

REVIEW ARTICLE

Cardiac mechanomedicine: Putting evidence into practice

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Abstract

Cardiovascular diseases constitute a leading global health burden, contributing significantly to morbidity and mortality worldwide. Traditional diagnostic and therapeutic strategies primarily focus on biochemical markers and imaging findings, often neglecting the fundamental mechanical mechanisms that govern cardiac physiology and pathophysiology. The heart, as a highly dynamic mechanical organ, depends on a precisely regulated biomechanical microenvironment, and alterations in this microenvironment can contribute to disease initiation and progression. This review summarizes the concept of cardiac mechanomedicine and its major research domains, including the biomechanical properties of the heart under physiological and pathological conditions. It also details how cardiac cells and tissues respond to mechanical stimuli. Finally, the review highlights recent advances in measuring mechanical biomarkers, alongside new diagnostic tools and therapeutic interventions targeting mechanical pathways, underscoring the clinical potential of this field.

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(yangyan3@xjtu.edu.cn)**Citation:** Li G, Shi T, Zhao C, Kong Y, Wang S, Yan Y. Cardiac mechanomedicine: Putting evidence into practice. *Brain & Heart*. doi: 10.36922/BH026200022**Received:** May 13, 2026**Revised:** July 21, 2026**Accepted:** August 7, 2026**Published online:** September 7, 2026**Copyright:** © 2026 Author(s). This is an Open-Access article distributed under the terms of the Creative Commons Attribution License, permitting distribution, and reproduction in any medium, provided the original work is properly cited.**Publisher's Note:** AccScience Publishing remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.**Keywords:** Cardiac mechanomedicine; Biomechanics; Mechanobiology; Cardiovascular diseases; Mechanical microenvironment; Precision diagnosis and therapy

1. Introduction

Cardiovascular disease has become a major threat to global public health.¹ Traditional diagnostic and therapeutic strategies have predominantly focused on imaging and laboratory tests, overlooking the critical influence of the cardiac mechanical microenvironment—a dynamic system that regulates heart function across molecular, cellular, and tissue levels.

The heart is not merely an isolated mechanical pump; understanding its mechanical environment is essential to understanding cardiac physiology and pathophysiology. Heart failure phenotyping based solely on left ventricular ejection fraction (LVEF) is no longer sufficient in certain contexts and may fail to effectively guide therapeutic

decisions. As a macroscopic indicator of global systolic function, LVEF does not capture localized mechanical abnormalities or diastolic dysfunction. Furthermore, it fails to capture electromechanical uncoupling or abnormal myocardial strain under exercise stress. Advances in biomechanics and mechanobiology have opened new avenues for an in-depth mechanistic understanding of the initiation and progression of cardiac diseases, paving the way for transformative diagnostic and therapeutic strategies.²⁻⁴ Future heart-failure assessment may benefit from integrating myocardial stiffness, electromechanical synchrony indices, mechanical force-transmission pathways, and endocrine factors, including neurohormonal and mechanical feedback loops.

This article defines and systematically outlines cardiac mechanomedicine, an emerging interdisciplinary field that emphasizes the role of mechanical changes in heart disease. It explores how altered mechanical microenvironments drive core pathological processes, including myocardial fibrosis, myocardial ischemia, and heart failure, and delineates the molecular pathway networks from mechanosensing to signal transduction, gene expression,

and phenotypic remodeling. It also summarizes advances in non-invasive or minimally invasive techniques to detect disease-specific mechanical biomarkers and highlights the potential of innovative treatment strategies, including modulation of matrix stiffness, targeting of mechanosensitive signaling pathways, and application of smart biomaterials and mechanical circulatory support devices (Figure 1). Thus, cardiac mechanomedicine is a novel concept in cardiovascular research, complementing existing clinical assessment systems and offering new perspectives for cardiovascular disease management.

2. The concept of cardiac mechanomedicine

2.1. Mechanomedicine

Living organisms are inherently dynamic physical systems that function within complex mechanical microenvironments. From force-guided morphogenesis during embryonic development to the maintenance of tensional homeostasis in adult tissues, and to the role of mechanical dysregulation in disease initiation and progression, mechanical factors play a role as critical as biochemical signals.⁵⁻⁷ However, the impact of mechanical

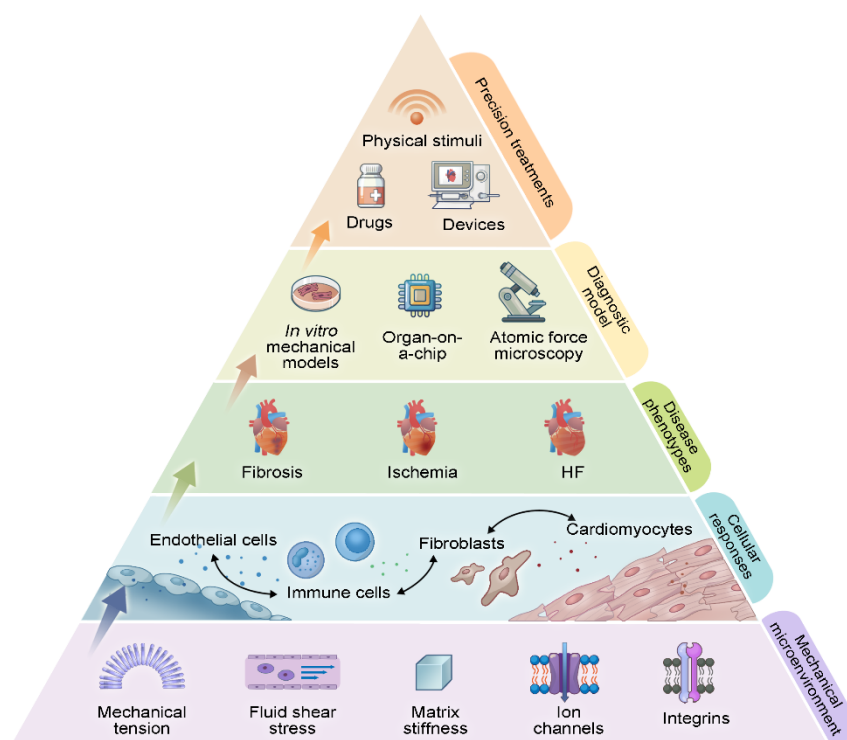


Figure 1. Integrative framework of cardiac mechanomedicine, which demonstrates how fundamental research into the mechanical properties of the heart translates into clinical diagnostics and therapies. Created with Photoshop. Abbreviations: HF: Heart failure.

forces and microenvironments remains underappreciated. Cells, tissues, and organs constantly sense and respond to biomechanical forces, including substrate stiffness, fluid shear stress, and tensile strain. These forces actively regulate cellular behavior and tissue homeostasis.

