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Review

Rethinking Intracellular Calcium Regulation: Emerging Role of Mitochondria-Associated Membranes in Heart Failure

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Abstract

Heart failure (HF) is a complex clinical syndrome characterized by structural and functional cardiac abnormalities that impair ventricular filling and ultimately compromise systemic perfusion. Despite advances in pharmacological and device-based therapies, morbidity and mortality remain high across all HF types. Emerging evidence indicates that alterations in mitochondrial bioenergetics, inflammatory processes, and intracellular calcium (Ca^{2+}) handling are key contributors to both systolic and diastolic dysfunction. Cardiomyocytes are the primary cells that require efficient excitation–contraction coupling, which closely links Ca^{2+} cycling to adenosine triphosphate (ATP) production. Disruption of this coupling leads to impaired energy supply, oxidative stress, and maladaptive remodeling of the heart. Mitochondria–endoplasmic reticulum contact sites (MERCSs), also known as mitochondria-associated membranes (MAMs), are critical microdomains that coordinate several processes, including Ca^{2+} handling. In this review, we examine the key components that regulate Ca^{2+} flux across these interfaces in HF. Thus, understanding how MERCSs/MAMs-mediated Ca^{2+} signaling contributes to bioenergetic failure and maladaptive remodeling of the heart may help identify novel therapeutic targets for HF.

Keywords: calcium; mitochondria-associated membranes; oxidative stress; energy metabolism; heart failure; mitochondria

1. Introduction

The left ventricle (LV) is primarily responsible for pumping blood from the heart to the body, making it larger than the right ventricle (RV). In patients with heart failure (HF), the LV must work harder to pump the same amount of blood. Heart failure (HF) is a clinical syndrome resulting from structural and/or functional cardiac abnormalities that impair ventricular filling, ejection of blood, or both. These abnormalities may involve systolic dysfunction, diastolic dysfunction, or a combination of both, and may arise from diverse underlying cardiac disorders. LV diastolic dysfunction is the sole cause of HF, particularly HF with a preserved ejection fraction (HFpEF). HF is classified by left ventricular ejection fraction (EF) as preserved (≥50%, HFpEF or diastolic HF) or reduced (≤40%, HFrEF or systolic HF). Normally, the LV pumps 55%–60% of its contents. A newer concept is HF with mildly reduced EF (HFmrEF), where the LV pumps with an ejection fraction between 41% and 49%, placing these patients between the HFrEF and HFpEF groups [1]. Although both types of HF show similar symptoms, they have different causes, medication responses, and pathophysiology [2].

Right-sided HF occurs when the RV cannot contract properly owing to pressure or volume overload or problems with the heart muscle itself. This type of HF, also called congestive heart failure, requires quick medical care because of the serious issues it can cause. Patients often have edema, especially in the legs and ankles, and sometimes develop pulmonary edema, making it difficult to breathe when lying down. HF generally affects other organs, such as the kidneys, which struggle to remove sodium (Na^{+}) and water, causing increased blood volume and tissue swelling [3].

Globally, about 64 million people are affected by HF. While its incidence has stabilized or even decreased in industrialized countries, its prevalence is increasing worldwide. This is due to factors like an aging population, better treatment, and higher survival rates from ischemic heart disease [4]. HF affects over 10% of people over 70 years of age, 1.4 million people under 60 years of age, and more than 5% of those aged 60 to 69 years of age. Additionally, HF is more common in women than in men. Reports indicate that men and younger individuals have higher survival rates than older women. Studies have shown that women have reduced LV output, leading to worse outcomes than men. However, medical treatments do not differ between men and women [5]. Therefore, pharmacological options should be considered for personalized therapy in patients with HF.

Recent findings indicate that problems with mitochondria, calcium (Ca^{2+}) mishandling, chronic inflammation, and poor interorganellar communication could be key areas for targeting to slow disease progression and improve patient outcomes. Notably, the increasing understanding of how mitochondria and the sarco(endo)plasmic reticulum (SR/ER) communicate through specific contact sites, known as mitochondria–ER contact sites (MERCSs) or

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mitochondria-associated membranes (MAMs), is crucial for the regulation of Ca^{2+} balance and cardiometabolic signaling. This has opened new avenues for the development of targeted therapies for HF.

