancement of SR Ca^{2+} release to maintain myocardial contractility; this state leads to activation of calcineurin/NFAT signaling, paradoxically promoting cardiac hypertrophy and heart failure in mice[12]. In addition, loss of the RAD GTPase results in enhanced LTCC function, manifesting as an adaptive hypertrophic phenotype that promotes beneficial Ca^{2+} dynamics[45,47]. By precisely regulating Ca^{2+} influx, LTCC directly or indirectly initiates the protein synthesis program in cardiac hypertrophy. Moreover, in hypertrophic cardiomyopathy (HCM), abnormal LTCC activity not only alters contractility but also affects mitochondrial metabolism: increased Ca^{2+} influx through LTCC leads to mitochondrial Ca^{2+} overload, increased ROS generation, and a hypermetabolic state, thereby aggravating the HCM phenotype, whereas inhibiting LTCC or employing peptide therapies targeting the channel-mitochondria axis can ameliorate this phenotype[48,49].

RyR2 and SR Ca^{2+} release: Ca^{2+} signal amplification and precise termination in CICR

The RyR2 is a Ca^{2+} release channel located on the SR membrane of cardiomyocytes. The small amount of Ca^{2+} entering the cytosol precisely activates RyR2 on the SR, achieving exponential amplification of the Ca^{2+}

signal. This is the core mechanism of cardiac ECC, the key to its generation of powerful contractile force, and an important determinant of cardiac function[50,51].

The small amount of Ca^{2+} entering the cell can activate the synchronous opening of RyR2 clusters on the SR, triggering massive release of Ca^{2+} stored in the SR, markedly elevating Ca^{2+} and driving myocardial contraction. This local Ca^{2+} release event is defined as a Ca^{2+} spark and constitutes the fundamental functional unit of CICR[52,53]; contraction is generated by the summation and integration of numerous Ca^{2+} sparks. In addition, a recently discovered circular RNA derived from the RyR2 locus (circ-RyR2) is downregulated in hypertrophy and heart failure, and restoring its expression normalizes Ca^{2+} handling without altering RyR2 protein levels, revealing a new layer of post-transcriptional regulation[54].

RyR2 activity is regulated by changes in the levels of various intracellular factors, such as divalent cations (Ca^{2+} and Mg^{2+}), nucleotides, associated proteins, and ROS[29,50]. The conventional view holds that CICR is the canonical initiation mechanism of cardiac ECC, in which LTCC-mediated Ca^{2+} influx serves as the trigger signal to activate RyR2; whereas recent studies propose that binding of Ca^{2+} to the Cav1.2 pore induces a conformational change that may activate RyR2 through physical coupling, which could be a complementary mechanism cooperating with CICR[55]. Studies have demonstrated that insufficient RyR2 expression attenuates SR Ca^{2+} release, thereby suppressing key hypertrophic pathways such as calcineurin, ERK, and Akt, and significantly alleviating pressure overload-induced cardiac hypertrophy and fibrosis[56]. Conversely, RyR2-R176Q knock-in mouse models exhibit accelerated development of pressure overload-induced cardiac hypertrophy and dysfunction, suggesting that RyR2-mediated Ca^{2+} leak participates in the remodeling process[57].

Differential regulation of ECC channels under pressure overload and volume overload

Although pressure overload and volume overload ultimately both lead to hypertrophic remodeling, the biomechanical and molecular programs they engage are not identical. Pressure overload increases systolic wall stress and primarily drives concentric hypertrophy, whereas volume overload increases diastolic wall stress and drives eccentric hypertrophy accompanied by chamber dilation; direct hemodynamic comparisons in patients with valvular heart disease have confirmed that these two loading states produce markedly distinct wall stress profiles[10,11]. At the level of ECC channels, the characteristics of pressure overload have been more thoroughly elucidated: it promotes RyR2-mediated SR Ca^{2+} leak, a caveolae-localized LTCC/CaMKII activation loop, and increased INa,L, which together favor cytosolic Ca^{2+} accumulation and activation of calcineurin/NFAT and CaMKII signaling[26,42,56,57]. By contrast, chronic volume overload and the associated diastolic stretch preferentially engage mechanosensitive pathways, including TRPV4-mediated Ca^{2+} influx (which in the aging heart participates in stretch-induced hypercontractility and time-dependent dysfunction) and eccentric growth signaling. However, the specific regulation of ECC channels under pure volume overload remains poorly defined and awaits direct comparative studies[15,16]. These differential regulatory patterns (summarized in Table 1) suggest that channel-targeted therapies may need to be individualized according to the predominant loading state.

NON-CANONICAL ION CHANNELS

Unlike the conventional ECC channels, the channels reviewed in this section—including members of the TRP family, Piezo1, and NMDAR—are expressed in multiple cardiac cell types and act either as direct mechanosensors (TRP channels, Piezo1) or as stress-coupled signaling platforms (NMDAR), linking mechanical stress to hypertrophic, fibrotic, and electrical remodeling. Their cell type-specific distribution is summarized in Table 2, while their activation characteristics, downstream pathways, and pharmacological modulators are summarized in Table 3.

Table 1. Summary of ion channels related to cardiomyocyte excitation-contraction coupling (ECC) under mechanical overload

Channel	Expression/activity changes	Regulatory factors	Hypertrophy/remodeling signaling cascades	Comparison between pressure overload and volume overload	References
Nav1.5	Increased late sodium current (INa,L); Nav1.5 downregulated in ischemia	Oxidative stress; CaMKII; NMDAR-AKT1-TBX3 axis	$[Na^+]i\uparrow \rightarrow$ impaired mitochondrial Ca^{2+} uptake, ROS↑; reverse-mode NCX → Ca^{2+} overload; prolonged APD, EAD, arrhythmias	Well documented in pressure overload and ischemia; insufficiently studied in volume overload	[26,27,36]
LTCC (Cav1.2)	Context-dependent: increased membrane stability under stretch; enhanced caveolae-localized activity under adrenergic stress; reduced activity can cause heart failure	Polycystin-1/AKT (mechanical); caveolae CaMKII loop; Rad GTPase; NFATc4/myocardin transcription	Ca^{2+} influx → CaMKII and calcineurin/NFAT activation; mitochondrial Ca^{2+} overload and ROS; HCM hypermetabolic state	Stretch and pressure overload regulation established; volume overload regulation unclear	[12,41-44,48]
RyR2	Hyperphosphorylation and oxidation → SR Ca^{2+} leak; channel cluster remodeling in heart failure	PKA/CaMKII phosphorylation; redox modification; FKBP12/12.6; circ-RyR2	Diastolic $Ca^{2+}\uparrow$, reduced contractility; DAD/arrhythmias; CaMKII activation → hypertrophic transcription	Required for pressure overload hypertrophy (animal models); role in volume overload undetermined	[29,54,56,57]
NCX1	Expression and activity upregulated in hypertrophy and heart failure; $[Na^+]i\uparrow$ favors reverse mode	Intracellular Na^+/Ca^{2+}; membrane potential; PIP2	Ca^{2+} extrusion (forward) and Ca^{2+} influx (reverse); involved in Ca^{2+} overload, contractile dysfunction, and arrhythmogenesis	Upregulation documented in pressure overload hypertrophy and human heart failure; limited comparative data for volume overload	[37,58,59]

Table 2. Cell type-specific distribution and functions of ion channels in mechanical stress-mediated cardiac remodeling