Biomechanics primarily focuses on the deformation, motion, and functional changes across scales ranging from molecules to whole organisms.^{8,9} Mechanobiology extends this framework to the molecular and cellular levels, examining how cells and tissues actively sense the mechanical signals of their surrounding physical environment, convert them into intracellular biochemical signals, and ultimately trigger specific biological responses including changes in gene expression and protein synthesis; alterations in proliferation, apoptosis, migration, and differentiation; and tissue remodeling.^{8,10-13} Its central aim is to systematically elucidate the decisive role of mechanical factors across the entire disease continuum and to reveal how disruptions in the mechanical microenvironment initiate and drive pathology. By integrating this indispensable dimension into disease understanding, mechanomedicine provides a foundational framework for developing novel, mechanically targeted diagnostic and therapeutic strategies.¹⁴⁻¹⁶

2.2. Cardiac mechanomedicine

The heart relies critically on its intrinsic biomechanical properties and their precise regulation for sustained function. Each heartbeat entails sophisticated electromechanical coupling, coordinated cardiomyocyte contraction and relaxation, complex intracardiac hemodynamics, and cyclic mechanical stress and strain across the cardiac walls. Building on mechanomedicine principles, we propose cardiac mechanomedicine as a dedicated extension of mechanomedicine and cardiology. It aims to establish a unified framework that systematically applies mechanomedicine to cardiovascular contexts, integrating multi-scale mechanical properties, mechanobiological mechanisms, and mechanically targeted interventions.

Cardiac mechanomedicine focuses on how major cardiac cell types—cardiomyocytes, fibroblasts, endothelial cells, immune cells—sense mechanical signals in their microenvironment, including static matrix stiffness, cyclic stretch, and fluid shear stress, through specialized mechanoreceptors such as integrins, ion channels, adhesion complexes, and the cytoskeleton. More importantly, it investigates how these mechanical signals are transduced into intracellular biochemical networks that activate key signaling pathways and subsequently regulate gene transcription in the nucleus. These

mechanoresponsive circuits ultimately govern cell fate decisions, functional status, phenotypic transitions, and the dynamic balance between extracellular matrix (ECM) synthesis and degradation.^{15,17} It also requires elucidating how these mechanical properties evolve during the onset and progression of cardiovascular diseases such as hypertension, cardiomyopathy, and heart failure. Common alterations include localized stress concentration, global reductions in strain, abnormally increased myocardial stiffness, and diminished compliance.¹⁸⁻²⁰

Novel non-invasive or minimally invasive diagnostic technologies are being developed for early detection and precise phenotyping, including biomechanical imaging and micro- and nanosensing technologies.^{17,21} Simultaneously, innovative “mechanically targeted” therapeutic strategies are being designed to correct pathogenic alterations in the mechanical microenvironment or to modulate dysregulated mechanosignaling pathways.^{22,23}

The ultimate goal of cardiac mechanomedicine is to construct a definitive causal axis from mechanical stimuli and microenvironment alterations to cellular mechanosensing, signaling network activation, altered gene expression, and ultimately tissue or organ dysfunction. By mapping this pathway, cardiac mechanomedicine aims to provide a systematic solution for cardiovascular disease, spanning from fundamental mechanisms to clinical applications.

3. Cardiac biomechanics in health and disease

3.1. Biomechanical properties in the healthy heart

The myocardium exhibits anisotropic mechanical behavior because the helical and laminar organization of cardiomyocyte bundles enables coordinated contraction during systole and effective relaxation during diastole. Intercalated discs can provide efficient and synchronous transmission of mechanical force between cardiomyocytes, ensuring coordinated contraction and relaxation of the ventricular wall.²⁴

Cardiac function hinges on the balance between active contraction and passive filling. Ventricular wall stress and myocardial strain are key biomechanical indicators of systolic performance. During diastole, the ventricular myocardium exhibits passive elastic properties with high compliance, allowing passive filling at relatively low atrial pressures. The myocardium's adaptability is further exemplified by its viscous and elastic properties, which buffer abrupt hemodynamic changes. Moreover, preload dynamically regulates contractile force, a relationship known as the Frank-Starling mechanism.¹⁹

3.2. Biomechanical properties in myocardial fibrosis

Myocardial fibrosis is a pathological condition characterized by the excessive deposition, abnormal cross-linking, and reduced degradation of the ECM, particularly collagen fibers. Etiologically, it serves as a common pathological endpoint across virtually all forms of heart disease, driven by factors such as hemodynamic overload, myocardial ischemia, and inflammation.²⁵ Furthermore, fibrosis is highly prevalent in heart failure patients, and its extent is recognized as a strong prognostic indicator of disease progression. Consequently, this process increases ECM volume fraction and structural disorganization, directly resulting in a marked pathological elevation in stiffness (Figure 2).^{26,27} Myocardial stiffness is a key determinant of cardiac function, reflecting both the intrinsic properties of the myocardium and the pressure and stress acting on the ventricular wall. Cardiac shear wave elastography is an emerging and promising echocardiographic technique that enables accurate assessment of myocardial stiffness. Integrating stiffness assessment into its clinical armamentarium could provide immense diagnostic and prognostic value.²⁸

