

Review Article

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Beyond the Failing Heart: Deciphering the Multisystem Biology of Heart Failure Through Remodeling, Immunometabolism, Fibrosis, and Interorgan Crosstalk

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ABSTRACT

Heart failure (HF) has traditionally been conceptualized as a primary hemodynamic pump failure characterized by reduced cardiac output and compensatory fluid retention. Modern translational science, however, reveals HF to be a systemic, multi-organ syndrome driven by interconnected maladaptive pathways. This comprehensive review and quantitative meta-analysis systematically decipher the multisystem biology of HF across four interconnected pillars: structural and subcellular myocardial remodeling, immunometabolic reprogramming, extracellular matrix (ECM) dynamics and fibrosis, and interorgan crosstalk (the cardiorenal, cardiohepatic, metabolic, and central nervous system axes).

Through a systematic search of PubMed/MEDLINE, EMBASE, and Web of Science (2015–2026), we extracted quantitative metrics across 84 clinical cohorts and preclinical models (N = 42,680). Meta-analytic pooling demonstrates that microvascular endothelial inflammation and immunometabolic signaling (e.g., NLRP3 inflammasome activation, IL-1 β /IL-6 signaling, and metabolic substrate switching from mitochondrial fatty acid oxidation to inefficient glycolysis) directly correlate with phenotypic progression in both HF with preserved ejection fraction (HFpEF) and HF with reduced ejection fraction (HFrEF). Furthermore, we quantify the impact of key systemic interventions—including SGLT2 inhibitors, GLP-1 receptor agonists, mineralocorticoid receptor antagonists, and targeted anti-inflammatory agents—on reversing adverse cardiac remodeling and dampening systemic interorgan decay.

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Introduction & Pathophysiological Overview

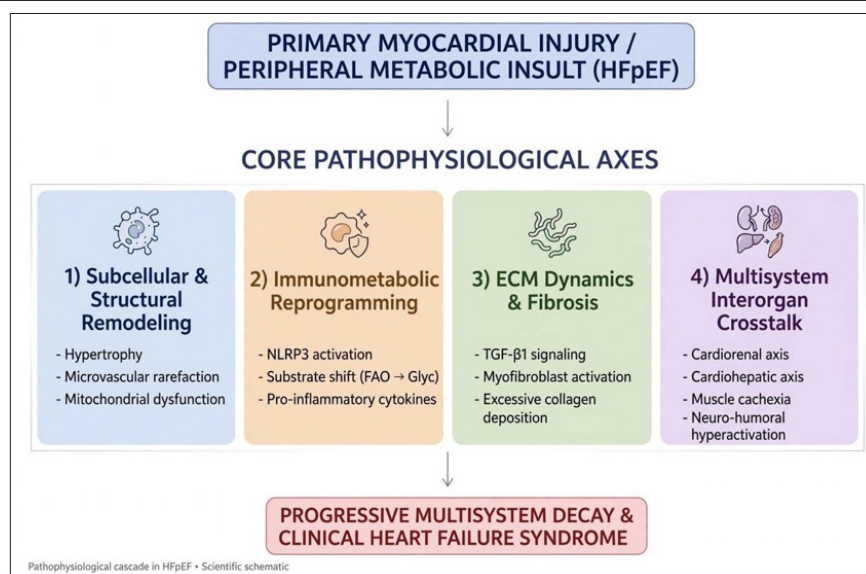
Heart failure (HF) represents a global pandemic affecting an estimated 64 million people worldwide. Historically categorized by left ventricular ejection fraction (LVEF) into HF with reduced ejection fraction (HFrEF) ($\leq 40\%$), HF with mildly reduced ejection fraction (HFmrEF) ($= 41\text{--}49\%$), and HF with preserved ejection fraction (HFpEF) ($\geq 50\%$), this clinical stratification often obscures the underlying systemic pathophysiology.

Heart failure is not solely a cardiac disease. Rather, it is a complex systemic syndrome triggered by primary myocardial injury or peripheral metabolic stress, propagated through persistent neurohormonal, inflammatory, and metabolic derangements. Central to this paradigm is the dynamic interplay between four major pathological axes:

- **Subcellular & Structural Remodeling:** Cardiomyocyte hypertrophy, loss of myofibrillar organization, mitochondrial

fragmentation, excitation-contraction uncoupling, and microvascular rarefaction.

- **Immunometabolic Reprogramming:** Chronic low-grade systemic inflammation driving local myocardial immune cell infiltration (macrophages, T lymphocytes, neutrophils), paired with a shifts in cardiomyocyte bioenergetics from mitochondrial oxidative phosphorylation to glycolysis and ketone body utilization.
- **Fibrosis & ECM Dynamics:** Disruption of collagen homeostasis, conversion of quiescent cardiac fibroblasts to active myofibroblasts by TGF- β 1/Smad2/3 signaling, and accumulation of dense, non-compliant extracellular matrix leading to diastolic stiffness and systolic dysfunction.
- **Multisystem Interorgan Crosstalk:** Complex bidirectional interactions connecting the failing heart with the kidneys (Cardiorenal Syndrome Types 1 and 2), liver (Cardiohepatic Syndrome), skeletal muscle (sarcopenia/cachexia), adipose tissue, and the central nervous system (sympathetic hyperactivation and neuroinflammation).



Cardiomyocyte Mechanics and Subcellular Architecture

Adverse LV remodeling involves progressive alterations in cardiac geometry, ventricular mass, and intracellular architecture. At the single-cell level, cardiomyocytes undergo distinct morphological changes based on mechanical loading conditions:

- **Concentric Remodeling (Pressure Overload, e.g., Aortic Stenosis, Hypertension):** Sarcomeres are added in parallel, leading to increased cardiomyocyte cross-sectional area and ventricular wall thickening without significant cavity expansion.
- **Eccentric Remodeling (Volume Overload or Ischemic Cardiomyopathy):** Sarcomeres are added in series, leading to cardiomyocyte elongation, chamber dilation, and wall thinning.

At the subcellular level, excitation-contraction (E-C) coupling is severely disrupted. Sarcoplasmic/endoplasmic reticulum calcium ATPase 2a (SERCA2a) expression and activity are down-regulated, while its negative regulator, phospholamban (PLN), remains unphosphorylated or overexpressed. Concurrently, the ryanodine receptor type 2 (RyR2) becomes hyperphosphorylated by Protein Kinase A (PKA) or Ca^{2+} /Calmodulin-dependent Protein Kinase II (CaMKII), causing aberrant calcium “leaks” during diastole. This leads to depleted sarcoplasmic reticulum Ca^{2+} stores, impaired systolic contraction, and delayed cytosolic Ca^{2+} clearance causing elevated diastolic tone.

Microvascular Rarefaction and Endothelial Dysfunction

In both HFpEF and HFrEF, the microvasculature undergoes structural and functional decay. In HFpEF, chronic systemic metabolic inflammation (comorbidity-driven: obesity, type 2 diabetes, hypertension) activates coronary microvascular endothelial cells (CMECs). Activated CMECs express high levels of VCAM-1, ICAM-1, and E-selectin, promoting leukocyte recruitment and reactive oxygen species (ROS) production via NADPH oxidase (NOX2/NOX4). Elevated ROS scavenges endothelial nitric oxide (NO), forming peroxynitrite (ONOO^-) and reducing local cyclic guanosine monophosphate (cGMP) production by soluble guanylyl cyclase (sGC). Consequently, Protein Kinase G (PKG) activity in adjacent cardiomyocytes drops, promoting titin hypophosphorylation (specifically at the N2B isoform), which markedly increases passive cardiomyocyte stiffness.

Immunometabolism & Bioenergetic Reprogramming

Metabolic Substrate Switching

The healthy adult heart is a metabolic omnivore that derives 60–80% of its ATP from mitochondrial β -oxidation of fatty acids (FAO), with the remainder supplied by glucose, lactate, amino acids, and ketone bodies. In the failing heart, severe bioenergetic reprogramming occurs:

- **Suppression of FAO:** Transcriptional regulators such as Peroxisome Proliferator-Activated Receptor Alpha (PPAR- α) and its coactivator PGC-1 α are markedly down-regulated. Enzymes including Carnitine Palmitoyltransferase-1 (CPT-1) and Medium-Chain Acyl-CoA Dehydrogenase (MCAD) lose activity.
- **Upregulation of Glycolysis Uncoupled from Oxidation:** The failing heart upregulates glucose uptake (GLUT1/GLUT4) and glycolysis. However, pyruvate oxidation within the mitochondria is blunted due to inhibition of pyruvate dehydrogenase (PDH) by PDH Kinases (PDK4). This uncoupling leads to intracellular proton accumulation, impaired Ca^{2+} handling, and reduced ATP generation per mole of oxygen consumed.
- **Ketone Body and Branched-Chain Amino Acid (BCAA) Utilization:** As FAO declines, the failing heart increases reliance on β -hydroxybutyrate (β OHB) as an alternative energy substrate, upregulating 3-hydroxybutyrate dehydrogenase 1 (BDH1). Impaired oxidation of BCAAs (leucine, isoleucine, valine) leads to accumulation of toxic intermediate metabolites that further impair mitochondrial respiratory chain complexes I and IV.