Cell type	Major channels	Mechanical stimuli sensed	Downstream pathways	Remodeling outcomes	References
Cardiomyocytes	Nav1.5; LTCC; RyR2; NCX1; TRPC1/3/6; TRPV2; TRPM4/7; Piezo1; NMDAR	Pressure/volume overload; sarcomere stretch; glutamatergic stimulation (NMDAR)	Calcineurin/NFAT; CaMKII/HDAC; ROS feedback loops; mitochondrial Ca^{2+} overload	Concentric/eccentric hypertrophy; contractile dysfunction; arrhythmogenic electrical remodeling	[1,26,32,70]
Endothelial cells	TRPV4; Piezo1; TRPC1/3/5	Shear stress; cyclic circumferential stretch	TRPV4 sparklet → IKCa/SKCa → EDH; Piezo1 → calpain, angiogenic alignment	Vasomotor dysregulation; impaired angiogenesis; microvascular rarefaction	[65,79,80,90]
Vascular smooth muscle cells	TRPM4; Piezo1; TRPC6	Intravascular pressure; wall tension	Myogenic depolarization → Cav1.2 Ca^{2+} influx; transglutaminase/ECM cross-linking	Increased myogenic tone; arterial stiffening; elevated cardiac afterload	[90,92,93]
Cardiac fibroblasts	TRPM7; TRPV4; Piezo1	Matrix stiffness; interstitial strain	TGF-β/Smad; p38 MAPK/IL-6; myofibroblast differentiation	Myocardial fibrosis; stiffening; arrhythmogenic substrate (especially atrial fibrillation)	[33-35,94]
Perivascular sensory neurons and macrophages	TRPV1 (neurons); Piezo1 (macrophages)	Cardiac distension; ischemic metabolites; cyclic hydrostatic pressure	CGRP/SP release; cardiac sympathetic afferent reflexes; Piezo1 → NF-κB/inflammasome	Sustained sympathetic excitation; neuroinflammation; progression of fibrosis and hypertrophy	[68,69,95]

Table 3. Mechanosensitive and non-canonical ion channels in the cardiovascular system: distribution, activation, downstream signaling, and pharmacological modulators

Channel	Principal cellular distribution	Activating stimuli	Major downstream signaling pathways	Agonists	Antagonists	References
TRPC1	Cardiomyocytes; endothelial cells	Store depletion; membrane stretch; GqPCR	Ca^{2+} influx → calcineurin/NFAT; hypertrophic transcription	(No selective agonist)	SKF-96365; 2-APB (non-selective)	[63,96]
TRPC3	Cardiomyocytes; vascular smooth muscle	DAG (OAG); mechanical stretch; GqPCR	Calcineurin/NFAT; Nox2 stabilization → ROS amplification	OAG	Pyr3; SAR7334	[7,31,64]
TRPC6	Cardiomyocytes; vascular smooth muscle	Membrane stretch; DAG; Ang II/GqPCR	Calcineurin/NFAT positive feedback loop; fibrotic signaling	OAG; flufenamic acid	Larixyl acetate; SAR7334; BI 749327	[32,64,97,98]
TRPV1	Perivascular sensory neurons; cardiomyocytes	Capsaicin; high temperature (> 42 °C); protons; anandamide	Neuropeptide (CGRP) release; CaMKII; sympathetic afferent activation	Capsaicin; resiniferatoxin	Capsazepine; SB-366791	[68,69]
TRPV2	Cardiomyocytes	Membrane stretch; insulin/IGF signaling	Ca^{2+} overload; structural maintenance and degeneration	2-APB (non-selective)	Tranilast; SKF-96365	[66]
TRPV3	Cardiomyocytes; endothelial cells	Camphor; carvacrol; high temperature	Calcineurin/NFATc3; hypertrophic signaling	Camphor; carvacrol	(No selective antagonist)	[67]
TRPV4	Endothelial cells; cardiac fibroblasts; cardiomyocytes	Shear stress; osmotic/mechanical stretch; EET	eNOS/EDH-mediated vasodilation; TGF-β-dependent fibroblast differentiation; CaMKII	GSK1016790A; 4α-PDD	HC-067047; GSK2193874	[15,34,65,99]
TRPM4	Cardiomyocytes; vascular smooth muscle	Elevated $[Ca^{2+}]i$; membrane stretch	Depolarization → CaMKII and calcineurin activation; myogenic tone	(No selective agonist)	9-Phenanthrol; flufenamic acid	[70,92]
TRPM7	Cardiomyocytes; cardiac fibroblasts	Mg^{2+} depletion (Mg^{2+} inhibition); mechanical stretch	Kinase-dependent signaling; TGF-β/Smad profibrotic signaling; conduction/repolarization	Naltriben	Waixenicin A; NS8593; 2-APB	[33,71,72]
Piezo1	Cardiomyocytes; endothelial cells; fibroblasts; macrophages	Membrane tension; shear stress; cyclic hydrostatic pressure	Calpain/calcineurin/NFAT; CaMKII/HDAC4/MEF2; p38 MAPK/IL-6; innate immunity	Yoda1; Jedi1/2	GsMTx4; Dooku1 (Yoda1 antagonist); ruthenium red (non-selective)	[1,77,95,100-102]
NMDAR	Cardiomyocytes; endothelial cells	Glutamate + glycine/D-serine (co-agonists)	Sustained Ca^{2+} influx; mitochondrial dysfunction/ROS; NF-κB; AKT1-TBX3-Nav1.5	NMDA; glutamate	Memantine; MK-801; ketamine; Mg^{2+} (voltage-dependent block)	[9,36,81,86]

The TRP channel family

TRP channels constitute an important class of non-selective cation channels, first identified in Drosophila melanogaster in 1969; in 2004, the TRP family was classified into seven subfamilies. Channels widely expressed in human tissues include TRPC, TRPV, TRPM, TRPA, TRPP, and TRPML, and corresponding channels are also present in the cardiovascular system. Among them, members of the TRPC, TRPV, and TRPM subfamilies play key roles in mechanosensing. TRP channels typically exist as homo- or heterotetramers, with each subunit containing six transmembrane domains; the intracellular N- and C-termini harbor multiple regulatory sites that respond to diverse stimuli such as mechanical force, temperature, and chemical agents, hence their designation as "polymodal sensors." These channels exhibit varying degrees of Ca^{2+} permeability, and mechanically induced channel opening can mediate extracellular Ca^{2+} influx, elevating intracellular Ca^{2+} concentration and initiating downstream signaling cascades[7,60].

It is now generally accepted that, under mechanical stretch, TRP channels respond to mechanical stimuli by mediating Ca^{2+} influx, thereby activating the CaMKII and NFAT pathways. Following NFAT translocation into the nucleus, the expression of hypertrophy-associated genes (such as ANP and BNP) is upregulated,

promoting cardiomyocyte hypertrophy. In addition, Ca^{2+} influx can also activate signaling pathways such as MAPK and PI3K/Akt, which synergistically regulate the progression of cardiac hypertrophy; this constitutes an important component of the calcium-dependent mechanisms driving pathological cardiac hypertrophy[61,62].

The TRPC subfamily

The TRPC subfamily is an important subgroup of TRP channels involved in regulating calcium signaling. Seven TRPC channel isoforms exist in mammals, and their activity is enhanced predominantly under pathological conditions. Among them, TRPC1, TRPC3, and TRPC6 are canonical mechanosensitive members highly expressed in cardiomyocytes. Studies employing patch-clamp electrophysiology combined with mechanical stretch stimulation and TRPC knockout mice have confirmed that TRPC1, TRPC3, and TRPC6 can respond to mechanical stretch, undergo conformational changes, mediate Ca^{2+} influx, activate CaMKII, and induce cardiomyocyte hypertrophy[41,63]. Mechanistically, TRPC6 is a core component of the calcineurin signaling circuit in pathological cardiac remodeling: calcineurin/NFAT activation upregulates TRPC6 expression, and the resulting Ca^{2+} influx further activates calcineurin, forming a positive feedback loop that sustains hypertrophic growth; pharmacological or genetic co-blockade of TRPC3 and TRPC6 suppresses pathological cardiac hypertrophy in mice[32,64]. Beyond transcriptional regulation, TRPC3 stabilizes Nox2 and amplifies ROS generation under mechanical stress, forming a TRPC3-Nox2 feed-forward loop that drives adverse remodeling and interstitial fibrosis[31].

The TRPV subfamily

TRPV subfamily members (such as TRPV1, TRPV3, and TRPV4) possess both mechanosensitivity and chemosensitivity, among which TRPV4 is a relatively well-characterized mechanosensitive channel. Microperfusion-based simulation studies have revealed that TRPV4 mediates Ca^{2+} influx in response to mechanical stimuli such as blood flow shear stress and osmotic pressure changes: in vascular endothelial cells, basal Ca^{2+} influx events through TRPV4 channels (TRPV4 sparklets) activate Ca^{2+}-sensitive K^+ channels, producing endothelium-dependent hyperpolarization and vasodilation—a mechanism that is an important determinant of vascular resistance and blood pressure[65]. TRPV2 is a stretch-sensitive channel in cardiomyocytes; its genetic deletion leads to dilated cardiomyopathy, whereas its pathological overactivation promotes Ca^{2+} overload and myocyte degeneration, indicating that TRPV2 is essential for maintaining cardiac structure and function[66]. Furthermore, TRPV3 channel activation can enhance CaMKII activity via a calmodulin-dependent pathway, affect the calcineurin/NFATc3 pathway, and aggravate cardiac hypertrophy in rats[67]; pharmacological TRPV1 antagonism attenuates cardiac hypertrophy and heart failure in mice, although the relative contributions of cardiomyocyte versus neuronal TRPV1 pools remain to be fully elucidated[68,69].