Diastolic dysfunction is characterized by increased ventricular wall stiffness, which impairs the ventricle's ability to expand adequately during diastole, compromising passive filling. To maintain sufficient ventricular filling volume, the left atrium must generate higher pressure to drive blood into the left ventricle, resulting in increased left ventricular end-diastolic pressure, which is commonly observed in the early stages of various cardiac diseases.^{20,29-31}

Systolic dysfunction occurs when diffuse interstitial fibrosis acts as a "cement-like" matrix that infiltrates the spaces between cardiomyocytes, disrupting the effective transmission of mechanical force through intercalated discs.³² This impairs the synchrony of myocardial contraction, reduces contraction efficiency, and weakens overall systolic function.^{24,32,33} In more severe injury, cardiomyocyte death and replacement by non-contractile and abnormally stiff scar tissue further impair ventricular pumping capacity.^{34,35}

In electromechanical uncoupling, the stiff fibrotic matrix not only impedes mechanical force transmission but also disrupts the electrophysiological microenvironment of cardiomyocytes. It can interfere with normal electrical conduction pathways, increase the risk of conduction block, and serve as a substrate for lethal arrhythmias.^{36,37}

3.3. Biomechanical properties in myocardial ischemia

Myocardial ischemia dynamically alters cardiac mechanical function.³⁸⁻⁴⁰ In the acute phase, reduced coronary blood

flow disrupts mitochondrial function and rapidly depletes energy in cardiomyocytes, leading to a marked decline in contractility in the ischemic region.⁴¹ Over time, if ischemia results in cardiomyocyte necrosis, the body initiates a repair process that often leads to adverse ventricular remodeling.

In the infarct zone, necrotic cardiomyocytes are replaced by scar tissue composed predominantly of dense collagen, which lacks both elasticity and contractility. This region loses active contraction and becomes markedly stiff.

The non-infarct zone maintains cardiac output; the non-infarcted myocardium undergoes adaptive hypertrophy. However, under the influence of pathological stimuli, this adaptive hypertrophy often undergoes an irreversible transition to pathological hypertrophy. At this stage, cardiomyocytes may exhibit degenerative changes, including disorganized myofibrillar architecture and altered contractile protein phenotype, accompanied by progressive cardiomyocyte apoptosis and interstitial fibrosis within the non-infarct zone.³⁵ Collectively, these changes lead to a progressive decline in ventricular compliance and a persistent increase in myocardial stiffness. Because stroke volume decreases, the ventricular cavity gradually dilates to accommodate the residual blood volume after each contraction and remodels from a normal elliptical shape toward a spherical shape, while the wall thins. This geometric alteration further exacerbates ventricular wall stress, establishing a vicious cycle that drives progressive systolic dysfunction, manifested by a sustained decline in LVEF and eventual progression to heart failure.⁴²

3.4. Biomechanical properties in heart failure caused by ischemia

Severe myocardial ischemia can lead to acute and chronic heart failure. The essence of heart failure is a failure of the heart's pumping function; however, the underlying biomechanical phenotypes induced by ischemic injury are highly heterogeneous. This section focuses on ischemic etiologies, but heart failure also encompasses other causes, such as hypertensive, valvular, and genetic cardiomyopathies, each with distinct biomechanical characteristics.

3.4.1. Heart failure with reduced ejection fraction (left ventricular ejection fraction $\leq 40\%$)

The ventricular cavity is typically markedly dilated, and the walls may be thin due to myocyte loss and scar formation following infarction. Ventricular wall stress, particularly systolic stress, is significantly elevated, and cardiac work efficiency is reduced. The Frank-Starling mechanism is impaired or minimally effective, limiting the ability to increase stroke volume even with elevated preload.

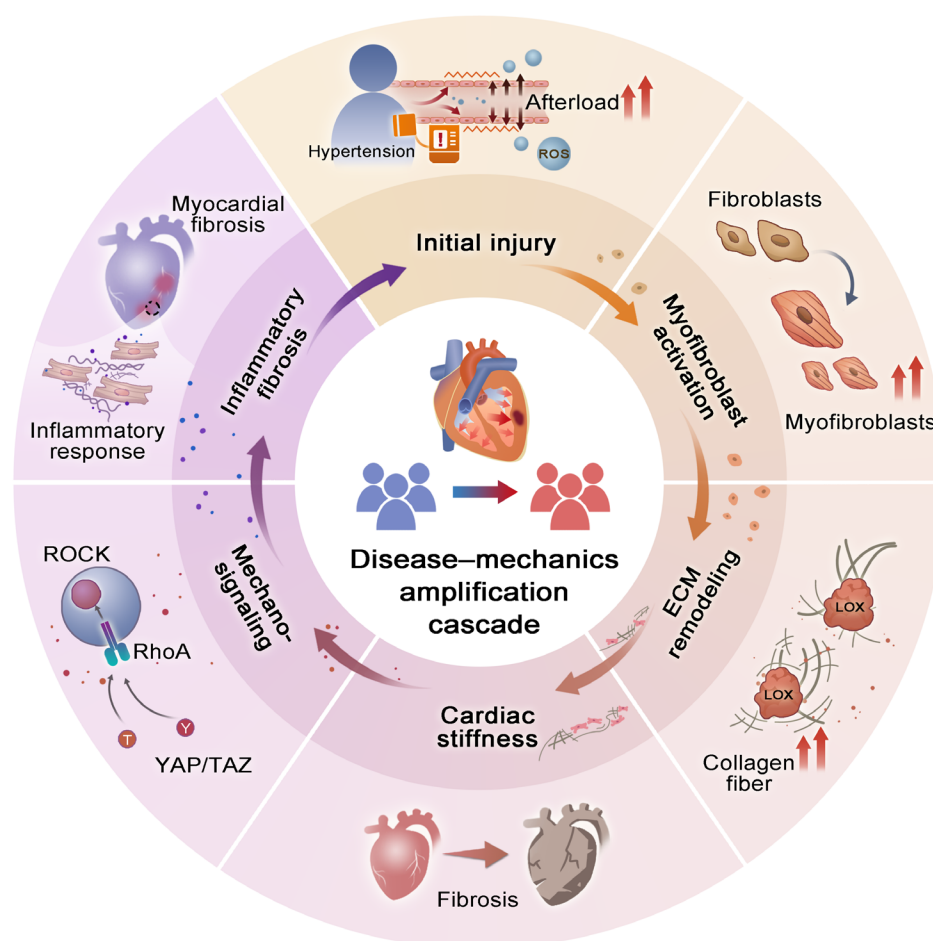


Figure 2. Disease–mechanics amplification cascade in myocardial fibrosis, indicating how an initial injury triggers a cascade of cellular responses that feed back to amplify both the disease state and the abnormal mechanical environment. Created with Photoshop.