Calcium regulation is a crucial area for new HF treatments that could significantly change outcomes and improve function. This is due to its important role in excitation–contraction coupling (ECC), mitochondrial bioenergetics, and cardiomyocyte survival. Recently, it has been shown that this regulation is controlled by MERCSs/MAMs, which allow efficient signal exchange required for cellular balance. Changes in the molecular makeup of MAMs and the number of MERCSs suggest that these structures are dynamic. They are involved not only in Ca^{2+} homeostasis but also in lipid trafficking and biosynthesis, reactive oxygen species (ROS) production, mitochondrial dynamics, autophagy, inflammasome activation, and cell death signaling pathways [6,7]. Notably, the close proximity of the SR/ER and mitochondria creates localized Ca^{2+} "hotspots" which enable rapid mitochondrial Ca^{2+} uptake. This allows metabolic adaptation to energy needs but also makes cardiomyocytes highly susceptible to Ca^{2+} overload and mitochondrial dysfunction under disease conditions.

For instance, changes in Ca^{2+} flux and mitochondrial lipidomics have been linked to MERCSs instability in skeletal muscles. This emphasizes the importance of interorganellar communication in maintaining mitochondrial health and cell function [8,9]. In the cardiovascular area, more evidence shows that faulty MAMs signaling leads to poor mitochondrial Ca^{2+} uptake, oxidative stress, inflammation, and maladaptive cardiac remodeling, which are key features of HF progression [7]. Nevertheless, it remains unclear whether Ca^{2+} homeostasis and its control by MERCSs/MAMs are consistent across different types of HF, especially between HFpEF and HFrEF. Thus, we aim to provide an updated overview of how MERCSs/MAMs dynamics affect Ca^{2+} handling, mitochondrial function, and cardiomyocyte cell fate, which may lead to novel treatments to improve heart function and outcomes in HF patients.

2. Pathophysiology of HF

HF is a clinical condition marked by signs and/or symptoms of structural and/or functional heart problems. It is confirmed by high levels of natriuretic peptides and/or signs of pulmonary or systemic congestion, leading to the heart's inability to pump sufficient blood to meet the body's needs [10]. This condition is linked to various other health issues, such as coronary artery disease (CAD), atherosclerosis, hypertension, obesity, diabetes, and chronic kidney disease, all of which harm cardiovascular health and contribute to the onset and worsening of heart dysfunction in chronic HF [11]. Importantly, the pathogenesis of HF is highly heterogeneous and involves several interconnected processes that lead to cardiomyocyte dysfunction, changes in the heart's structure, activation of neurohormones, inflammation, and metabolic issues. In the following sections, we briefly outline the key structural, inflammatory, energetic, and cellular pathways that lead to the development and progression of HF (Fig. 1).

2.1 Structural and Functional Aspects

An increase in the hemodynamic load, whether absolute or relative, reduces the heart muscle's natural ability to contract and its strength. These changes are also caused by ventricular remodeling, which is common in patients with chronic heart-pump problems. Generally, patients with HF have stiff systolic and diastolic left ventricles, high LV cavity filling pressures, reduced arterial distensibility, left atrial hypertension, pulmonary venous congestion, and microvascular dysfunction [12].

Patients with HFpEF have thicker heart walls and more fibrous tissue due to collagen buildup, which makes the heart stiffer. The left atrium enlarges because of the long-term high pressure in the LV. Diastolic dysfunction is the hallmark of HFpEF, as a stiff heart prevents the LV from relaxing and filling with blood adequately. This is worsened by higher LV end-diastolic pressure (LVEDP), changes in blood vessel elasticity, and reduced heart reserve, leading to difficulty in exercising [13] (Fig. 1, upper-left panel A). In patients with HFrEF, the heart's ventricular cavity enlarges, and both systolic and end-diastolic volumes increase. The LV becomes more spherical, which harms its contraction, and eccentric remodeling occurs. Similar to HFpEF, myocardial fibrosis contributes to both systolic and diastolic dysfunction. In addition, necrosis and apoptosis reduce the active contractile mass (Fig. 1, upper right panel B).