The TRPM subfamily

TRPM subfamily members display structural and functional diversity, and TRPM4 and TRPM7 have been shown to be mechanosensitive. TRPM4 is a Ca^{2+}-activated non-selective cation channel. Studies using a pressure overload-induced mouse model of cardiac hypertrophy combined with TRPM4 knockout mice have found that this channel is upregulated in pressure overload-induced cardiac hypertrophy; by modulating membrane potential (mediating Na^+ influx that causes depolarization) and Ca^{2+} homeostasis (affecting L-type calcium channel activity), it activates the CaMKII signaling pathway and promotes the development of cardiac hypertrophy[70]. TRPM7 is a bifunctional protein possessing both ion channel and protein kinase activities; it can mediate Ca^{2+} influx in response to mechanical load and regulate the downstream Rac1/Cdc42 and ERK pathways through its kinase domain, thereby modulating cardiomyocyte proliferation and differentiation and playing a role in cardiovascular remodeling; indeed, differences in the timing of Trpm7

deletion during cardiogenesis can disrupt ventricular function, conduction, and repolarization in adult mice to varying degrees, indicating that TRPM7 is indispensable for maintaining normal cardiac electrophysiology and structure[71]. Mechanosensitive activation of TRPM subfamily members can regulate ionic homeostasis, providing the ionic foundation required to initiate downstream hypertrophic signaling pathways[72].

In addition, Ca^{2+} influx mediated by mechanosensitive TRP channels can induce ROS generation. Studies using fluorescent probes show that mitochondrial dysfunction is a major source of ROS generation; mechanically induced calcium signaling and ROS generation exert synergistic effects in pathological cardiovascular remodeling, and TRP channel-mediated Ca^{2+} influx is a critical link in this process. Cardiac ion channel dysfunction leads to intracellular calcium overload, causing mitochondrial damage and massive ROS release, while high ROS concentrations stimulate the endoplasmic reticulum and induce endoplasmic reticulum stress. After PERK phosphorylation, eIF2α is inactivated, which in turn selectively upregulates ATF4; ATF4 then promotes the expression of fibrosis-related genes and drives fibroblast proliferation, activation, and collagen secretion. Concurrent with activation of the PERK/ATF4 signaling pathway, ROS can also inhibit potassium channel activity and activate TRP channels through oxidative modification, further aggravating intracellular calcium overload and forming a vicious cycle of "ROS generation-calcium overload-ROS generation" that continuously drives fibroblast activation and the progression of myocardial fibrosis[24,25,30].

The Piezo1 channel

Piezo1 was identified as a mechanosensitive cation channel in 2010 and is now regarded as one of the best-characterized ion channels for direct mechanosensitivity. Its core function is to directly sense mechanical stimuli such as mechanical stretch and membrane tension, mediating Ca^{2+} influx and initiating downstream signal transduction, thereby playing a key role in maintaining cardiovascular physiological homeostasis[8,73].

The unique trimeric propeller-like structure of Piezo1 enables it to directly sense tension changes in the lipid bilayer: when a cell is subjected to mechanical stretch or shear force, alterations in membrane tension act directly on the transmembrane domains of Piezo1, triggering rapid conformational changes and channel opening—a process that does not require the participation of the cytoskeleton or auxiliary proteins and is termed the "force-from-lipids" or direct mechanical activation model. The landmark 2010 study by Coste *et al.*[73], which screened for mechanosensitive currents using whole-cell patch-clamp techniques, first demonstrated the mechanoactivation properties of Piezo1[73]. Subsequent studies demonstrated in lipid bilayer reconstitution experiments that, after purified Piezo1 protein was reconstituted into artificial lipid membranes, channel-opening currents could be recorded upon application of membrane tension alone, establishing the molecular basis of its role as a "direct mechanosensor"[74,75].

As a non-selective cation channel with relatively high Ca^{2+} permeability, Piezo1 mediates rapid extracellular Ca^{2+} influx upon mechanically induced opening, elevating intracellular Ca^{2+} concentration and thereby activating multiple downstream signaling pathways. Upon mechanical stimulation, activated Piezo1 induces Ca^{2+} influx, disrupting intracellular calcium homeostasis. Intracellular Ca^{2+} binds to CaM, which in turn activates calcineurin (CaN) and CaMKII. Calcineurin promotes NFAT nuclear translocation and forms a feedback loop with the negative regulator RCAN1; meanwhile, CaMKII phosphorylates HDAC4 and promotes its nuclear export, thereby relieving the repression of the MEF2 transcription factor and ultimately inducing cardiac hypertrophy. In addition, Piezo1 can regulate the expression of the Ca^{2+}-activated TRPM4 protein in cardiomyocytes, thereby further amplifying the CaMKII/HDAC4/MEF2 pathway and promoting cardiac hypertrophy[1,70,76].

Two complementary landmark studies established Piezo1 as the principal cardiac mechanosensor that initiates the hypertrophic response. Using cardiomyocyte-specific Piezo1 knockout and overexpression mouse models, Yu *et al.*[1] demonstrated that Piezo1 is both necessary and sufficient for the hypertrophic response to pressure overload: cardiomyocyte-specific Piezo1 knockout protected mice from transverse aortic constriction-induced hypertrophy and fibrosis, whereas cardiomyocyte-specific Piezo1 overexpression was sufficient to induce hypertrophy even in the absence of mechanical stress; mechanistically, Piezo1-mediated Ca^{2+} influx activates both the CaMKII/HDAC4/MEF2 and calcineurin/NFAT signaling axes, driving hypertrophic gene transcription[1,2]. Zhang and colleagues independently demonstrated that Piezo1-mediated mechanotransduction promotes cardiac hypertrophy by impairing intracellular Ca^{2+} homeostasis and activating calpain/calcineurin signaling, and that Piezo1 is upregulated in both mouse and human hypertrophic myocardium[77]. Consistent with these loss-of-function and gain-of-function data, mice carrying a systemic gain-of-function PIEZO1 mutation spontaneously develop cardiac hypertrophy and fibrosis, further supporting a causal role for enhanced Piezo1 activity in adverse remodeling[78].

The direct mechanosensitive properties and Ca^{2+} regulatory functions of Piezo1 make it a critical molecular link connecting mechanical stimuli to cellular responses, playing an indispensable role in maintaining cardiovascular homeostasis. In the vascular system, Piezo1 integrates mechanical signals with physiological mechanics: endothelial Piezo1 senses shear stress and is essential for normal vascular development and the alignment of endothelial cells along the direction of blood flow[79,80].

Non-canonical ion channels: the N-methyl-D-aspartate receptor (NMDAR)

The N-methyl-D-aspartate receptor (NMDAR) belongs to the ligand-gated ion channel family; its canonical function is to mediate excitatory neurotransmission in the central nervous system (CNS) and to participate in the long-term regulation of synaptic plasticity. In recent years, studies employing immunohistochemistry, Western blot, and RT-PCR techniques have confirmed that NMDAR is also stably expressed in the cardiovascular system, mainly distributed in the cardiac conduction system and working cardiomyocytes, representing an important non-canonical calcium ion channel that regulates cardiac function[9,81].