Abbreviations: ECM: Extracellular matrix; LOX: Lysyl oxidase; RhoA: Ras homolog family member A; ROCK: Rho-associated coiled-coil-containing protein kinase; ROS: Reactive oxygen species; TAZ: Transcriptional co-activator with PDZ-binding motif; YAP: Yes-associated protein.

Overactivation of neurohormonal systems is particularly prominent in this form of heart failure, driving ongoing adverse remodeling and further worsening mechanical function.^{43–45}

3.4.2. Heart failure with preserved ejection fraction (left ventricular ejection fraction $\geq 50\%$)

The core pathophysiological abnormality is diastolic dysfunction.⁴⁶ In the context of ischemia, this is often driven by chronic subclinical ischemia and microvascular dysfunction. The most critical biomechanical feature is a marked increase in overall myocardial and ventricular stiffness. This stiffness arises from the combined effects of multiple pathological substrates. Extensive interstitial and perivascular fibrosis leads to abnormal ECM

stiffening, increased intrinsic cardiomyocyte stiffness, and microvascular endothelial dysfunction with capillary rarefaction, promoting a chronic inflammatory state that further drives fibrosis and cellular dysfunction.^{47–50} Although systolic function appears preserved, myocardial reserve function is frequently impaired, and secondary changes including left atrial enlargement and pulmonary hypertension are commonly present. Neurohormonal activation represents a common pathway in heart failure progression.

In both heart failure with reduced ejection fraction and heart failure with preserved ejection fraction, reduced cardiac output or elevated filling pressure triggers excessive neurohormonal activation. This exacerbates cardiomyocyte hypertrophy and apoptosis, promotes

fibroblast activation and interstitial fibrosis, and induces peripheral vasoconstriction and sodium–water retention, thereby increasing preload. Together, these changes create a vicious cycle of mechanical overload, adverse myocardial remodeling, and progressive deterioration of cardiac function.

4. Cardiac mechanobiology

Cardiac cells are not passive recipients of the mechanical environment; instead, they possess a sophisticated mechanosensory apparatus and intricate signal networks that transduce external physical forces into biological signals, ultimately governing cell fate and function.

4.1. Mechanobiological mechanisms of cell–cell interactions

Cardiomyocytes are tightly connected via intercalated discs, which are composed of adherent junctions, desmosomes, and gap junctions.^{51,52} These junctional complexes are far more than passive “glue”; they serve as critical hubs for mechanosensing and force transmission. Intercellular tension, generated by active contraction or passive stretch, is transmitted through transmembrane cadherins, which engage intracellular catenin family members, particularly β -catenin. This mechanical signal can modulate β -catenin stability and its nuclear transcriptional activity, thereby regulating the expression of genes involved in cell proliferation, differentiation, and survival—processes central to cardiac development, homeostasis, and pathological hypertrophy.⁵³ More importantly, the structural and functional integrity of gap junctions (composed of connexin proteins) within the intercalated disc is essential for rapid electrical impulse conduction, while adherens junctions and desmosomes ensure synchronized and efficient transmission of mechanical forces.^{33,54} Any factor that compromises the mechanical integrity of the intercalated disc leads to electromechanical uncoupling, triggering arrhythmias and contractile dysfunction.⁵⁵

4.2. Mechanobiological mechanisms of extracellular matrix interactions

Cardiac cells bind specific ECM ligands through cell-surface integrin receptors, forming focal adhesions. Focal adhesions are key mechanotransduction platforms (Figure 3). Here, we discuss the mechanotransduction pathways within these adhesions under both physiological and pathological conditions.

When the ECM to which a cell is anchored undergoes deformation or changes in its biophysical properties, the resulting mechanical signals are transmitted to the cell

through integrins. This triggers conformational changes and recruits signaling proteins within the focal adhesion, activating key intracellular kinases, including focal adhesion kinase, Src family kinases, Rho family GTPases (especially Ras homolog family member A [RhoA]), and its downstream effector Rho-associated kinase.^{56–58} The activated focal adhesion kinase–Src and RhoA/Rho-associated kinase signaling axes regulate cytoskeletal dynamics and tension generation, thereby modulating cell spreading, migration, and contractility.^{59,60} These pathways can also activate downstream cascades such as mitogen-activated protein kinase and phosphoinositide 3-kinase/protein kinase B, regulating gene transcription, protein synthesis, and cell cycle progression.^{61,62}

Piezo1 is a mechanically activated ion channel highly expressed in vascular endothelial cells that directly senses shear stress from blood flow.⁶³ Upon activation by mechanical forces, Piezo1 opens to allow calcium influx, initiating signaling pathways that regulate endothelial cell alignment and vascular remodeling.⁶³ This mechanosensing function of Piezo1 is essential for maintaining vascular homeostasis and proper blood flow dynamics.