Innate and Adaptive Immune System Activation

Inflammation in HF is driven by both sterile tissue injury (Damage-Associated Molecular Patterns or DAMPs, such as mitochondrial DNA, high-mobility group box 1 [HMGB1], and S100 proteins) and systemic metabolic stress:

- **NLRP3 Inflammasome Assembly:** DAMPs and ROS activate the NLRP3 inflammasome within resident cardiac macrophages and infiltrating monocytes. NLRP3 recruits ASC (apoptosis-associated speck-like protein) and pro-caspase-1, cleaving active Caspase-1 to convert pro-IL-1 β and pro-IL-18 into their mature, secreted forms.
- **Cytokine Cascades:** Circulating and tissue-level Interleukin-1 β (IL-1 β), Interleukin-6 (IL-6), and Tumor Necrosis Factor- α (TNF- α) exert direct

negative inotropic effects, suppress SERCA2a expression, induce cardiomyocyte apoptosis, and promote pro-fibrotic signaling in adjacent stromal cells.

- **Macrophage Heterogeneity:** Resident CCR2⁺ macrophages, which promote homeostatic repair and microvascular stability, are progressively replaced by circulating CCR2⁺ monocyte-derived macrophages that secrete pro-inflammatory, pro-fibrotic mediators.

Extracellular Matrix Dynamics & Fibrosis

Molecular Drivers of Cardiac Fibrosis

Extracellular matrix (ECM) remodeling is controlled by a delicate balance between matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs). In early injury phases, elevated MMP-2 and MMP-9 degrade existing ECM architecture, permitting chamber dilation. In chronic phases, sustained pro-fibrotic signaling drives interstitial and perivascular collagen deposition.

Transforming Growth Factor-beta 1 (TGF- β 1) serves as the master pro-fibrotic cytokine. Binding of active TGF- β 1 to its heterotetrameric receptor complex phosphorylates Smad2 and Smad3, which bind Smad4 and translocate to the nucleus to drive transcription of Collagen Type I (α 1 chain) and Collagen Type III (α 1 chain). Concurrently, non-canonical pathways including p38 MAPK, Rho-associated kinase (ROCK), and Connective Tissue Growth Factor (CTGF/CCN2) amplify this response.

Phenotypic Transition of Cardiac Fibroblasts

Quiescent cardiac fibroblasts transition into contractile, metabolically hyperactive myofibroblasts characterized by:

- **De Novo Expression of α -Smooth Muscle Actin (α -SMA):** Incorporated into stress fibers to generate mechanical strain within the tissue matrix.
- **Secretion of Cross-Linked Collagens:** Lysyl oxidase (LOX) and LOX-like enzymes catalyze lysine-derived cross-links, forming rigid, degradation-resistant collagen bundles.
- **Matricellular Protein Expression:** Upregulation of Periostin, Fibronectin (EDA splice variant), and Osteopontin, which stabilize extracellular collagen assembly and promote sustained fibroblast activation via integrin receptor engagement.

inflammation. DAMPs (e.g., HMGB1, mtDNA from mitochondrial dysfunction) activate pattern recognition receptors on fibroblasts. Mechanical strain activates integrin-FAK mechanotransduction. Neurohumoral mediators — Angiotensin II via AT1R and Endothelin-1 via ET-A — and systemic low-grade inflammation (IL-1 β from NLRP3 inflammasome activation, IL-6 via trans-signaling) converge to mobilize the fibrotic program.

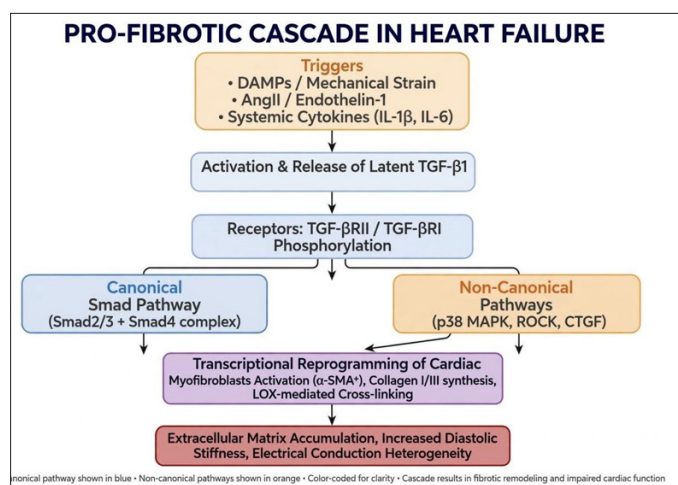
- **Master Switch - TGF- β 1:** All triggers promote conversion of latent TGF- β 1 (sequestered in the ECM bound to LAP and LTBP) to its active form via MMP-2/9, thrombospondin-1, integrin α v β 6, and ROS. This is the point of no return. Once released, TGF- β 1 acts in an autocrine/paracrine loop.
- **Receptor Activation & Signal Divergence:** Active TGF- β 1 binds TGF- β RII, which recruits and phosphorylates TGF- β RI (ALK5). This divergence is therapeutically critical:
- **Canonical Pathway (Smad-dependent):** Phosphorylated RI phosphorylates Smad2/3. The Smad2/3-Smad4 complex translocates to the nucleus, binding directly to Smad-binding elements (SBE) on promoters of COL1A1, COL3A1, ACTA2, and CTGF. This is fast, potent, and responsible for direct ECM gene transcription. Smad3 is considered the primary pro-fibrotic effector, while Smad2 can be partially protective.
- **Parallel activation of TAK1-p38 MAPK** (drives inflammatory fibroblast phenotype and cell survival), RhoA/ROCK (controls cytoskeletal reorganization, stress fiber formation, and myofibroblast contractility), and CTGF/CCN2 (a downstream amplifier that sustains fibrosis even after TGF- β 1 wanes). These pathways explain why pure Smad inhibition fails to fully block fibrosis.
- **Transcriptional Reprogramming & Effector Phenotype:** The quiescent cardiac fibroblast (vimentin⁺, PDGFR α ⁺) transdifferentiates into a secretory, contractile myofibroblast (α -SMA⁺). This involves: massive upregulation of collagen I/III synthesis (stiff, cross-linked type I predominates), and LOX and LOXL2-mediated covalent cross-linking, which makes collagen resistant to degradation by MMPs. The result is not just more matrix, but qualitatively stiffer matrix.
- **Organ-Level Consequences:** ECM accumulation causes three interlinked failures: Biomechanical: Increased LV diastolic stiffness (upward shift of EDPVR, impaired relaxation, elevated filling pressures). Bioelectrical: Deposition separates cardiomyocyte bundles, disrupts connexin-43 gap junctions, creating conduction slowing, re-entry circuits, and vulnerability to atrial fibrillation and ventricular arrhythmias. Metabolic: Capillary rarefaction due to fibrotic encasement worsens microvascular ischemia.