Functionally, there is a reduced EF of 40%, systolic dysfunction, reduced cardiac output, and activation of the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system to help compensate for the damage [13,14]. At the cellular level, patients with HFpEF have larger cardiomyocyte diameters and higher myofibrillar densities than those with HFrEF. Lastly, mortality is higher in patients with HFrEF; however, hospital admissions and readmissions for noncardiac reasons are more common in patients with HFpEF [15]. Structural changes in HF affect not only the heart muscle but also involve significant changes in cell ultrastructure, Ca^{2+} handling, mitochondrial organization, and interorganellar communication. Growing evidence indicates that disturbances in MERCSs/MAMs may lead to ventricular dysfunction by affecting Ca^{2+} signaling, mitochondrial bioenergetics, and stress response pathways, thereby linking subcellular remodeling to whole-organ cardiac failure [7].

In addition to cardiomyocyte hypertrophy, factors such as extracellular matrix remodeling, endothelial dysfunction, chronic low-grade inflammation, and impaired Ca^{2+} handling contribute to myocardial stiffness and diastolic dysfunction in HFpEF. Titin hypophosphorylation and

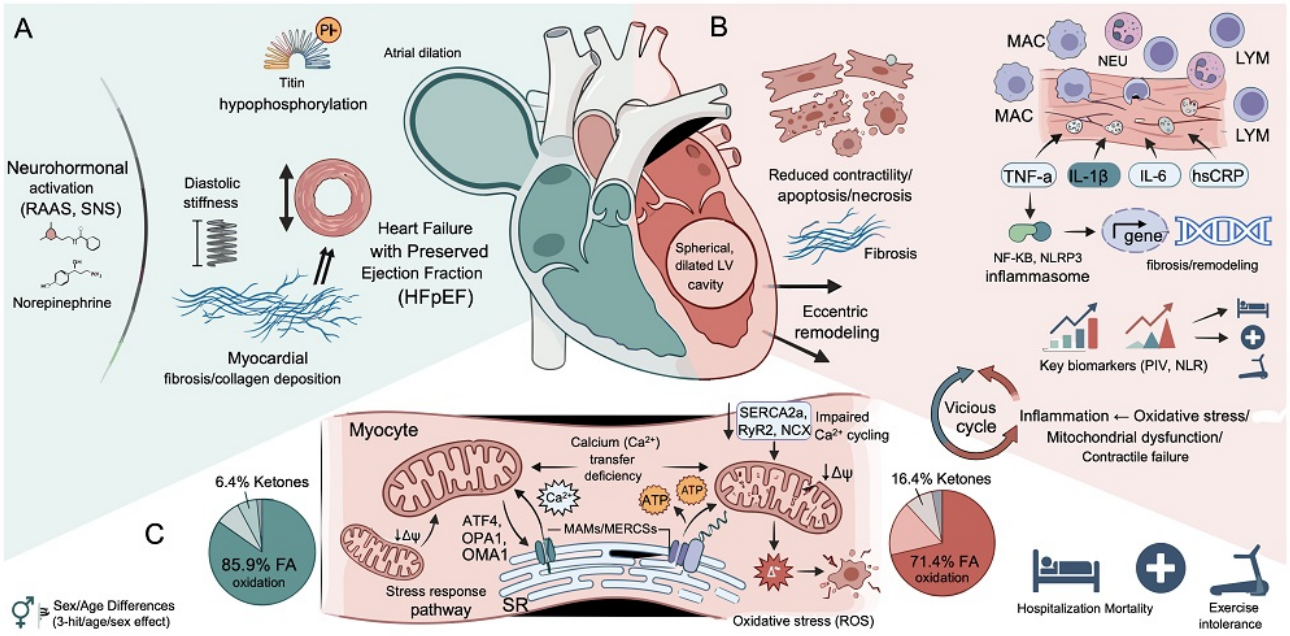


Fig. 1. The pathophysiology of HF involves structural remodeling, inflammation, bioenergetic dysfunction, and Ca^{2+} dysregulation. HFpEF (upper-left panel A) shows diastolic dysfunction with myocardial fibrosis, collagen buildup, atrial dilation, titin hypophosphorylation and stiffer ventricles. HFrEF (upper-right panel B) is characterized by reduced contractility, cell death, ventricular enlargement, eccentric remodeling, and worsening systolic dysfunction. Both types progress due to neurohormonal activation of the RAAS and SNS. In the upper-right panel B: Inflammatory pathways involving immune cells release pro-inflammatory substances such as TNF-α, IL-1β, IL-6, and hsCRP, activating NF-κB- and NLRP3-dependent pathways, leading to fibrosis, negative remodeling, and contractile issues. Lower central panel C: Changes in intracellular Ca^{2+} handling due to impaired SERCA2a activity, RyR2 dysfunction, and altered Na^{+}/Ca^{2+} exchanger (NCX) activity affect excitation–contraction coupling and energy efficiency. At the subcellular level, disrupted communication between the SR/ER and mitochondria through MERCSs/MAMs affects mitochondrial Ca^{2+} transfer and ATP production, causing oxidative stress, mitochondrial dysfunction, and activation of stress-response pathways involving ATF4, OPA1, and OMA1. HF phenotypes have different metabolic patterns, with HFpEF mainly using fatty acid oxidation and HFrEF using more ketone bodies and other substrates than HFpEF. These changes create a cycle linking inflammation, mitochondrial dysfunction, oxidative stress, impaired Ca^{2+} homeostasis and progressive HF. Abbreviations: HF, heart failure; ATF4, activating