NMDAR exhibits markedly high Ca^{2+} permeability and displays slow inactivation kinetics, which is closely related to its ability to maintain prolonged open states[82,83]. The high calcium permeability and slow inactivation of NMDAR are directly determined by its molecular structure: a conserved glycine on the M4 transmembrane helix of the GluN1 subunit maintains the channel pore diameter and long-term open state through a hinge-like effect, directly determining the channel's calcium permeability and inactivation rate[84]. Studies combining site-directed mutagenesis with electrophysiological recordings have shown that mutating this site significantly reduces calcium ion permeability and accelerates channel inactivation. Voltage-dependent calcium channels achieve high selectivity and high conductance for calcium ions through two high-affinity calcium-binding sites; by contrast, NMDAR contains only a single low-affinity calcium-binding site. Although its Ca^{2+} selectivity is relatively low, the lower binding affinity slows the ion dissociation rate, allowing it to sustain a robust Ca^{2+} influx.

Under physiological conditions, NMDAR expressed in myocardial tissue helps regulate normal cardiac rhythm and cardiomyocyte excitability, maintaining cardiac electrophysiological homeostasis. Excessive NMDAR activation can induce electrical abnormalities such as atrial fibrillation and ventricular arrhythmias, contribute to the progression of heart failure, and promote the formation of an arrhythmogenic substrate[36,85].

Studies in cultured neonatal rat cardiomyocytes have found that NMDAR activation triggers substantial Ca^{2+} influx that specifically targets mitochondria, leading to mitochondrial calcium overload, mitochondrial dysfunction, oxidative stress, and apoptosis[86]. The calcium load model holds that acute cell death correlates

with the absolute amount of Ca^{2+} influx, whereas the pathway-specific hypothesis suggests that lethality depends more critically on how or where calcium enters the cell rather than on the absolute amount of calcium influx. NMDAR-mediated Ca^{2+} influx is accompanied by more pronounced mitochondrial calcium accumulation and greater toxicity, reflecting differences in the degree of calcium load mediated by distinct Ca^{2+} influx pathways. Meanwhile, studies have found that calcium accumulation is accompanied by upregulated ROS generation, and this mitochondrial Ca^{2+} overload is a recognized determinant of heart failure progression, disrupting energy metabolism and promoting cell loss[87]. Furthermore, by detecting mitochondrial permeability transition pore opening and mitochondrial matrix metalloproteinase (MMP)-2/9 activity, it was found that MMP activation and mitochondrial dysfunction can disrupt intracellular Ca^{2+} homeostasis, thereby triggering arrhythmias—a phenomenon that may relate to NMDAR-mediated sustained Ca^{2+} signaling[88]. Additional studies employing specific NMDAR antagonists combined with cardiomyocyte-specific knockdown of NMDAR subunits, whole-cell patch-clamp recording of sodium current (I_Na), Western blot analysis of the AKT1/TBX3 pathway, and electrocardiographic repolarization parameter analysis have demonstrated that pathological activation of cardiac N-methyl-D-aspartate (NMDA) receptors can activate AKT1 and upregulate the expression of the transcription factor TBX3, thereby impairing Nav1.5 function, reducing sodium current, slowing cardiac conduction, prolonging ventricular repolarization, increasing repolarization heterogeneity, and reducing repolarization reserve. At the same time, this process also promotes the expression of fibrosis-related genes. Together, these mechanisms generate a dual structural and electrophysiological arrhythmogenic substrate. Moreover, sustained Ca^{2+} influx mediated by NMDAR activation can lead to intracellular calcium overload, triggering oxidative stress and mitochondrial dysfunction and further exacerbating ion channel dysfunction.

As an ionotropic glutamate receptor, NMDAR-mediated sustained Ca^{2+} influx also plays an important role in cardiac hypertrophy. Studies have shown that the NMDAR antagonist memantine can effectively prevent thyroxine-induced hypertension but cannot completely block the development of cardiac remodeling, suggesting that sustained Ca^{2+} signaling may be only one component of the hypertrophic mechanism and that other signaling pathways may also participate in this process[89].

Cell type-specific functions of ion channels in cardiac remodeling

Because the myocardium is a multicellular tissue, mechanosensitive and ECC-related channels exert distinct effects on the principal cell types in which they act, and the net effect of any given channel on cardiac remodeling reflects the sum of its actions across different cell populations [Figure 2].

Cardiomyocytes

Cardiomyocytes express the full complement of ECC channels (Nav1.5, LTCC, RyR2, NCX1) as well as mechanosensitive channels including TRPC1/3/6, TRPV2, TRPM4, TRPM7, Piezo1, and NMDAR. In these cells, mechanical stress activates Piezo1 and TRPC channels to produce sustained Ca^{2+} influx, mobilizing calcineurin/NFAT and CaMKII/HDAC signaling to drive hypertrophic growth, while channel-ROS feedback loops amplify this response and promote electrical instability (see Section "CONVENTIONAL SIGNALING PATHWAYS" and Sections "The TRP channel family"-"Non-canonical ion channels: the NMDAR" for details)[1,31,32,70].

Endothelial cells

Endothelial cells are the frontline sensors of hemodynamic forces. Endothelial TRPV4 channels generate basal Ca^{2+} influx events (TRPV4 sparklets) that activate intermediate- and small-conductance Ca^{2+}-sensitive K^+ channels, producing endothelium-dependent hyperpolarization and vasodilation; this mechanism is a major determinant of vascular resistance and blood pressure[65]. Endothelial Piezo1 senses shear stress and is essential for normal vascular development and the alignment of endothelial cells along the direction of blood

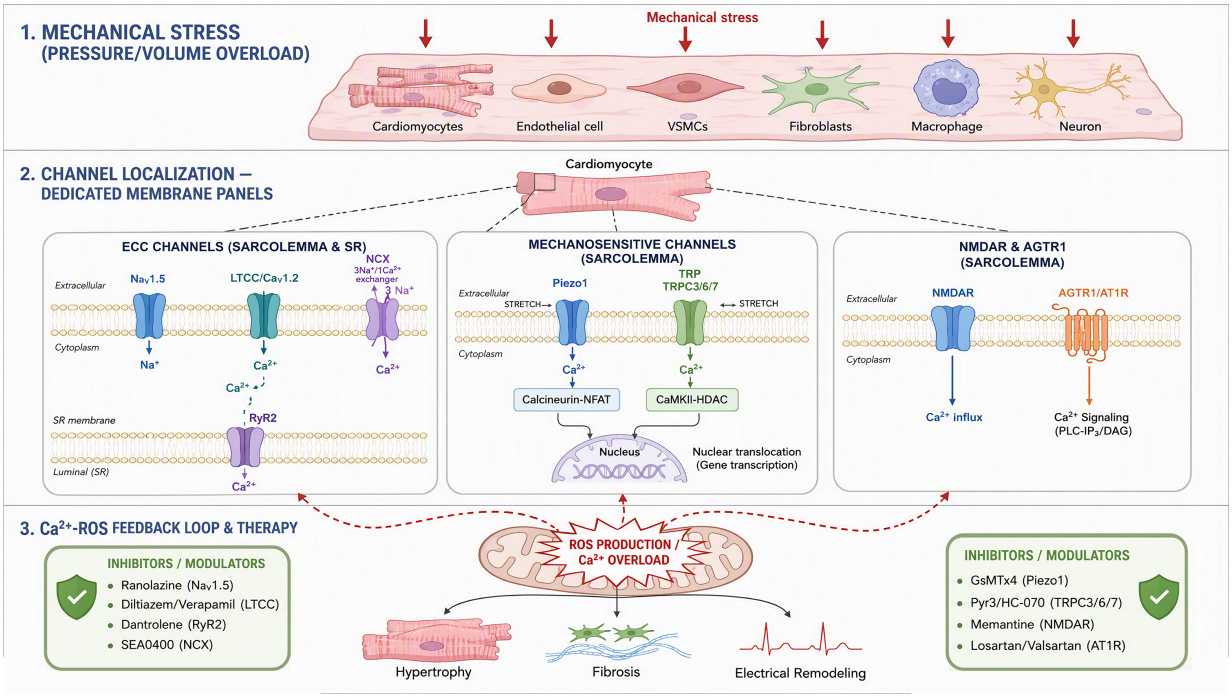

Figure 2. Cell-type-specific ion channel mechanisms of mechanical stress-induced cardiac remodeling. Pressure and volume overload generate mechanical stress that activates distinct ion-channel repertoires in cardiomyocytes, endothelial cells, vascular smooth muscle cells, cardiac fibroblasts, and perivascular sensory neurons and macrophages. Channel-mediated Ca^{2+}/Na^{+} influx engages downstream signaling (calcineurin/NFAT, CaMKII/HDAC/MEF2, EDH-dependent vasodilation, myogenic tone, TGF-β/Smad-dependent fibrogenesis, sympathetic afferent activation, and innate immune activation). Mitochondrial Ca^{2+} overload generates ROS, which feedback to enhance channel activity through CaMKII oxidation, RyR2 oxidation, TRP S-nitrosylation, TRPC3-Nox2 coupling, and Na^{+}-dependent mitochondrial ROS, forming self-reinforcing loops that drive hypertrophy, fibrosis, electrical remodeling, and vascular/neuro-immune dysfunction; candidate channel-directed therapeutic strategies are indicated at the bottom. The figure was created with Matplotlib (Python) and Adobe Illustrator.

flow; its disruption impairs vascular remodeling and angiogenesis[79,80]. Endothelial TRPC channels (TRPC1, TRPC3, TRPC5) also participate in angiogenesis, barrier function, and vasomotor regulation, and their dysfunction contributes to the microvascular abnormalities accompanying cardiac overload states[90,91].