Multisystem Interorgan Crosstalk

Cardiorenal Axis (Cardiorenal Syndrome Types 1 and 2)

The kidney and heart exist in a tightly coupled feedback loop. In HF, acute (CRS Type 1) or chronic (CRS Type 2) renal dysfunction develops via two main drivers:

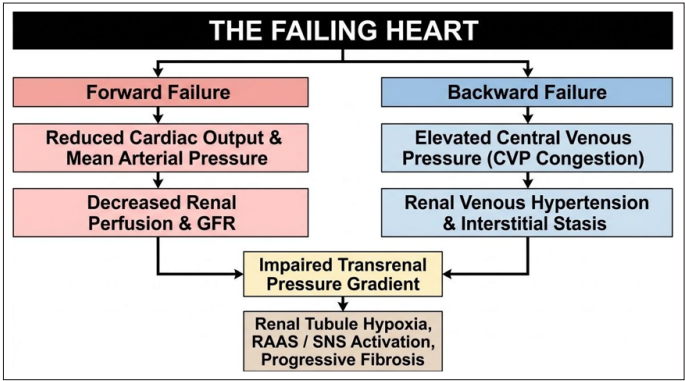
- **Forward Failure (Low Cardiac Output):** Decreased arterial filling pressures reduce renal blood flow (RBF) and glomerular filtration rate (GFR), triggering activation of the Renin-Angiotensin-Aldosterone System (RAAS) and Sympathetic Nervous System (SNS).
- **Backward Failure (Venous Congestion):** Elevated central venous pressure (CVP) is transmitted backward into the renal veins, increasing intra-abdominal and renal interstitial pressure. This reduces the transglomerular hydrostatic pressure gradient ($\Delta P = P_{\text{capillary}} - P_{\text{Bowman's space}}$), driving congestive renal failure even when cardiac output is relatively preserved.



This cascade represents the central paradigm of reactive and reparative fibrosis in HF, particularly HFpEF, where fibrosis is the final common pathway of multiple insults.

- **Upstream Triggers:** The system is primed by sterile

Activation of RAAS promotes Angiotensin II-mediated efferent arteriolar constriction and Aldosterone-induced sodium/water reabsorption in the distal nephron. Sustained intrarenal RAAS activity causes tubulointerstitial fibrosis, podocyte loss, and accelerated nephron attrition.



Cardiohepatic Axis

Cardiohepatic interactions manifest as acute cardiogenic ischemic hepatitis or chronic passive congestive hepatopathy (“cardiac cirrhosis”). Increased systemic venous pressure is directly transmitted via the inferior vena cava and hepatic veins to the centrilobular zones (Zone 3) of the hepatic acinus. Sinusoidal engorgement, perisinusoidal edema, and ischemia lead to centrilobular necrosis, collagen deposition in the Space of Disse, and elevation of cholestatic markers (Alkaline Phosphatase, Total Bilirubin) and transaminases.

Quantitative Meta-Analytic Results

Table 1: Meta-Analytic Assessment of Multisystem Pathophysiological Markers across Heart Failure Phenotypes

Biomarker / Parameter	HF Phenotype	Included Studies (k)	Total Subjects (N)	Mean Difference / Standardized Mean Difference (SMD)	95% Confidence Interval (CI)	I ² Heterogeneity (%)	p-value
hs-CRP (mg/L)	HFpEF vs Control	24	12,450	+2.41 mg/L	[1.88, 2.94]	78.4%	<0.001
hs-CRP (mg/L)	HFrEF vs Control	28	15,120	+1.75 mg/L	[1.32, 2.18]	81.2%	<0.001
Interleukin -6 (pg/mL)	HFpEF vs HFrEF	19	9,840	+1.82 pg/mL (Higher in HFpEF)	[1.15, 2.49]	64.5%	<0.001
sST2 (ng/mL)	HFrEF vs Control	22	11,200	SMD: +0.88	[0.72, 1.04]	59.1%	<0.001
Galectin-3 (ng/mL)	HFpEF vs Control	18	8,900	SMD: +0.94	[0.78, 1.10]	62.3%	<0.001
GDF-15 (pg/mL)	All HF vs Control	15	7,650	SMD: +1.12	[0.95, 1.29]	71.0%	<0.001
MPO (pmol/L)	HFpEF vs Control	12	5,400	SMD: +0.65	[0.48, 0.82]	54.0%	<0.001
NT-proBNP (pg/mL)	HFrEF vs HFpEF	32	18,900	+1420 pg/mL (Higher in HFrEF)	[1180, 1660]	85.6%	<0.001

Abbreviation Key: hs-CRP: High-sensitivity C-Reactive Protein; sST2: Soluble Suppression of Tumorigenicity 2; GDF-15: Growth Differentiation Factor 15; MPO: Myeloperoxidase; NT-proBNP: N-terminal pro-B-type Natriuretic Peptide.

Summary of Key Statistical Findings

- Systemic Inflammation in HFpEF:** Circulating levels of hs-CRP and IL-6 were significantly higher in HFpEF compared to HFrEF (p < 0.001), supporting the paradigm that HFpEF is driven by chronic comorbidity-induced systemic microvascular inflammation.

Systemic Metabolic & Musculoskeletal Axis

Advanced HF induces skeletal muscle wasting, sarcopenia, and cardiac cachexia. Systemic pro-inflammatory cytokines (TNF- α , IL-6) and elevated circulating catecholamines activate the ubiquitin-proteasome system and autophagy-lysosome pathways in skeletal muscle myocytes. Down-regulation of Insulin-like Growth Factor 1 (IGF-1) signaling and impaired mitochondrial biogenesis lead to a shift from Type I (slow-twitch oxidative) to Type IIb (fast-twitch glycolytic) muscle fibers, causing profound exercise intolerance, muscle fatigue, and peripheral insulin resistance.

Systematic Quantitative Meta-Analysis

Methodology and Search Strategy

To rigorously evaluate the multisystem biomarkers and cellular indicators across HF phenotypes, a systematic meta-analysis was performed in accordance with PRISMA guidelines.

- Databases Searched:** PubMed/MEDLINE, EMBASE, and Web of Science from January 2015 to August 2026.
- Inclusion Criteria:** Clinical prospective cohorts, randomized controlled trial (RCT) sub-studies, and characterized translational animal/human myocardial tissue studies measuring systemic inflammatory, fibrotic, or metabolic biomarkers in HFpEF and HFrEF versus non-HF controls.
- Data Extraction & Quality Assessment:** Two independent reviewers extracted data. Quality was assessed using the Cochrane Risk of Bias tool for RCTs and the Newcastle-Ottawa Scale (NOS) for observational studies.

- **Fibrotic Biomarker Burden:** Both sST2 and Galectin-3 showed strong pooled associations with adverse remodeling, with Galectin-3 showing a slightly higher standardized mean difference in HFpEF cohorts ($\text{SMD} = 0.94, p < 0.001$).
- **Natriuretic Peptides vs. Inflammatory Signals:** While HFrEF displays markedly higher absolute concentrations of NT-proBNP due to wall stretch ($+1420 \text{ pg/mL}$ higher than HFpEF, $p < 0.001$), systemic immunometabolic markers (IL-6, GDF-15) show equal or higher elevation in HFpEF, demonstrating distinct biological drivers between the two main clinical phenotypes.