Yes-associated protein (YAP) and transcriptional co-activator with PDZ-binding motif (TAZ) are among the most critical transcriptional co-activators in cardiac mechanobiology. Under normal physiological matrix stiffness, the Hippo pathway kinases large tumor suppressor kinase 1/2 are activated, leading to phosphorylation of YAP/TAZ and their cytoplasmic retention and degradation.⁶⁴

Under pathological conditions, stiffened matrices robustly drive the transformation of quiescent fibroblasts into activated myofibroblasts with strong contractile and secretory capabilities via integrin-RhoA/Rho-associated coiled-coil-containing protein kinase (ROCK) signaling.^{65,66} These myofibroblasts extensively synthesize and deposit ECM components, such as collagen, and generate powerful contractile forces through α -smooth muscle actin expression, promoting tissue contraction, progressive matrix stiffening, and a vicious cycle.^{67–69} A stiff extracellular environment promotes pathological cardiomyocyte hypertrophy, increasing susceptibility to apoptosis and potentially inducing secretion of pro-fibrotic factors that act on fibroblasts via paracrine signaling.^{70–72}

Vascular endothelial cells, when exposed to a pathologically stiff matrix, may lose their endothelial characteristics and acquire a mesenchymal or fibroblast-like phenotype, further contributing to myocardial fibrosis and microvascular rarefaction or dysfunction.^{73–75}

Integrin-mediated signaling, increased RhoA activity, and elevated cytoskeletal tension collectively inhibit

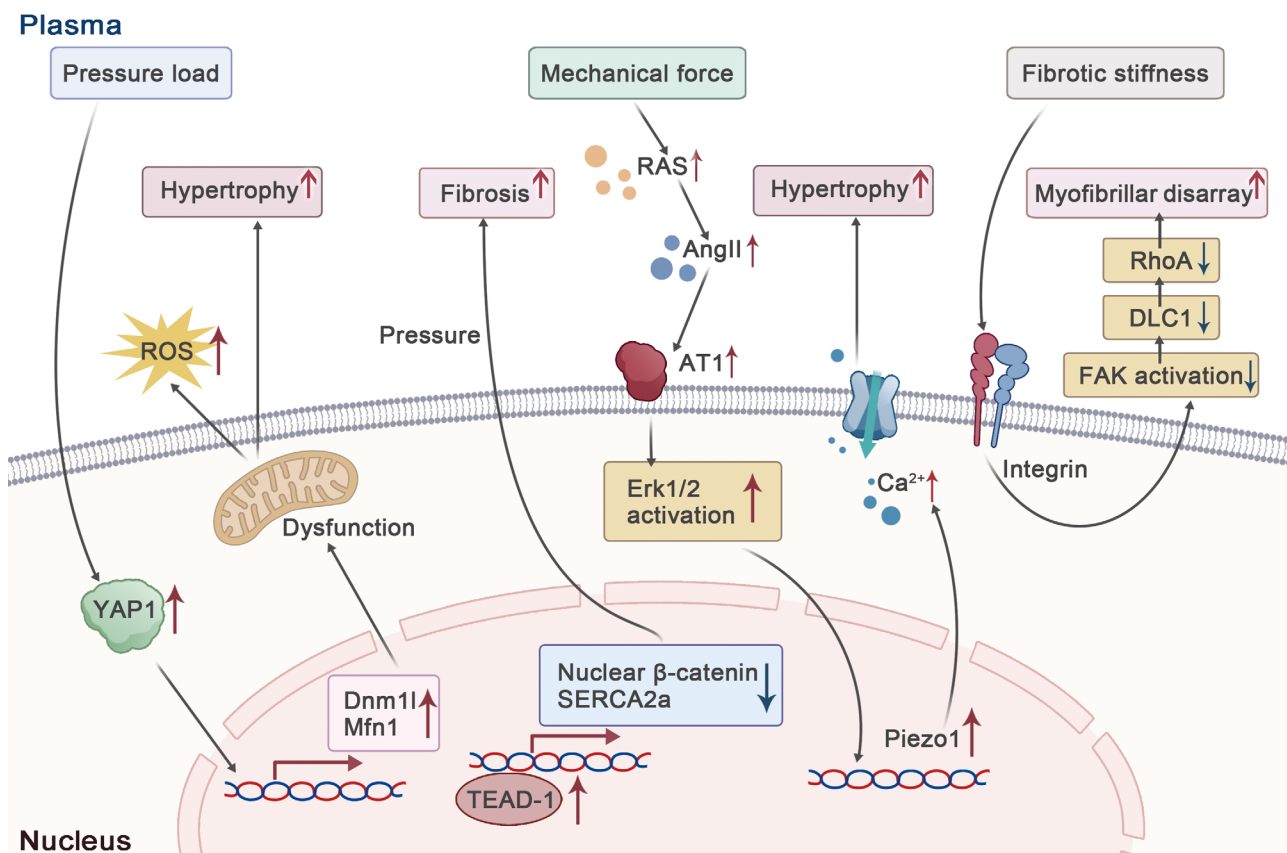


Figure 3. Schematic diagram of mechanosensors and intricate signal networks on the surface of cardiomyocytes. Created with Photoshop.

Abbreviations: AT1: Angiotensin II type 1 receptor; AngII: Angiotensin II; DLC1: Deleted in liver cancer 1; Dnm1: Dynamin 1; Erk1/2: Extracellular signal-regulated kinase 1/2; FAK: Focal adhesion kinase; Mfn1: Mitofusin 1; Piezo1: Piezo-type mechanosensitive ion channel component 1; RAS: Renin-angiotensin system; ROS: Reactive oxygen species; SERCA2a: Sarco/endoplasmic reticulum Ca²⁺-ATPase 2a; TEAD-1: TEA domain transcription factor 1; YAP1: Yes-associated protein 1.

the Hippo pathway. This results in the accumulation of non-phosphorylated YAP/TAZ, which translocate to the nucleus. Once in the nucleus, YAP/TAZ bind transcription factors such as TEAD, strongly driving expression of genes involved in cell proliferation (particularly in fibroblasts), anti-apoptosis, pro-fibrotic responses, and pro-inflammatory signaling.⁷⁶⁻⁷⁸ YAP/TAZ are now widely recognized as core effectors of cellular mechanosensing, particularly in response to matrix stiffness, and play key roles in driving myocardial fibrosis, pathological hypertrophy, and heart failure.^{77,79}

Piezo1 expression peaks under physiological shear stress of 30 dyn/cm², whereas abnormally high shear stress inhibits its expression.⁸⁰ Piezo1 mediates mechano-feedback mechanisms that help control vascular tone and barrier integrity, making it a crucial factor in cardiovascular health and disease.