Vascular smooth muscle cells (VSMCs)

In VSMCs, mechanosensitive channels regulate myogenic tone and structural adaptation of the vessel wall. TRPM4 is indispensable for pressure-induced myogenic constriction of cerebral and peripheral arteries, coupling membrane stretch to depolarization and Ca^{2+} influx through VGCCs[92]. Piezo1 is expressed in VSMCs and participates in hypertension-dependent arterial remodeling: smooth muscle Piezo1 activity promotes Ca^{2+}-dependent transglutaminase activation and extracellular matrix cross-linking, thereby increasing arterial stiffness and amplifying cardiac afterload—an extracardiac mechanism by which mechanosensitive channels aggravate cardiac pressure overload[93]. VSMC TRPC channels (particularly TRPC6) also mediate agonist- and stretch-induced Ca^{2+} influx and vascular hyperreactivity in hypertension[90].

Cardiac fibroblasts

Cardiac fibroblasts lack contractile filaments but are rich in mechanosensitive channels that convert matrix mechanics into profibrotic signals. TRPM7-mediated Ca^{2+} signaling confers profibrotic properties on human atrial fibroblasts, and TRPM7 is upregulated in fibroblasts from patients with atrial fibrillation, linking channel activity to the fibrotic substrate of arrhythmias[33]. TRPV4 channels mediate the differentiation of

cardiac fibroblasts into myofibroblasts by integrating mechanical and soluble (e.g., TGF-β) signals, promoting extracellular matrix deposition and myocardial stiffness[34]. Piezo1 in human atrial fibroblasts regulates cellular mechanical properties and matrix stiffness sensing and stimulates p38 MAPK-dependent interleukin-6 secretion, coupling mechanical stress to paracrine inflammatory amplification in the remodeling heart[35,94].

Perivascular sensory neurons and macrophages

Perivascular sensory neurons expressing TRPV1 and other TRP channels innervate the heart and coronary vessels, sense mechanical and chemical stimuli, and release neuropeptides such as calcitonin gene-related peptide (CGRP). In heart failure, enhanced cardiac sympathetic afferent activity—partly dependent on TRPV1-expressing afferent fibers—sustains sympathetic excitation; targeted ablation of these TRPV1-expressing cardiac sympathetic afferent fibers with resiniferatoxin attenuates cardiac remodeling and improves cardiovascular dysfunction in rats with heart failure, revealing a neurogenic contribution to adverse remodeling[68,69]. Cardiac macrophages, in turn, express Piezo1, which senses cyclic hydrostatic pressure and is essential for innate immune activation; Piezo1-mediated mechanosensing in myeloid cells couples tissue mechanics to inflammatory gene expression, thereby modulating the inflammatory phase of cardiac remodeling[95].

THERAPEUTIC TARGETS AND ADVANCES IN PHARMACOLOGICAL RESEARCH

The mechanistic insights described above identify several nodes at which ion channel function can be therapeutically targeted. This section summarizes the major channel-targeting strategies and then stratifies them by disease context and evidence level [Table 4]. At the outset, note that, except for CCBs, most of these strategies remain at the preclinical stage. Preclinical evidence includes TRPC inhibition in ischemic heart disease and pressure-overload hypertrophy[96-98], TRPV4 blockade in heart failure[99], and Piezo1 modulators such as Yoda1, GsMTx4, and Dooku1[100-102].

CCBs

CCBs share a common mechanism of action: they exert their therapeutic effects by reducing calcium influx across the membrane. They are broadly divided into two subclasses: dihydropyridines (DHPs) and non-dihydropyridines (non-DHPs). These two drug classes have comparable antihypertensive efficacy but differ markedly in their pharmacological properties. DHP CCBs generally have stronger vasodilatory effects than non-DHP agents, whereas non-dihydropyridines have stronger negative chronotropic and negative inotropic effects, making them more suitable for patients with concomitant arrhythmias or those requiring β-blocker therapy. Dihydropyridines are indicated for hypertension, chronic stable angina, and vasospastic angina; non-dihydropyridines are likewise indicated for atrial fibrillation or atrial flutter and paroxysmal supraventricular tachycardia, and possess additional antiarrhythmic properties. The two subclasses have similar blood-pressure-lowering capacity; however, non-DHPs may offer advantages in managing chronic kidney disease and diabetic nephropathy, including antiproteinuric effects not replicated by DHPs; these effects may slow the progression of kidney disease[103-105].

CCBs have broad antihypertensive efficacy unaffected by sex, race, age, or dietary sodium intake, and they are approved to treat hypertension, angina, arrhythmias, and other conditions. Although CCB monotherapy has declined with the advent of newer antihypertensive agents, they have now become foundational components of many fixed-dose combination regimens, with the potential to improve blood pressure control and reduce cardiovascular event risk. CCBs remain first-line agents for hypertension and, compared with other antihypertensive drug classes, reduce the risk of adverse cardiovascular events, stroke, cardiovascular death, and myocardial infarction. They are well tolerated, with relatively few side effects, and can be used

Table 4. Channel-targeted therapeutic strategies stratified by disease context and evidence level

Disease context	Candidate strategies (targets)	Representative drugs/interventions	Rationale	Evidence level	References
Pressure overload (hypertension, aortic stenosis)	Piezo1 inhibition; TRPC3/6 blockade; TRPM4 inhibition; RyR2 stabilization; AGTR1 blockade (inverse agonists)	GsMTx4; larixyl acetate; SAR7334; dantrolene; ARBs	Block mechanosensitive Ca^{2+} influx and calcineurin/NFAT activation; stabilize SR Ca^{2+} release; inhibit stretch-induced AGTR1 signaling	Cellular and animal models; Piezo1 upregulation confirmed in human hypertrophic myocardium	[1,14,64,70,77,97,114]
Volume overload (valvular regurgitation)	TRPV4 modulation; ECC channel monitoring; mechanosensor profiling	TRPV4 antagonists (preclinical); (no validated channel therapy yet)	Diastolic stretch recruits TRPV4 and mechanosensitive pathways; ECC channel regulation understudied	Cellular and animal models; direct comparative data lacking	[10,11,15]
HFrEF	RyR2 stabilization; NCX/INa,L modulation; NMDAR antagonism (exploratory); CCBs contraindicated in overt HFrEF	Dantrolene; SEA0400; memantine (preclinical)	Correct SR Ca^{2+} leak, Na^{+}-dependent mitochondrial ROS, and excitotoxic Ca^{2+} influx	Animal model and human tissue data; no positive clinical trials for novel targets yet	[27,58,105,112,114]
HFpEF	Fibroblast-targeted TRPM7/TRPV4/Piezo1 inhibition; ROS-targeted antioxidants; endothelial TRPV4 blockade	HC-067047/GSK2193874; SS-31; mitoTEMPO (preclinical)	Attenuate fibrosis, myocardial stiffness, microvascular edema, and oxidative stress	Cellular and animal models; correlational evidence for TRPM7 in human atrial fibrosis	[33,34,99,117]
Ischemic heart disease	NMDAR blockade; TRPC inhibition; NCX inhibition	Memantine; SKF-96365-class compounds; SEA0400 (preclinical)	Limit ischemia-induced excitotoxic Ca^{2+} influx, Nav1.5 downregulation, and reperfusion Ca^{2+} overload	Cellular and animal models; human relevance unconfirmed	[36,96,116]

safely in the management of hypertension and angina; however, their use is associated with an increased risk of heart failure. In addition, CCB toxicity warrants attention because it can cause substantial morbidity and mortality; specific antidotal treatments are available, including intravenous calcium, glucagon, and high-dose insulin/euglycemic glucose regimens[106-109]. Nevertheless, the negative inotropic effects of non-dihydropyridine CCBs render them contraindicated in established heart failure with reduced ejection fraction, so their role is largely limited to prevention rather than reversal of remodeling[105].