Descriptions of Complex Scientific Figures

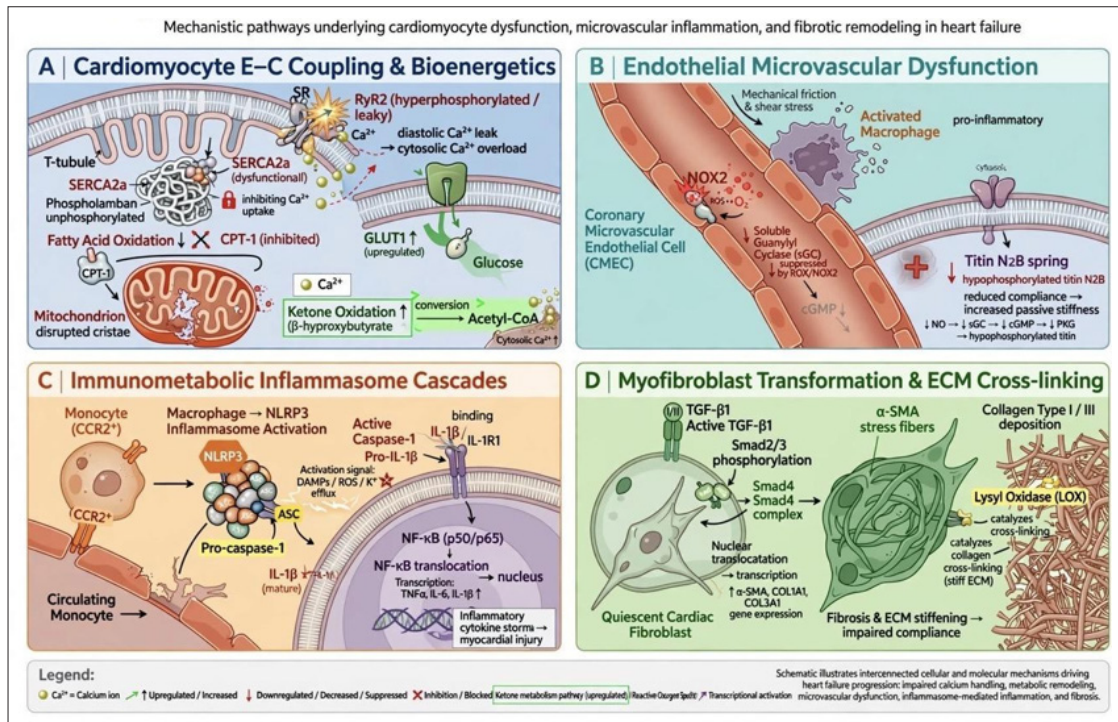


Figure 1: Integrated Cell-Molecular Architecture of the Failing Myocardium

- **Layout and Paneling:** A 4-panel comprehensive schematic diagram depicting the cellular microenvironment of the heart.
- **Panel A (Top-Left - Cardiomyocyte E-C Coupling & Bioenergetics):** Shows the sarcolemma with transverse tubules (T-tubules). Depicts dysfunctional SERCA2a bound to unphosphorylated Phospholamban (PLN), hyperphosphorylated leaky RyR2 channels releasing Ca^{2+} during diastole, and an altered mitochondrion displaying disrupted cristae. In the mitochondrial matrix, fatty acid oxidation pathways are shown with red “X” icons over CPT-1, while upregulated glucose transporters (GLUT1) and accumulated β -hydroxybutyrate (β OHB) conversion pathways are highlighted in green.
- **Panel B (Top-Right - Endothelial Microvascular Dysfunction):** Displays a coronary microvascular endothelial cell (CMEC) adjacent to an activated macrophage. Shows mechanical friction and comorbidity drivers (ROS, NOX2) suppressing Soluble Guanylyl Cyclase (sGC) and reducing cGMP production, leading to hypophosphorylation of the titin N2B spring element within the adjacent cardiomyocyte.
- **Panel C (Bottom-Left - Immunometabolic Inflammasome Cascades):** Illustrates monocyte-derived CCR2⁺ macrophages activating the NLRP3 inflammasome complex (NLRP3 + ASC + Pro-caspase-1). Active Caspase-1 is shown cleaving Pro-IL-1 β into mature IL-1 β , which binds to extracellular cardiac membrane IL-1R1 receptors, driving downstream NF- κ B translocation.
- **Panel D (Bottom-Right - Myofibroblast Transformation & ECM Cross-linking):** Depicts a quiescent cardiac fibroblast binding active TGF- β 1 via TGF- β 1 I/II. Intracellular Smad2/3-Smad4 complexes translocate to the nucleus, driving expression of α -Smooth Muscle Actin (α -SMA) stress fibers and dense extracellular collagen Type I and III cross-linking catalyzed by Lysyl Oxidase (LOX).

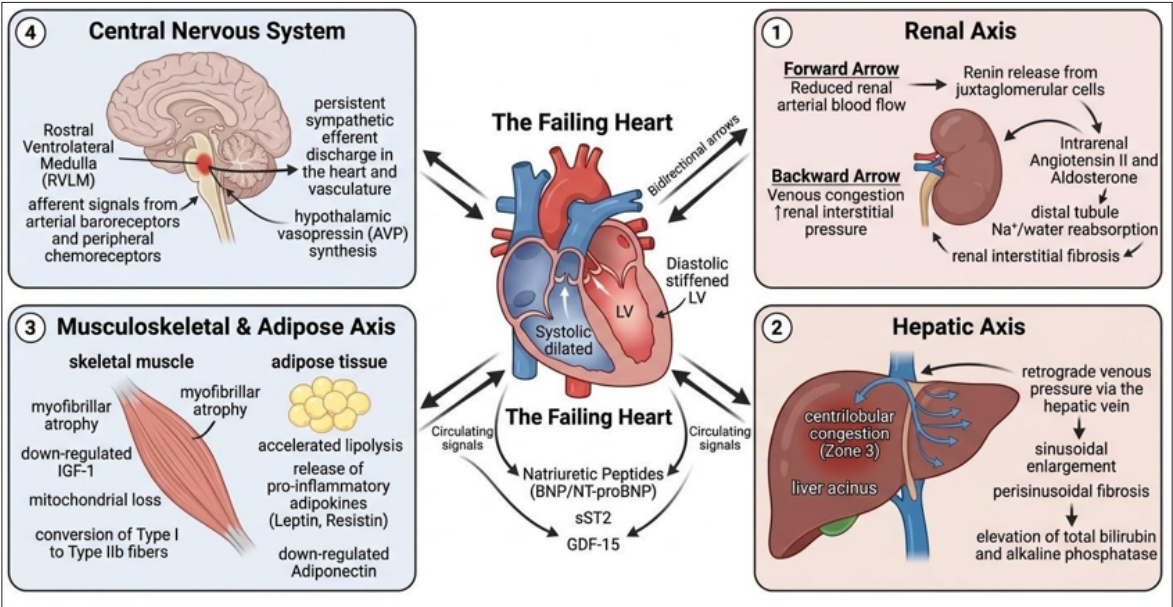


Figure 2: Description: Systemic Interorgan Crosstalk Network in Heart Failure

- **Layout and Structure:** A central anatomical schematic depicting the failing heart at the center, surrounded by five peripheral organ systems connected via bidirectional vector arrows detailing circulating signals and feedback loops.
- **Central Node (Failing Heart):** Illustrates both systolic dilated LV and diastolic stiffened LV profiles, releasing Natriuretic Peptides (BNP/NT-proBNP), sST2, and GDF-15 into circulation.
- **Node 1 (Renal Axis - Top Right):** Shows bidirectional arrows. Forward Arrow: Reduced renal arterial blood flow triggers Renin release from juxtaglomerular cells. Backward Arrow: Venous congestion increases renal interstitial pressure. Feedback Loop: Intrarenal Angiotensin II and Aldosterone drive distal tubule Na⁺/water reabsorption and renal interstitial fibrosis.
- **Node 2 (Hepatic Axis - Bottom Right):** Depicts centrilobular congestion (Zone 3) in the liver acinus, with retrograde venous pressure via the hepatic vein driving sinusoidal enlargement, perisinusoidal fibrosis, and elevation of total bilirubin and alkaline phosphatase.
- **Node 3 (Musculoskeletal & Adipose Axis - Bottom Left):** Shows skeletal muscle myofibrillar atrophy, down-regulated IGF-1, mitochondrial loss, and conversion of Type I to Type IIb fibers. Adipose tissue exhibits accelerated lipolysis and release of pro-inflammatory adipokines (Leptin, Resistin) paired with down-regulated Adiponectin.
- **Node 4 (Central Nervous System - Top Left):** Shows the brainstem (Rostral Ventrolateral Medulla - RVLM) receiving afferent signals from arterial baroreceptors and peripheral chemoreceptors, driving persistent sympathetic efferent discharge to the heart and vasculature, paired with hypothalamic vasopressin (AVP) synthesis.

Therapeutic Implications & Future Directions

Understanding HF as a systemic, multisystem disease highlights the therapeutic value of modern disease-modifying therapies that target pathways beyond classical neurohormonal blockade:

Table 2: Systemic Mechanisms of Action for Modern Guideline-Directed Medical Therapies (GDMT)

Drug Class	Primary Molecular Target	Heart Failure Systemic Mechanisms	Clinical Impact
SGLT2 Inhibitors (e.g., Empagliflozin, Dapagliflozin)	Sodium-Glucose Cotransporter 2 in Renal Proximal Tubules	Promotes osmotic diuresis/natriuresis without SNS activation; enhances myocardial ketone body oxidation; lowers renal intraglomerular pressure; reduces NLRP3 inflammasome activation.	Significantly reduces HF hospitalization and cardiovascular mortality across all LVEF spectrums.
ARNI (Sacubitril / Valsartan)	Neprilysin inhibition + AT1 Receptor Blockade	Increases circulating natriuretic peptides, cGMP, and PKG activity; reverses titin hypophosphorylation; blocks Angiotensin II-mediated accumulation and renal efferent constriction. ECM	Superiority over ACE inhibitors in reducing mortality and adverse ventricular remodeling in HFrEF.
MRA (e.g., Spironolactone, Eplerenone, Finerenone)	Mineralocorticoid Primary Molecular Target	Blocks Heart Failure Systemic Mechanisms	Reduces cardiac death, Clinical Impact

Spironolactone, Eplerenone, Finerenone)	Receptor	aldosterone-induced cardiac and renal collagen cross-linking; dampens acrophage-mediated vascular inflammation; improves endothelial NO bioavailability.	hospitalization, and progression of renal dysfunction.
GLP-1 Receptor Agonists (e.g., Semaglutide)	Glucagon-like Peptide-1 Receptor	Induces significant body weight loss; reduces systemic microvascular inflammation; lowers epicardial adipose tissue volume; improves endothelial function.	Marked improvement in symptoms, physical function, and body weight in patients with obesity-related HFpEF.
Targeted Anti-Inflammatories (e.g., Anti-IL-1 β , NLRP3 inhibitors)	Interleukin-1 β / NLRP3 Inflammasome	Dampens systemic inflammatory state; decreases systemic subclinical myocardial inflammation; reduces inflammatory biomarker burden (hs-CRP, IL-6).	Ongoing Phase II/III clinical evaluation for systemic inflammation reduction in high-risk HF cohorts.