4.3. Mechanobiological mechanisms of cell-tissue interactions

Cardiomyocyte anisotropy, the integrity of the intercellular junctional network, and the degree of integration with the surrounding ECM collectively determine the macroscopic and functional properties of myocardial tissue, such as the overall stress-strain relationship, electrical conduction velocity, and anisotropy ratio.^{24,81} Conversely, the tissue's macroscopic mechanical state feeds back to influence the mechanical microenvironment perceived by individual cells. For instance, during myocardial ischemia, the local necrotic area loses contractile function and becomes a low-stress zone, while the adjacent surviving myocardium experiences increased mechanical load, forming a high-stress zone. This regional heterogeneity in stress distribution triggers regional remodeling processes, such as local compensatory hypertrophy and exacerbated local fibrosis, through the mechanobiological mechanisms

described above. These regional changes may ultimately propagate to affect the structure and function of the entire ventricle.^{38,82,83}

Stretch-activated channels in cardiomyocytes are primarily classified into two major categories: non-selective cation channels and potassium-selective channels. Some classic voltage-gated channels also exhibit mechanosensitivity.

Piezo1 and Piezo2 are non-selective cation channels directly gated by mechanical forces. Piezo1 is expressed in both cardiomyocytes and cardiac fibroblasts.⁸⁴ Transient receptor potential cation channel subfamily C member 1/6 also belongs to the non-selective cation channels.⁸⁵ When end-diastolic ventricular pressure increases, Piezo1 and transient receptor potential cation channels open, mediating a small influx of Ca^{2+} . This induces further calcium release from the sarcoplasmic reticulum via ryanodine receptors, thereby enhancing myocardial contractility.⁸⁶ This process supports the Frank–Starling mechanism.

Potassium channel subfamily K member 2 is the most extensively studied stretch-activated potassium channel. Increased membrane tension or shear stress directly opens these channels, which mediate potassium efflux and produce a hyperpolarizing effect.⁸⁷ This serves as a feedback inhibitory mechanism. By generating a hyperpolarizing current to counteract pathological depolarization from non-selective cation channels, it shortens action potential duration and prevents triggered activity, thereby protecting the heart from arrhythmias when the myocardium is stretched.⁸⁸

4.4. Mechanobiological mechanisms of cell–blood flow interactions

Vascular endothelial cells form the primary cellular interface for sensing hemodynamic shear stress. High shear stress generated by laminar flow, such as that on the inner side of the aortic arch, is considered a “healthy force” that maintains endothelial homeostasis. It promotes endothelial cell alignment in the direction of flow, upregulates anti-inflammatory, anticoagulant, and antioxidant gene expression, suppresses adhesion molecule expression, and maintains vasodilation function.^{89,90} Conversely, low shear stress, oscillatory shear stress, or turbulent flow are classified as “pathological forces.” These forces disrupt endothelial cell alignment, induce endothelial activation, and are characterized by increased expression of pro-inflammatory factors, chemokines, and adhesion molecules, decreased endothelial nitric oxide synthase activity, and enhanced pro-coagulant activity. This dysfunctional endothelial phenotype creates a crucial

environment that initiates and promotes atherosclerotic plaque formation.^{90–92}

Shear forces generated by intracardiac blood flow patterns act on endocardial endothelial cells and may modulate their functional state, thereby contributing to processes such as intracardiac thrombosis or endocardial fibrosis.^{89,93} Cardiomyocytes are directly exposed to cyclic changes in intracavitary pressure. High systolic pressure generates substantial tensile forces on cardiomyocytes, whereas reduced diastolic pressure allows cellular relaxation. This cyclic tensile strain constitutes a necessary physiological stimulus essential for maintaining normal cardiomyocyte structure and function, transduced through stretch-activated ion channels, integrins, and other mechanosensitive pathways.^{94,95} However, under pathological conditions, sustained pressure overload imposes excessive and prolonged mechanical strain on cardiomyocytes. These pathological tensile forces activate the pro-hypertrophic, pro-fibrotic, and pro-apoptotic signaling pathways described above, thereby driving maladaptive myocardial remodeling.^{96,97}

5. Mechanodiagnostics of cardiovascular diseases

Identifying and quantifying specific mechanical alterations during disease progression is a fundamental prerequisite for applying the principles of cardiac mechanomedicine into precision diagnostics. Related technologies span from basic laboratory research to clinical application, bridging molecular-scale mechanosensing with organ-level functional assessment.

5.1. Clinical evaluation of myocardial mechanics

Current clinical examinations can evaluate cardiac mechanical properties. Speckle Tracking Echocardiography enables quantitative assessment of myocardial deformation in both longitudinal and circumferential axes. It is highly sensitive to regional myocardial dysfunction, such as segmental strain reduction from myocardial ischemia, and to global subclinical impairment in cardiac function. For example, an early reduction in Global Longitudinal Strain may be evident in patients with heart failure with preserved ejection fraction, even when LVEF remains within the normal range. This capability far exceeds traditional visual wall motion analysis and ejection fraction assessment.^{98,99}

Key techniques including cardiac magnetic resonance imaging (CMR) feature tracking, myocardial tagging, and magnetic resonance elastography can evaluate myocardial function and stiffness through high-precision imaging and strain analysis.^{100–103} Among these, myocardial tagging is considered the reference standard for strain assessment. It

applies a magnetization-saturation grid to the myocardium before imaging. By tracking grid deformation during the cardiac cycle, it directly visualizes and precisely quantifies three-dimensional myocardial strain, strain rate, and torsion/untwisting motion, providing the most comprehensive and accurate myocardial mechanics.