Mechanosensitive channel modulators: Piezo1 and TRP channels

Pharmacological tools targeting mechanosensitive channels are being developed rapidly, although none has yet entered clinical trials for cardiac remodeling. For Piezo1, the spider venom peptide GsMTx4 blocks cation-selective mechanosensitive channels and is widely used in studies of Piezo1 function; the small molecule Yoda1 is a selective Piezo1 agonist, and its analog Dooku1 antagonizes Yoda1-evoked activation—these compounds constitute lead pharmacophores for future Piezo1-targeted drug development[100-102]. For TRP channels, combined blockade of TRPC3/TRPC6—whether by genetic means or with selective small molecules—suppresses pathological cardiac hypertrophy in mice; the natural diterpene larixyl acetate (a TRPC6 inhibitor) attenuates pressure overload-induced heart failure; and endogenous natriuretic peptide signaling also exerts antihypertrophic effects by inhibiting TRPC6 channel activity[64,97,98]. Within the TRPV subfamily, the TRPV4 antagonist GSK2193874 prevents and reverses pulmonary edema in experimental heart failure by normalizing endothelial barrier function, demonstrating the translational potential of vascular TRPV4 blockade; TRPV1 antagonism, in turn, attenuates hypertrophy and heart failure in mice through mechanisms that may involve both cardiac and neuronal TRPV1 pools[68,99].

NMDAR antagonists

The NMDA receptor is a subtype of glutamate receptor that regulates synaptic plasticity and intracellular Ca^{2+} homeostasis. Its uncontrolled activation leads to Ca^{2+} overload, causing cell contraction and alterations in intracellular pH. Uncontrolled NMDAR activation is a key factor in synaptic dysfunction. Targeting NMDA receptors with antagonists is a promising therapeutic strategy for neurological diseases, and studies in a variety of brain disorders have demonstrated favorable therapeutic effects. Memantine is an NMDA receptor antagonist clinically approved for the treatment of moderate-to-severe Alzheimer's disease and is currently the only NMDA receptor antagonist marketed for this indication. It improves symptoms but cannot cure the disease or halt its progression. Multiple NMDA receptor antagonists (including ketamine and MK-801) have shown therapeutic potential in experimental models of stroke, epilepsy, Parkinson's disease, and other encephalopathies[110,111].

Beyond their roles in the CNS, NMDA receptor activation also contributes to myocardial disease pathogenesis. Memantine exerts cardioprotective effects in heart failure (HF) by attenuating cardiac remodeling, lipid peroxidation, and neutrophil infiltration. Memantine may also enhance the chemotherapeutic efficacy of doxorubicin while reducing doxorubicin-induced cardiac oxidative stress and inflammation[112,113]. However, the efficacy of NMDAR blockade appears to be context-dependent: in a thyroxine-induced model, memantine prevented hypertension but not the associated cardiac remodeling; and to date, no clinical trials of NMDAR antagonists for cardiac disease have been reported. These agents should therefore be regarded as hypothesis-generating candidate strategies whose utility will depend on disease drivers and require confirmation in human tissue and clinical studies[9,89].

RyR2 stabilizers

Because excessive RyR2 phosphorylation and oxidation increase SR Ca^{2+} leak in hypertrophy and heart failure, stabilizing RyR2 is a mechanistically rational strategy. Dantrolene, the classic RyR inhibitor used for malignant hyperthermia, stabilizes inter-domain interactions within RyR2 and markedly improves both failing cardiomyocyte and whole-heart function in animal models of heart failure, correcting Ca^{2+}-handling defects without suppressing physiological Ca^{2+} release[114]. More recent work shows that pharmacological RyR2 stabilization attenuates cardiac hypertrophy in pressure overload models by downregulating the TNF-α/NF-κB/NLRP3 inflammatory axis via calcineurin inhibition, linking correction of SR Ca^{2+} leak to anti-inflammatory and antihypertrophic effects[115]. These findings position RyR2 stabilizers as candidate agents with both structural and arrhythmic endpoints, although their effects in human myocardium and clinical settings remain to be established.

Modulation of the NCX

NCX1 is upregulated in hypertrophy and heart failure and contributes to contractile dysfunction and arrhythmogenesis, making NCX a long-standing therapeutic candidate[58,59]. Selective NCX inhibitors such as SEA0400 preferentially block reverse-mode (Ca^{2+} influx) exchange, attenuate Ca^{2+} overload-related injury in experimental models, and show antiarrhythmic efficacy in the setting of triggered activity[59,116]. However, the bidirectionality of NCX flux means that the net effect of inhibitors depends on cellular Na^+ load and membrane potential, and clinical translation has been limited by concerns about suppressing forward-mode Ca^{2+} extrusion in the failing heart[58]. Targeting intracellular Na^+ homeostasis upstream of NCX—for example, by reducing INa,L—is a complementary strategy that can simultaneously reduce mitochondrial oxidative stress and Ca^{2+} overload[26,27].

ROS-targeted interventions

Given the channel-ROS mutual amplification loop described in Section "Ion channels and cardiac remodeling: the Ca^{2+}-Na^+-ROS signaling triad", blocking oxidative stress at its source is an attractive adjunctive strategy. Mitochondria-targeted antioxidants have shown the most consistent cardiac efficacy: the

mitochondria-targeted peptide SS-31 (elamipretide) improves hypertensive cardiomyopathy in mice by preserving mitochondrial function, and scavenging mitochondrial superoxide with mitoTEMPO reduces vascular oxidative stress and blood pressure in experimental hypertension[117,118]. By lowering ambient ROS levels, such interventions are expected to secondarily normalize the redox state of RyR2, CaMKII, and TRP channels, thereby breaking the Ca^{2+}-ROS feed-forward cycle[28-30]. It should be noted, however, that non-targeted antioxidant vitamins have repeatedly failed in cardiovascular outcome trials, and the benefit of ROS-targeted therapy most likely depends on the subcellular localization and timing of the intervention[117,118].

Combined multi-node intervention

Intracellular calcium overload contributes to the pathogenesis of multiple cardiovascular diseases. Conventional CCBs reduce calcium influx by blocking L-type voltage-gated calcium channels (LTCCs) and are classic treatments for hypertension and angina. NMDARs are also expressed in the heart, and their overactivation mediates pathological calcium influx, triggering calcium overload. These two calcium influx systems form an interactive network under pathological conditions. CCBs and NMDAR antagonists target voltage-gated and ligand-gated calcium influx pathways, respectively, and their combined application could achieve multi-node blockade of calcium overload.

Because mechanical stress activates multiple Ca^{2+}-permeable pathways in parallel, simultaneously modulating multiple nodes may in theory yield additive protection. In isolated rat heart preparations, combined application of verapamil and glutamatergic modulation affected cardiac dynamics, coronary flow, and oxidative stress indices, providing preliminary proof of concept for combined targeting of LTCCs and glutamate receptors[119]. Combined regimens of CCBs and NMDAR antagonists are strictly hypothesis-generating: no controlled animal or clinical study has tested this combination for cardiac remodeling, and both drug classes have hemodynamic adverse effects (hypotension, bradycardia) that may be additive. Any future evaluation should therefore begin with rigorously designed preclinical studies in well-defined overload models, explicitly assessing effects independent of blood pressure changes, before clinical translation can be considered[89,112].