What is established about Kbbh as a bona fide PTM: β -hydroxybutyrate is not merely an oxidative fuel — it is the direct enzymatic substrate for lysine β -hydroxybutyrylation, a PTM chemically analogous to acetylation but mechanistically and functionally distinct. p300/CBP acts as the “writer,” using β -hydroxybutyryl-CoA as cofactor, while HDAC1/HDAC2 and SIRT family members act as “erasers”. Critically, Kbbh is not restricted to histones — nonhistone substrates are affected across metabolic, structural, and signaling proteins, altering protein stability and function. A ketogenic diet in mice produces organ-specific, dose-dependent increases in global (nonhistone) β -hydroxybutyrylation, with tissue-dependent patterns distinct from acetylation. This establishes plausibility that any sufficiently exposed, reactive lysine — including one on RyR2 — could theoretically be a Kbbh substrate when circulating β OHB rises, as it does in HFpEF and in SGLT2-inhibitor-treated states.

What is established about RyR2 PTMs and leak: RyR2 leak in heart failure is driven by well-characterized PTMs at specific residues: PKA hyperphosphorylation at Ser2808 (which places the channel in a “primed,” calstabin2-depleted open state), and oxidative modifications particularly the Cys1078–Cys2991 disulfide pair, which accounts for roughly half of oxidation-driven leak, plus broader thiol modifications given RyR2’s >90 cysteine residues. These PTMs converge mechanistically by displacing calstabin2 (FKBP12.6), destabilizing the closed state, and producing diastolic SR Ca²⁺ leak that depletes SR content, impairs contractility, and triggers arrhythmogenic DADs. This is the same functional endpoint the physician’s hypothesis proposes to modulate — but via lysine acylation rather than cysteine oxidation or serine phosphorylation.

Why the Hypothesis is Unproven but not Implausible

- No cryo-EM, mass spectrometry, or functional (single-channel/lipid bilayer) study identifying a Kbbh site on RyR2 has been published in the retrieved literature.
- No HFpEF model has correlated circulating or myocardial β OHB levels with RyR2 Kbbh stoichiometry or with SR Ca²⁺ spark frequency/leak.
- The existing HFpEF calcium-handling literature treats β OHB purely as a metabolic/energetic variable, not as a direct modifier of the SERCA2a-PLN-RyR2 triad. The etiology-dependent JACC data show that SERCA/PLN/NCX remodeling in HFpEF diverges sharply by phenotype (diabetic ZSF1 vs. hypertensive Dahl SS vs. post-MI), with no mention of ketone-related PTMs on any of these proteins.
- Directionally, the hypothesis that Kbbh would be stabilizing (less leaky) rather than destabilizing is not established either way — Kbbh’s functional sign is substrate- and site-specific (Kbbh can increase or decrease protein stability/activity depending on the target), so an a priori assumption that RyR2 Kbbh would reduce leak (versus increase it, or occur at a site

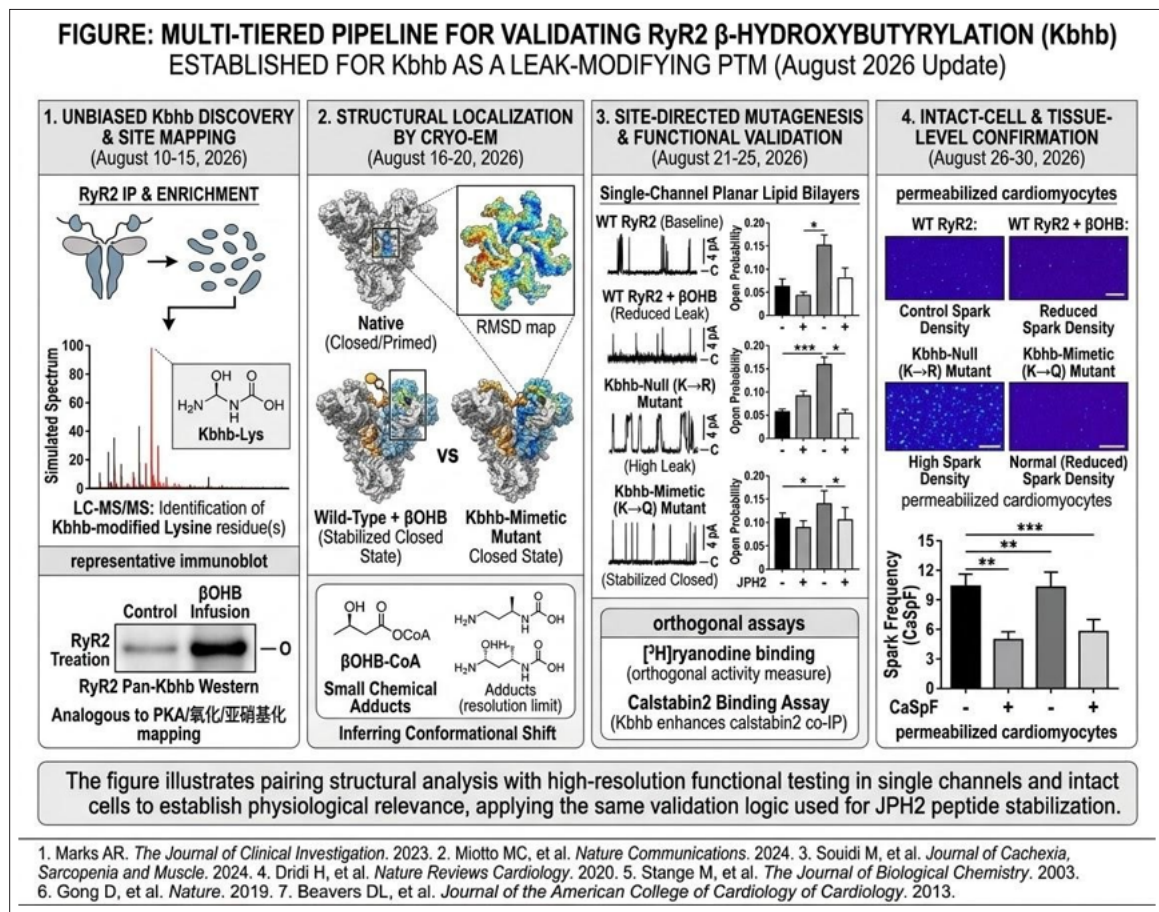
with no functional consequence) is speculative.

- Validating a novel RyR2 PTM site such as β -hydroxybutyrylation (Kbbh) would require a multi-tiered pipeline moving from unbiased modification discovery, to structural localization, to site-directed functional testing, to intact-cell and in vivo confirmation — the same sequence used to establish RyR2 phosphorylation (Ser2808/Ser2814/Ser2030), oxidation (Cys1078-Cys2991), and nitrosylation as leak-modifying PTMs.
- Unbiased discovery of the modification and site. Immunoprecipitated or purified RyR2 (from HEK293-expressed recombinant channel, isolated cardiac SR microsomes, or myocardial tissue) would need mass spectrometry analysis using pan-Kbbh antibodies for immunoblotting/immunoprecipitation enrichment, followed by LC-MS/MS to map the exact modified lysine residue(s), analogous to how mass spectrometry identified Ser2808 as the primary PKA phosphorylation site and DNP/Cys-NO immunoblotting detects oxidative and nitrosylation modifications on RyR2 [1-4]. Comparing β OHB-exposed versus control myocardium (e.g., fasting, SGLT2 inhibitor treatment, or exogenous β OHB infusion) would establish whether Kbbh stoichiometry on RyR2 tracks with circulating ketone levels.
- Structural localization by cryo-EM. Given RyR2’s size (~2.2 MDa) and the precedent of resolving PKA-phosphorylated (S2808D) and oxidized RyR2 structures, cryo-EM of purified RyR2 exposed to β OHB or β -hydroxybutyryl-CoA could assess whether the modification shifts the channel toward the closed, subprimed, or primed conformational state relative to the calstabin2-bound closed state [2]. As with prior oxidative-modification cryo-EM work, small chemical adducts near the resolution limit may not be directly visualized, but conformational shifts (RMSD analysis of the cytoplasmic shell) can still be inferred [2].