When integrated with finite element analysis, coronary computed tomography (CT) angiography allows for the simulation and calculation of stress and strain distribution within atherosclerotic plaque under hemodynamic pressure, offering a key mechanical indicator of plaque vulnerability to rupture.¹⁰⁴⁻¹⁰⁶ CT-based myocardial strain analysis, similar to CMR feature tracking, is an emerging technique that utilizes conventional coronary CT angiography or cardiac CT cine sequences to assess myocardial deformation by tracking tissue motion characteristics, providing complementary information for multimodal assessment.¹⁰⁷ Although invasive, it remains the gold standard for precise hemodynamic measurement. By constructing pressure–volume loops and analyzing the end-diastolic pressure–volume relationship, it enables accurate quantification of ventricular chamber (dP/dV), which is one of the most reliable measures of diastolic function. Pressure-volume loop analysis holds irreplaceable value in guiding heart failure treatment and advancing cardiovascular research.¹⁰⁸⁻¹¹⁰

5.2. Preclinical assessment of myocardial mechanics

Various cardiac cells can be co-cultured within three-dimensional biomaterial scaffolds to recapitulate specific disease microenvironments, such as elevated matrix stiffness in myocardial fibrosis or mechanical unloading/overloading following myocardial infarction.¹¹¹ One study developed a multi-scale mechanobiological model to systematically simulate the dynamic changes of the heart during physiological and pathological hypertrophy, spanning from the organ and tissue levels down to the cellular level.¹¹² This approach enables real-time monitoring of dynamic changes in cellular behavior, gene expression, and protein secretion, and supports high-throughput screening of potential drugs that can reverse pathological mechanical responses.^{113,114}

Based on microfluidic technology, organ-on-a-chip systems construct microphysiological models to realistically simulate the structural organization and functional dynamics of cardiac tissue, as well as the mechanical environments of cell–cell, cell–matrix, and cell–flow interactions. These are increasingly employed to investigate cardiac disease mechanisms, evaluate drug efficacy and cardiotoxicity, and advance the development of personalized medicine.¹¹⁵⁻¹¹⁷

Atomic force microscopy uses a tiny scanning probe to directly and quantitatively measure elastic modulus and viscoelastic properties at the microscopic level, from single cells to subcellular domains. It enables detection of subtle, localized alterations in mechanical properties in early pathological stages, serving as a key bridge connecting microscale mechanobiological changes to macroscopic tissue function and disease progression.¹¹⁸⁻¹²⁰

Mechanosensitive fluorescent probes have emerged as cutting-edge tools in recent biophysics and cardiovascular basic research. These molecular devices directly convert mechanical forces, including cellular shear stress and intracellular cytoskeletal tension, into measurable changes in fluorescence signals, such as intensity, emission wavelength, or fluorescence lifetime. Researchers have developed conformation-sensitive probes to track local rearrangements along the Piezo1 blade. When low-intensity fluid shear stress activates the tagged channels, these probes elicit detectable fluorescence signals.¹²¹

6. Mechanotherapeutics for cardiac diseases

A deep understanding of cardiac biomechanics and mechanobiological mechanisms has catalyzed the development of innovative therapies that directly target pathological mechanical alterations and their downstream maladaptive pathways.¹²²

6.1. Clinical treatments

Several medications have been shown to benefit patients by improving cardiac mechanical properties. A prime example is sodium-glucose co-transporter 2 inhibitors, such as dapagliflozin. Although they do not directly target myocardial contractile proteins, they effectively reduce ventricular wall stress by decreasing volume overload, thereby improving myocardial strain.¹²³ Meanwhile, mineralocorticoid receptor antagonists exert anti-inflammatory and anti-fibrotic effects that reduce ECM stiffness, improving diastolic compliance over the long term.¹²³⁻¹²⁵ Large-scale clinical trials, such as EMPEROR-preserved and DELIVER, have shown that although these drugs primarily target the kidneys, measurable changes in cardiac mechanical parameters do occur.^{126,127} These medications optimize the cardiac mechanical environment through indirect pathways.

In patients with end-stage heart failure, left ventricular assist devices provide robust mechanical circulatory support. They significantly reduce left ventricular load, improve end-organ perfusion, partially reverse ventricular remodeling, and enhance survival rates and quality of life.^{128,129} Percutaneous mechanical circulatory support

systems, such as Impella and extracorporeal membrane oxygenation, provide cardiopulmonary assistance that facilitates recovery of cardiac function.¹³⁰

6.2. Preclinical treatments

Several strategies with potential in cardiac mechanomedicine still require clinical validation. Reversing myocardial fibrosis requires interrupting the self-perpetuating cycle: increased matrix stiffness leads to fibroblast activation and myofibroblast persistence, which in turn results in excessive ECM deposition and further increases stiffness.¹³¹ A key therapeutic strategy therefore focuses on reducing matrix stiffness by targeting ECM synthesis and cross-linking, particularly by inhibiting lysyl oxidase (LOX) and LOX-like enzymes. Potent LOX/LOX-like inhibitors are under development to soften fibrotic myocardium and improve diastolic function.^{132,133} Additionally, restoring the balance between matrix metalloproteinases and their tissue inhibitors to promote the degradation of excessive pathological ECM is another viable strategy.¹³⁴ Targeting mechanosignaling pathways also offers a promising therapeutic strategy for myocardial fibrosis, with key approaches including inhibition of the RhoA/ROCK pathway or p38, disruption of the YAP/TAZ-TEAD interaction, modulation of integrin-mediated signaling, and regulation of titin-based myocardial stiffness through phosphorylation.¹³⁵⁻¹³⁹

Furthermore, several mechanobiology-inspired strategies have been shown to promote angiogenesis. Leveraging the critical role of fluid shear stress in regulating endothelial cell function and angiogenesis, bioengineered scaffolds with tailored mechanical properties can be designed for implantation into ischemic myocardium. These scaffolds provide not only structural support but also guide endothelial cell migration, alignment, and lumen formation through biomechanically informed microstructure.^{140,141} The release of growth factors such as vascular endothelial growth factor can synergistically enhance therapeutic angiogenesis.¹⁴²⁻¹⁴⁴ Some studies also explore the use of external physical stimuli to enhance angiogenesis in ischemic tissues.^{145,146}

7. Conclusion

Left ventricular ejection fraction classification fails to reflect key parameters such as myocardial stiffness, fibrosis burden, or mechanical conduction abnormalities.¹⁴⁷ Cardiac mechanomedicine offers alternative variables, including myocardial stiffness, extracellular volume measured by CMR, global longitudinal strain, and the activation status of mechanosensitive channels.²⁹ These metrics are closely associated with the core pathophysiological mechanisms of ischemic cardiomyopathy and heart failure, providing

potential targets for future clinical interventions.