Stratification by disease context and evidence level

The therapeutic relevance of individual channel targets varies with the underlying disease context—pressure overload, volume overload, ischemic heart disease, or heart failure with reduced (HFrEF) or preserved (HFpEF) ejection fraction—and with the evidence level (which we categorize as cellular, animal model, human tissue, or clinical evidence) [Table 4]. Several overall patterns emerge. First, the evidence base is strongest for pressure overload models: cardiomyocyte Piezo1, TRPC3/6, TRPM4, and RyR2 have all been validated genetically and pharmacologically in animals, and upregulation of Piezo1 and TRPM7 has been corroborated in human hypertrophic and fibrillating myocardium[1,33,70,77]. Second, for HFrEF, the channel-targeting candidates with the most advanced translational prospects are RyR2 stabilizers and NCX/INa,L modulation, both supported by animal and human tissue data, whereas CCBs are contraindicated in overt HFrEF but are suitable for upstream prevention of hypertensive hypertrophy[58,105,114]. Third, for HFpEF and volume overload states—contexts characterized by diastolic dysfunction, fibrosis, and microvascular dysfunction—endothelial TRPV4, fibroblast TRPM7/TRPV4/Piezo1, and ROS-targeted interventions are biologically plausible but are currently supported mainly by animal and cellular evidence, representing an important knowledge gap[15,34,99]. Fourth, in ischemic heart disease, NMDAR blockade and TRPC inhibition have shown benefit in experimental ischemia-reperfusion and arrhythmia models, but likewise lack clinical confirmation to date[36,96]. This explicit stratification by evidence level should guide target prioritization in translational development.

DISCUSSION

This review systematically integrates the contributions of multiple ion channel families—ranging from classical voltage-gated channels to mechanosensitive and ligand-gated non-canonical receptors—to the pathophysiology of mechanical stress-induced cardiac remodeling. The central theme emerging from this integration is that cardiac remodeling is not driven by any single ion channel or signaling pathway in isolation, but rather arises from the emergent properties of a complex, multilayered mechano-calcium signaling network in which multiple channels engage in mutual functional crosstalk.

The traditional understanding of cardiac remodeling has been anchored in the LTCC-RAAS axis, with neurohumoral activation and voltage-gated Ca^{2+} influx regarded as the principal drivers of pathological hypertrophy. Although this framework has yielded important mechanistic insights and therapeutic successes—most notably establishing CCBs as first-line agents for hypertension and angina—it is increasingly clear that this model captures only part of the relevant biology. Mechanical stress, whether manifested as pressure overload or volume overload, activates a far broader repertoire of ion channels than previously appreciated[1,15]. Pressure overload predominantly engages Piezo1 and TRPC1/6 as direct mechanosensors, converting elevated wall stress into intracellular Ca^{2+} signals; whereas it has been proposed that volume overload may preferentially engage TRPV4 through sustained axial stretch, and may also involve NMDAR, direct experimental evidence for channel regulation under pure volume overload remains limited[9,15]. These distinctions are not merely academic: they carry important therapeutic implications, because the selective engagement of different channel ensembles under different hemodynamic conditions suggests that a "one-size-fits-all" channel blockade strategy may not be optimal. Within the RAAS, AGTR1 adds a receptor-level dimension to this paradigm: it can directly sense mechanical stress and activate hypertrophic ERK signaling in an angiotensin II-independent manner, thereby coupling mechanical load to RAAS-dependent growth programs even in the absence of systemic hormone generation[14,23].

The Ca^{2+}-Na^{+}-ROS triad

One of the most important unifying principles emerging from this review is a tightly integrated Ca^{2+}-Na^{+}-ROS signaling triad downstream of mechanosensitive channel activation. Mechanosensitive channel opening triggers an initial Ca^{2+} influx that activates calcineurin/NFAT and CaMKII, driving hypertrophic gene expression. Concurrently, Na^{+} influx through mechanosensitive and voltage-gated channels depolarizes the membrane, amplifying Ca^{2+} signals via reverse-mode NCX and enhanced LTCC opening. This Na^{+}-Ca^{2+} amplification loop is critical for the robustness of the hypertrophic response, but it also creates susceptibility to arrhythmogenesis. The third arm of the triad, ROS generation, is initiated by Ca^{2+}-dependent NOX activation and, critically, feeds back to enhance mechanosensitive channel activity and downstream signaling through well-defined oxidative modifications, including CaMKII methionine oxidation, RyR2 redox modification, and TRP channel S-nitrosylation[28-30]. This establishes a self-perpetuating vicious cycle of "ROS generation-calcium overload-ROS generation" that drives not only cardiomyocyte hypertrophy but also fibroblast activation and myocardial fibrosis. Two additional molecular couplings further reinforce this loop: TRPC3 stabilizes Nox2 under mechanical stress to amplify ROS generation; and elevated cytosolic Na^{+} in failing cardiomyocytes impairs mitochondrial Ca^{2+} uptake and antioxidant capacity, directly linking Na^{+} channel remodeling to oxidative stress[27,31]. The therapeutic implication is clear: effective intervention will likely require simultaneous targeting of multiple nodes within this triad, rather than isolated blockade of any single component.

Reappraising L-type calcium channels

The evidence reviewed here calls for a more nuanced re-evaluation of LTCC function in cardiac remodeling. Classically regarded as the principal gateway for pathological Ca^{2+} influx, LTCCs are now recognized to participate in a more complex regulatory architecture. Reduced LTCC activity can paradoxically promote

hypertrophy through compensatory RyR2 Ca^{2+} leak and calcineurin/NFAT activation—a finding that reveals a non-monotonic relationship between LTCC function and remodeling. Moreover, LTCCs are physically and functionally coupled to mitochondria via the cytoskeleton (F-actin, β-tubulin), and this coupling is aberrantly activated in hypertrophic cardiomyopathy models to drive mitochondrial hypermetabolism—a finding that introduces an entirely new dimension to LTCC biology. AID-variant peptides targeting the LTCC β2 subunit can dissociate this abnormal channel-cytoskeleton coupling and safely prevent the development of HCM without affecting Ca^{2+} current or blood pressure—representing a paradigm shift that suggests the structural scaffolding functions of LTCCs may be as pathologically important as their ionic conductance. Together, these findings argue for moving beyond simple LTCC blockade toward strategies that selectively modulate channel-protein interactions[12,42-45,47-49].

Type 2 ryanodine receptors

Ryanodine receptors are critical mediators of pathological remodeling, and the evidence reviewed here establishes RyR2 as an indispensable node in the hypertrophic signaling network. Gain-of-function mutations such as RyR2-R176Q cause diastolic SR Ca^{2+} leak and markedly accelerate pressure overload-induced hypertrophy and heart failure, whereas heterozygous RyR2 knockout attenuates the hypertrophic response by suppressing calcineurin, ERK, and Akt signaling. Circ-RYR2—a circular RNA derived from the RYR2 locus—is downregulated in hypertrophy and heart failure, and restoring its expression normalizes Ca^{2+} handling without altering RyR2 protein levels—a finding that introduces an exciting new layer of regulatory complexity. This discovery suggests that therapeutic strategies aimed at modulating non-coding RNA expression may offer a means of regulating RyR2 function more precisely than directly targeting the channel[54,56,57,114].

TRP channels

TRP channels, as multimodal sensors of cardiac stress, occupy a unique position at the interface of mechanical sensing and Ca^{2+} signaling. TRPC1/3/6 respond directly to stretch to activate CaMKII and drive hypertrophy, whereas TRPV4 integrates shear stress and osmotic signals to regulate vascular tone via the eNOS/NO pathway. TRPM4, a Ca^{2+}-activated non-selective cation channel, is upregulated in pressure overload hypertrophy and promotes remodeling through membrane depolarization-dependent CaMKII activation. A recently discovered functional interaction between TRPV4 and Piezo1 further underscores the networked nature of mechanosensitive signaling. Perhaps most importantly, TRP channel-mediated Ca^{2+} influx initiates and sustains the fibrotic ROS-calcium vicious cycle, positioning TRP channels as strategic upstream targets for interrupting pathological remodeling[31,32,41,63].