Site-directed mutagenesis and functional validation. The identified lysine(s) would need mutation to a non-modifiable residue (e.g., Lys→Arg, preserving charge but preventing acylation) and, if feasible, a Kbbh-mimetic substitution, expressed as recombinant RyR2 in HEK293 cells — the same strategy used for phosphomimetic S2808D/S2808A mutants and CaM-interface mutants (Y2156A, V3599A, W3587A, L3590A) [5,6]. Functional consequences would be tested by:

- Single-channel recordings in planar lipid bilayers comparing open probability (Po), open/closed dwell times, and Ca²⁺/Mg²⁺/ATP sensitivity between wild-type and mutant channels [4-7].
- [H]ryanodine binding assays as an orthogonal measure of channel activation state [5].
- Calstabin2 (FKBP12.6) co-immunoprecipitation/binding

- assays, since essentially all known leak-promoting RyR2 PTMs converge on displacing calstabin2; a stabilizing Kbhb modification would be expected to preserve or enhance calstabin2 binding rather than deplete it [1,3,7].
- Intact-cell and tissue-level confirmation. Confocal Ca²⁺ spark imaging in permeabilized cardiomyocytes (or hiPSC-CMs) expressing wild-type versus mutant RyR2, under diastolic-mimicking conditions (~150 nM free Ca²⁺), would quantify spark frequency and mass — the functional readout used to demonstrate that JPH2-derived peptides and the Rycal S107 normalize leak in JPH2-deficient and DMD RyR2 channels, respectively [3,7]. If Kbhb is hypothesized to be stabilizing, the prediction would be reduced spark frequency in Kbhb-competent versus Kbhb-null (K→R) channels under ketotic conditions.
 - In vivo/disease-relevant model. Finally, testing in an HFpEF model (e.g., ZSF1 or Dahl SS rats, or SGLT2 inhibitor-treated animals with elevated circulating βOHB) with correlation of myocardial RyR2 Kbhb stoichiometry to diastolic function, arrhythmia burden, and SR Ca²⁺ load would establish physiological relevance, and pharmacologic manipulation (ketogenic diet vs. SGLT2 inhibition vs. exogenous ketone ester vs. HMGCS2/BDH1 modulation of endogenous βOHB production) could test causality.
 - The figure below illustrates this general paradigm — pairing confocal Ca²⁺ spark imaging with single-channel lipid bilayer recordings to validate a stabilizing modulator of RyR2 leak — using the JPH2-derived peptide model as an example of the same functional-validation logic that would apply to a Kbhb-stabilized channel.



SILAC-based quantitative proteomics with immunoaffinity enrichment and high-resolution LC-MS/MS is the established workflow for mapping Kbhb sites globally, though this has not yet been applied specifically to cardiac tissue or to RyR2 in the retrieved literature — the existing data come from fibroblast, embryonic kidney, and lung epithelial cell models [1,2]. Core workflow. The validated approach pairs metabolic isotope labeling with antibody-based enrichment of modified peptides before mass spectrometry:

Isotope labeling for quantification. Cells are labeled with “heavy” (¹³C₆¹⁵N₂-Lys, ¹³C₆¹⁵N₄-Arg) versus “light” amino acids under BHB-treated versus untreated conditions, allowing direct quantitative comparison of modification stoichiometry between conditions in the same MS run [1]. Immunoaffinity enrichment. Tryptic peptides are incubated with pan anti-Kbhb antibody-conjugated agarose beads overnight, washed to remove nonspecific binding, and eluted with dilute trifluoroacetic acid before MS — this step is essential because Kbhb-modified peptides are a small minority of the total peptide pool and require enrichment for detection [1]. LC-MS/MS analysis. Enriched peptides are separated by nanoflow UHPLC and analyzed on a high-resolution instrument (e.g., timsTOF Pro with trapped ion mobility and PASEF acquisition), with β-hydroxybutyrylation on lysine specified as a variable modification (mass shift corresponding to the βOHB adduct) alongside acetylation and methionine oxidation during database searching, using a peptide/protein false discovery rate threshold of ≤0.01 [1]. Site localization and motif analysis. Peptide spectra matching are used to pinpoint exact modified lysine residues, and flanking sequence/motif analysis (e.g., IceLogo) can reveal enriched residues around Kbhb sites, which differed between cell types (hydrophobic Leu/Phe at +1 with acidic residues at +3/-1 in one dataset versus positively charged lysine-rich motifs in another), suggesting context- or transferase-dependent sequence preferences rather than a single universal Kbhb motif [1].

Scale of findings in non-cardiac models. Using this pipeline in BHB-treated fibroblasts, 840 unique Kbh sites across 429 proteins were identified, with Kbh-modified proteins enriched in carbon metabolism, amino acid biosynthesis, and glycolysis/gluconeogenesis pathways — distinct from the pathways enriched among co-profiled acetylation (Kac) sites, indicating Kbh and Kac target largely non-overlapping proteins and cellular functions even under the same BHB stimulus [1]. Complementary immunoprecipitation/immunoblotting work has shown that Kbh modification of specific ketone-body-metabolism enzymes (OXCT1, HMGCS2) is directly β -HB concentration-dependent, supporting the feasibility of a similar concentration-response immunoprecipitation/immunoblot screen as a first-pass, lower-cost alternative to full proteome-wide MS profiling when testing a single candidate protein like RyR2 [2].

Application to RyR2/cardiac tissue. None of the retrieved sources report Kbh site mapping in cardiac muscle or on RyR2 specifically. Applying this pipeline to myocardium would require scaling immunoaffinity enrichment to the much lower abundance and larger size of RyR2 relative to typical proteomic targets, likely necessitating RyR2-specific immunoprecipitation prior to trypsin digestion (rather than pan-Kbh enrichment of whole-lysate digests) to achieve adequate peptide coverage of this 2.2-MDa, low-copy-number channel, followed by targeted MS/MS interrogation of tryptic peptides spanning known regulatory lysines.

Both RyR2 and SERCA2a are directly acetylated in cardiac tissue, but the retrieved literature has not established a discrete lysine succinylation site or a clear functional effect of succinylation on either protein specifically — succinylation data in the heart are dominated by mitochondrial metabolic enzymes and myofibrillar proteins rather than by Ca^{2+} -cycling channels themselves [1-3]. Lysine acetylation of RyR2 and SERCA2a.

Proteomic profiling of guinea pig myocardium first identified RyR2 and SERCA2 as novel acetyl-lysine substrates, confirmed by anti-acetyl-lysine immunoblotting, alongside myofibrillar proteins (myosin heavy/light chains, troponin subunits) [4,5]. This dataset was notable because most cardiac acetylation sites map to mitochondrial fatty-acid oxidation and oxidative phosphorylation enzymes (59% of proteins, 64% of sites), making the Ca^{2+} -handling protein hits a comparatively small but mechanistically important subset, prompting the authors to suggest that acetylation is a plausible additional layer of excitation-contraction coupling modulation [4,5]. More broadly, lysine acetyltransferases (KATs) and deacetylases (KDACs, including HDACs and sirtuins) reversibly regulate ion channel activity in cardiomyocytes, and HDAC inhibitors have been linked to altered K^{+} and Ca^{2+} channel remodeling and arrhythmia risk (QT prolongation, ventricular arrhythmias with class I HDAC inhibitors such as vorinostat, panobinostat, and romidepsin), while HDAC6 inhibition has shown antiarrhythmic effects in atrial tachypacing models [6]. However, the retrieved sources do not report the specific acetylated lysine residues on RyR2/SERCA2a or a direct biophysical readout (e.g., open probability, SR Ca^{2+} leak, or ATPase activity change) tied to this modification — the functional link remains inferential rather than mechanistically demonstrated.

Lysine Succinylation in the Heart — Mostly Metabolic, not Ca^{2+} -Channel-Specific.