Cardiac mechanomedicine provides a novel framework for mechanistic understanding. By integrating mechanics and biology, it elucidates how mechanical forces are transduced into electrical and chemical signals via specific molecular channels. This framework allows us to re-examine the initiation and progression of myocardial hypertrophy, heart failure, and arrhythmias from a physical and biomechanical perspective, bridging the gaps in traditional paradigms.

However, regarding therapeutic applications, no specific drugs in clinical practice currently target these mechanosensitive channels. At this stage, our interventions targeting the cardiac mechanical environment still primarily rely on conventional approaches that improve macroscopic hemodynamics. Nevertheless, various experimental and pharmacological strategies are actively translating preclinical approaches into clinical applications.

A thorough understanding of cardiac biomechanical properties and their regulation under normal and disease conditions is essential to grasp cardiac function. Central to this is decoding how cardiac cells detect mechanical signals through mechanosensors and translate them into biological responses that control cell behavior, ECM remodeling, and overall heart function. Unraveling these mechanisms is key to understanding cardiovascular disease pathogenesis and advancing diagnostic and therapeutic innovations.

Cardiac mechanomedicine is rapidly evolving through interdisciplinary integration. Future progress will rely on combining multi-omics approaches to reveal how mechanical forces reshape molecular landscapes; leveraging artificial intelligence and machine learning to identify biomechanical biomarkers and predict disease from imaging and clinical data; and employing advanced biofabrication to create biomimetic disease models and next-generation implantable devices (Figure 4). Accelerating the translation of these innovations into clinical care is critical to advancing precision medicine and reducing the global burden of cardiovascular disease.

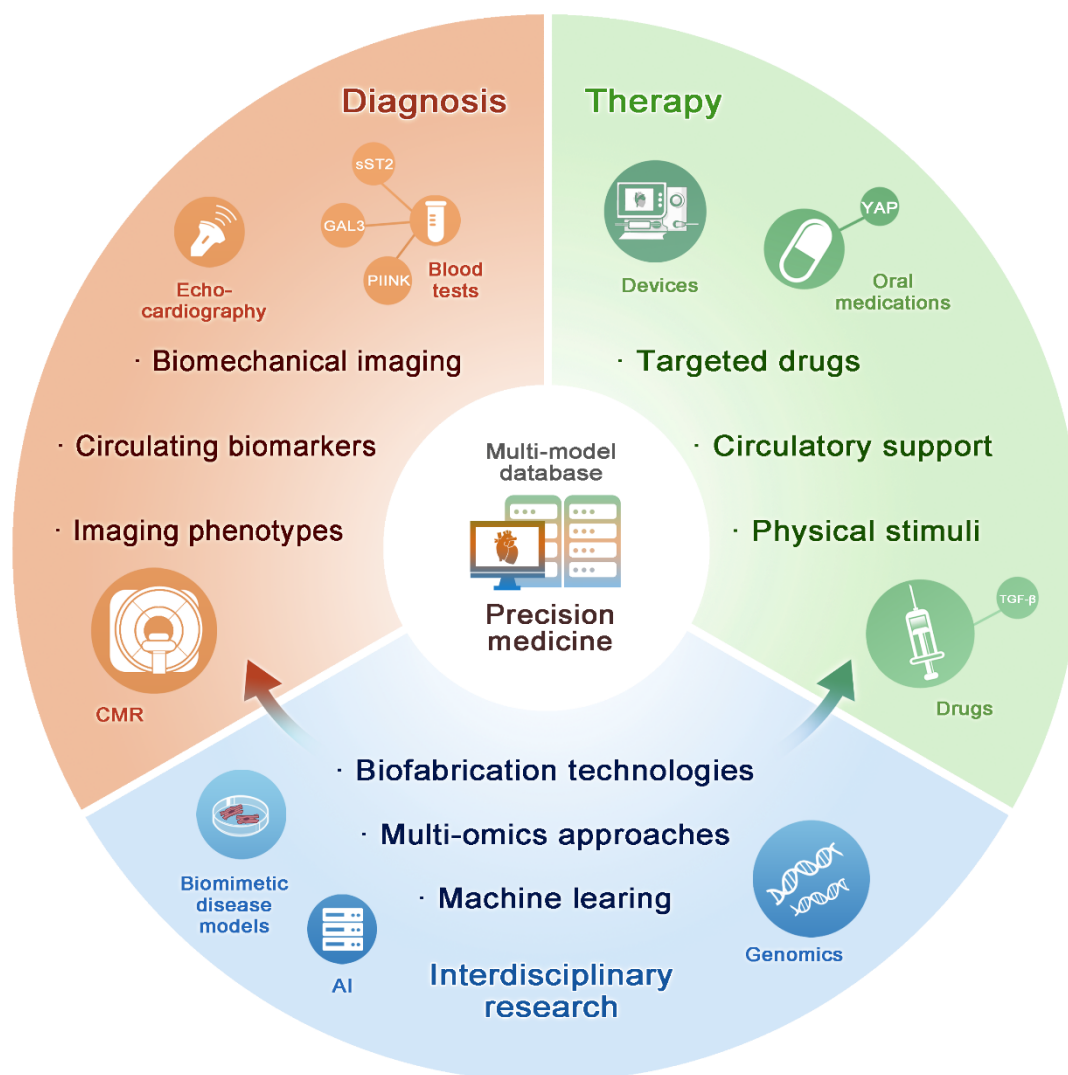


Figure 4. Interdisciplinary framework of cardiac mechanomedicine in precision medicine. The integrative, interdisciplinary framework of cardiac mechanomedicine leverages deep knowledge of cardiac biomechanics to bridge foundational research and clinical precision medicine. Created with Photoshop.

Abbreviations: AI: Artificial intelligence; CMR: Cardiovascular magnetic resonance.

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Conflict of interest

The authors declare no competing interests.

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