Piezo1 channels

Among mechanosensitive channels, Piezo1 is the best-characterized direct mechanosensor in the cardiovascular system. Its trimeric propeller-like architecture enables it to be directly gated by lipid bilayer tension, independent of cytoskeletal involvement. Cardiomyocyte-specific Piezo1 knockout and overexpression studies have established its critical role in initiating the pressure overload hypertrophic response through the dual signaling axes of CaM/CaN/NFAT and CaMKII/HDAC4/MEF2[1,2]. Notably, Piezo1 also regulates TRPM4 expression, forming a feed-forward mechanism that amplifies hypertrophic signaling[1,70]. The ability of Piezo1 to integrate vascular architecture with physiological shear stress further highlights its systemic importance in cardiovascular homeostasis[79,80]. Independent studies have shown that Piezo1-mediated mechanotransduction promotes hypertrophy by impairing Ca^{2+} homeostasis and activating calpain/calcineurin signaling, that Piezo1 is upregulated in human hypertrophic myocardium, and that mice carrying systemic PIEZO1 gain-of-function mutations spontaneously develop cardiac hypertrophy and fibrosis—evidence that collectively elevates Piezo1 from a candidate mechanosensor to a validated disease-modifying node[77,78]. As the field moves toward Piezo1-selective inhibitors—building on first-generation

pharmacological tools such as GsMTx4, Yoda1, and its antagonist analog Dooku1—the key challenge will be to prevent pathological cardiac remodeling while preserving the physiological functions of this channel in vascular adaptation[100-102].

NMDA receptors

The inclusion of NMDARs in the cardiac ion channel landscape is one of the more unexpected developments in this field. Beyond their classical identity as neuronal channels, NMDARs are also stably expressed in cardiomyocytes and the cardiac conduction system, where their high Ca^{2+} permeability and slow inactivation kinetics permit sustained Ca^{2+} influx that can trigger mitochondrial Ca^{2+} overload and ROS generation[9,81,86]. Pathological NMDAR activation generates an arrhythmogenic substrate through dual mechanisms—structural (promoting fibrosis) and electrophysiological (downregulating Nav1.5 via AKT1/TBX3, slowing conduction, and prolonging repolarization)[36,85]. The observation that memantine prevents thyroxine-induced hypertension but not cardiac remodeling suggests that NMDAR-mediated Ca^{2+} signaling is only one component of a broader hypertrophic mechanism, consistent with the network-level model proposed here[89]. Although memantine attenuates remodeling and oxidative stress in other experimental models of heart failure and cardiotoxicity, the evidence base remains preclinical and model-dependent; therefore, its therapeutic claims should be regarded as preliminary and hypothesis-generating, pending confirmation in human tissues and clinical studies[9,112,113].

Cell-type-specific integration

Because different channels regulate the diverse cell types of myocardial tissue, the net outcome of concerted actions across cell types strongly influences cardiac remodeling. Endothelial TRPV4 sparklets and Piezo1 regulate vascular tone and angiogenic remodeling; smooth muscle TRPM4 and Piezo1 determine myogenic tone and arterial stiffness, thereby modulating cardiac afterload; fibroblast TRPM7, TRPV4, and Piezo1 drive fibrogenesis and myocardial stiffening; and TRPV1-expressing perivascular sensory afferent nerves and Piezo1-expressing macrophages couple tissue mechanics to neurohumoral and inflammatory amplification loops[33,65,69,93,95]. This cellular diversity implies that systemic blockade of a broadly expressed mechanosensor may produce opposing effects in different cell types, and that mechanosensitive channel therapy may ultimately require cell-targeted delivery.

Therapeutic implications

The mechanistic framework described above carries direct translational implications, albeit with varying degrees of maturity. Among conventional targets, CCBs are of value primarily for preventing hypertensive hypertrophy, rather than for reversing established remodeling or treating HFrEF[105,106]. RyR2 stabilizers and Na^+/NCX-targeted strategies extend this classical pharmacology toward correcting SR Ca^{2+} leak and Na^+-dependent oxidative stress, supported by animal and human tissue evidence but without completed clinical trials[27,58,114]. Among emerging targets, Piezo1 and TRP channel modulators, NMDAR antagonists, and ROS-targeted interventions are supported mainly by cellular and animal evidence [Table 4], and their clinical utility will depend on disease context, cell-type targeting, and rigorous translational validation. It should be particularly emphasized that the proposal of combined CCB and NMDAR antagonist therapy should be regarded strictly as a rationale for future preclinical research, rather than as an evidence-supported treatment option (see Section "Combined multi-node intervention")[89,119].

Limitations and future directions

First, most evidence on the role of mechanosensitive channels in cardiac remodeling comes from rodent models, and species differences in channel expression and mechanotransduction properties may limit direct translation to human disease. Second, the quantitative contribution of Piezo1-, TRP-, and NMDAR-mediated Ca^{2+} influx relative to LTCC-mediated influx in human cardiomyocytes under physiological and

pathological mechanical loading remains incompletely defined. Third, developing truly channel subtype-selective drugs remains a major challenge; most currently available TRP and Piezo1 modulators lack the specificity required for clinical application. Fourth, the long-term effects of chronic suppression of mechanosensitive channels on cardiac contractile function—which depends on appropriate Ca^{2+} handling—require careful evaluation. Finally, mechanistic evidence is heavily skewed toward pressure overload models; direct comparative studies of channel regulation under volume overload are scarce, and therefore our distinction between pressure and volume overload [Table 1] should be regarded as preliminary[15,16]. In addition, individualized therapeutic strategies based on the relative activation of different channel ensembles in individual patients—for example, reflecting pressure overload-dominant versus volume overload-dominant physiological states—represent an exciting but as yet unrealized opportunity.

In summary, this review proposes an integrative framework in which mechanical stress-induced cardiac remodeling arises from the coordinated activity of multiple ion channels operating as an interconnected mechano-calcium signaling network. The shift from single-pathway to network-level understanding opens new avenues for targeted intervention and demands a fundamental reappraisal of research priorities and therapeutic strategies in the management of cardiac hypertrophy and heart failure.

CONCLUSION

This review proposes an integrated conceptual framework in which mechanical stress-induced cardiac remodeling is understood as the emergent output of a complex, multichannel mechano-calcium signaling network. We have systematically reviewed the contributions of three major classes of ion channels—classical ECC channels (the voltage-gated Na^+ channel Nav1.5, LTCC, the SR Ca^{2+} release channel RyR2, and the Na^+/Ca^{2+} exchanger NCX1), mechanosensitive channels (TRPC, TRPV, TRPM, Piezo1), and the non-canonical ligand-gated channel NMDAR—to the pathophysiology of cardiomyocyte hypertrophy, fibrosis, and electrical remodeling. The central unifying principle emerging from this integration is that these channels do not operate in isolation, but rather form a functionally interconnected network through shared downstream signaling nodes (calcineurin/NFAT, CaMKII, MAPK), reciprocal regulation by ROS, and mechanical signal amplification via the cytoskeleton.

Recognizing that mechanosensitive and non-canonical channels complement classical LTCC-mediated ECC and act in synergy with it under specific mechanical and pathological contexts compels us to carefully re-evaluate research priorities and therapeutic strategies for cardiac remodeling. The shift from single-pathway to network-level understanding opens new avenues for future research—including the hypothesis that combining classical CCBs with NMDAR antagonists may achieve multi-node blockade of Ca^{2+} overload (a strategy not yet validated in controlled animal or clinical studies targeting cardiac remodeling), as well as the potential of Piezo1-selective inhibitors to prevent pathological remodeling without compromising normal cardiac function. As the field advances, success in translating these mechanistic insights into clinical practice will depend on embracing the complexity of ion channel crosstalk, developing more selective pharmacological tools, and designing clinical trials that capture the mechanistic heterogeneity underlying phenotypically similar cardiac hypertrophy and heart failure.

DECLARATIONS

Authors' contributions

Conceptualization, investigation, writing-original, writing-review & editing: Shi W
Validation, visualization, investigation: Ma Z
Writing-review & editing, software: Liu C
Supervision, project administration, funding acquisition, writing-review & editing: Sun H

Availability of data and materials

Not applicable.

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During revision of this manuscript, Kimi (version Kimi K3, released 2026-7-16) was used to assist with English translation and the production of a graphical abstract to improve language, readability of some sentences, and visual presentation. The authors further manually checked and revised the translated text and graphical abstract. The tool did not influence the study design, data collection, analysis, interpretation, or the scientific content of the work. All authors take full responsibility for the accuracy, integrity, and final content of the manuscript.

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Conflicts of interest

All authors declared no conflicts of interest.

Ethical approval and consent to participate

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Consent for publication

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