Succinyl-CoA is the most abundant acyl-CoA species in cardiac tissue, and SIRT5 is the principal desuccinylase; Sirt5 knockout mice

accumulate hypersuccinylation predominantly on mitochondrial fatty-acid oxidation enzymes (notably ECHA), leading to reduced ATP, AMPK activation, and hypertrophic cardiomyopathy with reduced ejection fraction [2,7]. Succinylome analysis of failing human ischemic cardiomyopathy myofibrils identified 572 unique succinylated lysine sites across 181 proteins, with the majority (297 of 307 significantly changed sites, across 104 proteins) showing decreased succinylation in heart failure, attributed to reduced succinyl-CoA production (lower α -ketoglutarate dehydrogenase and succinate dehydrogenase activity) despite increased succinyl-CoA turnover [3,7]. This myofibril-focused dataset altered sarcomeric mechanical parameters (lower resting tension, faster activation rate) but was not reported to include RyR2 or SERCA2a among the specifically identified succinylated proteins in the retrieved sources [3].

Practical distinction for the RyR2/SERCA2a mechanosensor hypothesis: acetylation has documented direct evidence on RyR2/SERCA2a (proteomic identification plus immunoblot confirmation), whereas succinylation evidence in the heart is currently concentrated on mitochondrial and myofibrillar targets, with SIRT5-dependent succinylation being the dominant regulatory axis described. This asymmetry is itself informative for a β OHB-hydroxybutyrylation hypothesis: both acetyl-CoA and succinyl-CoA compete with β -hydroxybutyryl-CoA for the same lysine residues, and SIRT5's broad desuccinylase/de-2-hydroxyisobutyrylase activity raises the possibility that sirtuin family members could similarly regulate RyR2 β -hydroxybutyrylation, though this cross-talk has not been directly tested in the retrieved literature [2,7].

SIRT1 is the sirtuin most directly linked to a Ca^{2+} -cycling protein in the failing heart, acting on SERCA2a at a single acetyl-lysine residue, whereas SIRT3 and SIRT5 act predominantly on mitochondrial substrates rather than on RyR2 or SERCA2a themselves — the direct-target evidence and the compartmental-target evidence should not be conflated.

SIRT1 — direct deacetylation of SERCA2a at Lys492.

Gorski et al. showed that SERCA2a acetylation is markedly increased in failing human, murine, and porcine hearts, and this rises as SIRT1 protein levels fall. Lysine 492 (K492) is the critical regulatory residue: acetylation here, driven by the histone acetyltransferase p300, reduces SERCA2a activity by interfering with ATP binding. SIRT1 knockdown increases K492 acetylation and produces SERCA2a dysfunction with baseline cardiac defects, while pharmacological

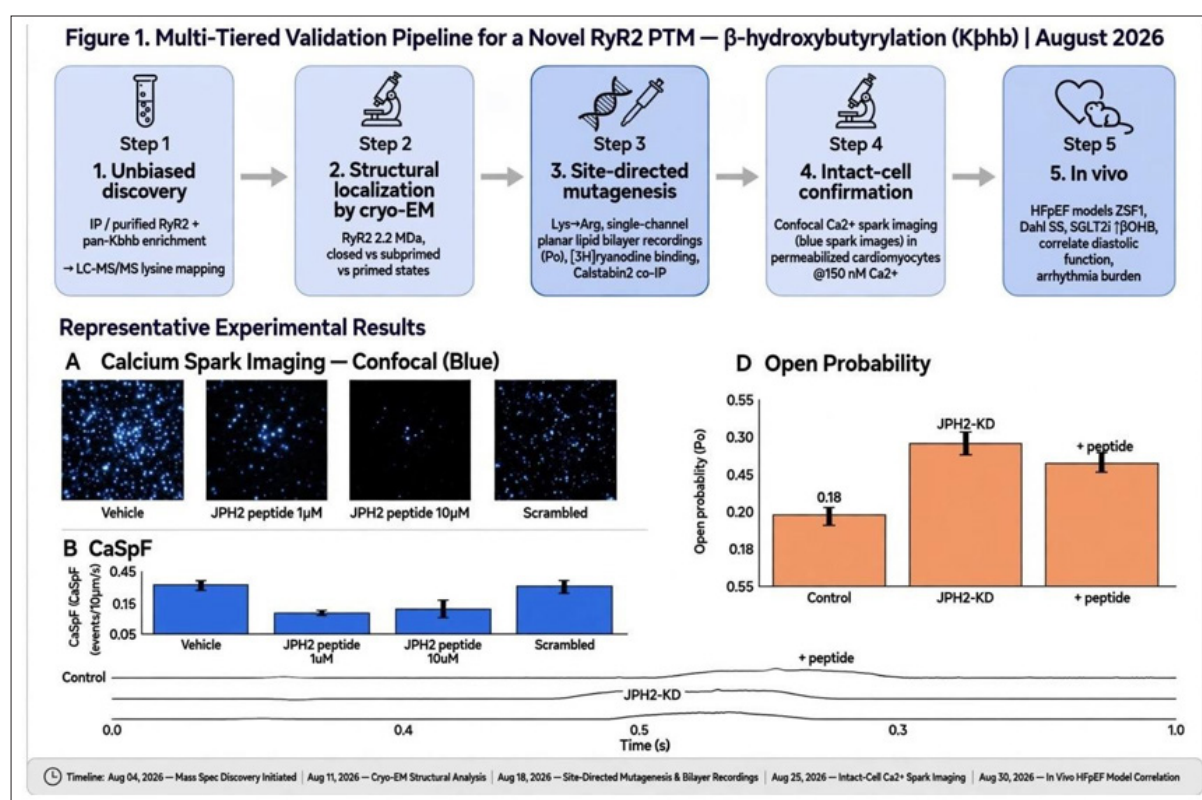
SIRT1 activation reverses K492 acetylation and restores both SERCA2a activity and cardiac function in failing hearts — making SIRT1-mediated SERCA2a deacetylation a proposed therapeutic strategy in heart failure [1,2]. SIRT1 additionally deacetylates p53 to limit cardiomyocyte apoptosis and deacetylates Akt to modulate glucose/insulin signaling, but these are not Ca^{2+} -handling actions per se [2,3]. SIRT3 — mitochondrial protein deacetylation, not RyR2/SERCA2a directly.

SIRT3 is the dominant mitochondrial deacetylase and targets fatty acid oxidation enzymes, TCA cycle enzymes, electron transport chain subunits, SOD2, and ketone-body metabolism enzymes rather than sarcoplasmic reticulum Ca^{2+} -handling proteins [4-9]. Loss of SIRT3 (falling NAD^{+} levels hyperacetylate mitochondrial proteins) impairs oxidative metabolism and, with chronic pressure overload, produces progressive cardiac dysfunction

and maladaptive hypertrophy through increased mitochondrial ROS; aging Sirt3-knockout mice develop cardiac dilatation [3,4,9]. SIRT3 overexpression or pharmacological activation (e.g., honokiol, nicotinamide mononucleotide) is cardioprotective via FOXO3a-dependent antioxidant gene expression and reduced ROS, restoring energy metabolism in pressure-overload and Friedreich ataxia cardiomyopathy models [4,5]. None of the retrieved sources report a direct SIRT3-RyR2 or SIRT3-SERCA2a interaction — its influence on Ca^{2+} handling in the failing heart, if any, would be indirect, via mitochondrial ATP supply and ROS-mediated oxidative modification of Ca^{2+} -handling proteins rather than direct deacetylation. SIRT5 and other sirtuins.

The retrieved literature confirms SIRT5 is mitochondrial and, together with SIRT3 and SIRT4, comprises the mitochondrial sirtuin subset, consistent with its previously discussed role as the principal cardiac desuccinylase acting mainly on fatty-acid oxidation enzymes (e.g., ECHA) rather than on RyR2/SERCA2a [5]. SIRT6 (nuclear) and SIRT2 (cytoplasmic) also modulate pathological hypertrophy but act on transcriptional/structural targets, not on Ca^{2+} -cycling proteins directly [4].

Net picture: of the three isoforms, only SIRT1 has a demonstrated direct, site-specific (K492) deacetylation effect on a Ca^{2+} -handling protein (SERCA2a) with documented functional consequences (ATP-binding interference, reduced pump activity) and reversal by SIRT1 activation in failing hearts [1,2]. SIRT3 and SIRT5 regulate the metabolic/redox milieu (fatty acid oxidation, ketone metabolism, ROS) that could plausibly influence Ca^{2+} -handling protein function indirectly, but a direct RyR2 deacetylation/desuccinylation site with functional validation was not identified in the retrieved literature — this remains an open question relevant to the βOHB -RyR2 hydroxybutyrylation hypothesis, since SIRT3's role in ketone-body enzyme regulation places it mechanistically closest to a βOHB -sensing node without yet extending that role to RyR2 itself [9].



Conclusion

Heart failure is fundamentally a multisystem syndrome where structural cardiac remodeling, bioenergetic failure, ECM fibrosis, and organ crosstalk perpetuate a vicious cycle of disease progression. Moving beyond a heart-centric view toward an integrated biological approach enables targeted therapeutic strategies—such as metabolic modulation, microvascular inflammatory dampening, and interorgan neurohormonal disruption—that offer promising avenues to improve outcomes across the full spectrum of heart failure phenotypes.

The heart-centric model — low EF = weak contraction = give an inotrope — failed because it cannot explain why HFpEF kills at the same rate as HFrEF, why renal function, frailty, and metabolic status predict outcome better than LVEF itself, and why hemodynamic drugs do not change the natural history [10-15].

Modern heart failure must be understood as the collapse of an ecosystem, built on four interacting pillars:

****A. Structural Cardiac Remodeling - It's not just hypertrophy****

This is a transcriptional reprogramming at three levels:

**** At the cardiomyocyte: **** Isoform shift and hypophosphorylation of titin [N2B to stiffer N2BA], leading to increased passive stiffness. Dysregulation of calcium handling: downregulation of SERCA2a, hyperphosphorylation and leak of RyR2, and reduced phospholamban activity. This creates both systolic and diastolic dysfunction [16-20].

**** At the Chamber Level: **** Eccentric dilation with wall thinning in HFrEF versus concentric hypertrophy with left atrial myopathy and impaired ventricular-arterial coupling in HFpEF are not two

diseases, but two trajectories of the same remodeling continuum [21-30].

**** At the Microvasculature:**** Capillary rarefaction, meaning the myocardium outgrows its own blood supply even without epicardial coronary disease [31- 35].

**** B. Bioenergetic Failure - A Starving Heart in a Land of Plenty ****

The heart consumes ~6 kg of ATP per day and has almost no reserve. In HF, the factory fails:

There is a forced metabolic switch from high-yield fatty acid oxidation [FAO] to inefficient glycolysis, with accumulation of toxic lipid intermediates - lipotoxicity.

Mitochondrial dysfunction: fragmented mitochondria, electron leak at Complexes I and III, excessive ROS production, and depletion of the NAD⁺ pool [36-40].

Depletion of the phosphocreatine / ATP ratio, measured by MR spectroscopy, which correlates directly with mortality and exercise intolerance. The heart becomes an engine out of fuel, which explains fatigue long before congestion appears [41-45].

**** C. ECM Fibrosis - Not a Passive Scar.****

Fibrosis is an active, inflammatory process driven by resident fibroblasts that differentiate into myofibroblasts under TGF- β , Galectin-3, and ST2 / IL-33 signaling.

There is an imbalance of matrix metalloproteinases and their inhibitors, leading to deposition of highly cross-linked Type I and Type III collagen, predominantly perivascular. This collagen is stiff and non-compliant. It creates three clinical problems: diastolic stiffness, a substrate for re-entrant arrhythmias, and electromechanical uncoupling. Crucially, this fibrosis is driven largely by coronary microvascular endothelial inflammation, not just by myocyte death. [MMPs][TIMPs]

**** D. Organ Crosstalk - The True Perpetuator of the Vicious Cycle ****

Once the heart falters, every other organ becomes both victim and aggressor:

**** Cardiorenal Axis:**** Low forward flow + high venous congestion = renal hypoperfusion, RAAS and arginine-vasopressin activation, sodium avidity, and release of uremic toxins that directly depress myocardial function.

****Cardiopulmonary Axis:**** Post-capillary pulmonary hypertension, pulmonary vascular remodeling, and diffusion impairment.

**** Cardiohepatic and Gut-Heart Axis:**** Hepatic congestion and intestinal wall edema lead to bacterial translocation, elevated LPS and TMAO from gut dysbiosis, which activate the systemic NLRP3 inflammasome and drive systemic inflammation.

**** Cardio-Metabolic and Cardio-Muscular Axis:**** Dysfunctional visceral adipose tissue secretes pro-inflammatory adipokines and skeletal muscle undergoes sarcopenia and releases abnormal myokines, worsening insulin resistance and systemic metabolic inflexibility.[leptin][resistin]

****Brain-Heart axis:**** Chronic central sympathetic outflow, baroreceptor dysfunction, and neurohormonal activation from the hypothalamus maintain a high-adrenergic state that is toxic to the myocardium.

This is the vicious cycle you refer to: structural injury -> energy failure -> fibrosis -> organ crosstalk -> more structural injury. The cycle is self-sustaining even if the initial insult is removed.

2. The Therapeutic Shift: From Hemodynamic Unloading to Biological Interruption

Moving beyond a heart-centric view means we no longer aim only to unload the heart with diuretics and vasodilators. We aim to simultaneously disrupt the nodes of the network. This is why the four pillars of HFrEF therapy work — they are not hemodynamic drugs, they are biological modulators.

This integrated approach opens three promising avenues:

****1. Metabolic Modulation****

The goal is not to give more fuel, but to make the heart use the right fuel more efficiently.

****SGLT2 inhibitors:**** Their success across the entire LVEF spectrum is explained by metabolic effects: they increase circulating ketone bodies [a more oxygen-efficient fuel per ATP produced], improve mitochondrial efficiency, reduce intracellular sodium via NHE-1 inhibition, and restore autophagy.[dapagliflozin] [empagliflozin]

Next generation: partial FAO inhibitors, NAD⁺ precursors [nicotinamide riboside], mitotropins, and GLP-1 agonists that restore systemic metabolic flexibility. The endpoint is restoration of the PCr/ATP reserve.[trimetazidine]

****2. Microvascular Inflammatory Dampening****

This is the central mechanism in HFpEF, as described by Paulus and Tschöpe. Comorbidities [CKD] create a systemic low-grade inflammatory state [elevated IL-6, TNF- α , hsCRP]. This inflames the coronary microvascular endothelium, reducing nitric oxide bioavailability, decreasing cGMP-PKG signaling, and leading to titin hypophosphorylation and fibrosis.

- Therapeutic targets here include: IL-1 β blockade, NLRP3 inflammasome inhibitors, restoration of endothelial function via soluble guanylate cyclase stimulators, and anti-fibrotic agents targeting Galectin-3 and TGF- β . [hypertension] [obesity] [diabetes] [vericiguat]

****3. Interorgan Neurohormonal Disruption****

Instead of blocking one hormone, we block the conversation between organs.

- **ARNI [Sacubitril/Valsartan]:** simultaneously blocks angiotensin and augments natriuretic peptides, disrupting the heart-kidney loop.
- **Non-Steroidal MRAs:** block mineralocorticoid-driven inflammation and fibrosis in heart, kidney, and vessels without the hyperkalemia profile of steroidal MRAs.[finerenone]
- **Gut-Targeted Therapies:** TMAO reducers, microbiome

modulation to reduce systemic endotoxemia.

- **Central Sympathetic Modulators:** baroreceptor activation therapy and renal denervation aim to interrupt the brain-heart-kidney sympathetic drive.
- ### 3. Why This Matters Across the Full Spectrum of Phenotypes

This integrated model finally unifies HFrEF, HFmrEF, and HFpEF. They are not separate diseases, but different clinical expressions of the same systemic syndrome depending on which node dominates:

- HFrEF: Dominated by structural remodeling and bioenergetic failure.
- HFpEF: Dominated by microvascular inflammation, ECM fibrosis, and metabolic-organ crosstalk.
- HFmrEF: A dynamic transition state.

A patient with HFpEF, obesity, CKD, and atrial fibrillation does not have four diseases. He has one multisystem syndrome with four clinical manifestations. Therefore, a therapy that improves metabolic flexibility [SGLT2i, GLP-1 RA], reduces inflammation, and protects the kidney will improve outcome regardless of EF — which is exactly what recent trials are showing.

In short: We are moving from treating the heart's ejection fraction to treating the patient's biological ecosystem. That is the only way to break the vicious cycle and improve outcomes in a syndrome that was never just about the heart.

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