transcription factor 4; FA, fatty acid; hsCRP, high-sensitivity C-reactive protein; IL, interleukin; NF-κB, nuclear factor kappa B; NLRP3, NOD-like receptor family pyrin domain-containing protein 3; OMA1, mitochondrial AAA protease 1; OPA1, optic atrophy 1; ATP, adenosine triphosphate; SR/ER, sarco(endo)plasmic reticulum; HFpEF, heart failure with a preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; RAAS, renin-angiotensin-aldosterone system; MERCSs, mitochondria–ER contact sites; MAMs, mitochondria-associated membranes; SERCA2a, sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPase 2a; RyR2, ryanodine receptor/calcium release channel; SNS, sympathetic nervous system; TNF-α, tumor necrosis factor-α; PIV, pan-immune-inflammation; NLR, neutrophil-to-lymphocyte ratio; LYM, lymphocytes; NEU, neutrophils. Created using FigureLabs; Silva-Palacios, A (2026), FL-PUB-20260706-PBOLDQ.

changes in cardiomyocyte passive tension are also significant factors. Additionally, mitochondrial dysfunction and disrupted mitochondria-SR/ER communication may lead to impaired energy flexibility and defective myocardial relaxation, highlighting the importance of subcellular remodeling in HFpEF progression [8,16]. Conversely, changes in Ca^{2+} cycling proteins, including sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPase 2a (SERCA2a), ryanodine receptor/calcium release channel (RyR2), and Na^{+}/Ca^{2+}-exchanger (NCX), along with a disrupted ECC process, are more evident in HFrEF, contributing to severe contractile dysfunction and energy deficiency (Fig. 1, lower-central panel C). Moreover, mitochondrial dysfunction, excessive ROS production, and altered mitochondrial dynamics are key factors in HFrEF progression [17]. Overall, structural and functional changes emphasize the complex and multifactorial nature of both HF phenotypes (Fig. 1).

2.2 Inflammatory Aspects

The link between HF and inflammation (systemic or local) is closely connected and involves complex interactions between the heart and other organs. Evidence shows that patients with systemic inflammatory disorders have a much higher risk of developing cardiovascular disease than

the general population [18]. Mostly, HF is characterized by elevated levels of pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), and high-sensitivity C-reactive protein (hsCRP), which are key mediators in disease progression but are also linked to poor clinical outcomes [19,20] (Fig. 1, upper right panel B). For example, mice fed a high-fat diet combined with L-NAME (*a.k.a.* the "two-hit" HFpEF model) exhibit severe cardiac dysfunction, including preserved ejection fraction, diastolic dysfunction, and a strong pro-inflammatory response. To counteract this, treatment with growth differentiation factor-15 (GDF-15) significantly attenuates these abnormalities [21]. Meanwhile, blocking IL-1β signaling slows HF progression and improves cardiac function. Indeed, patients with a history of heart attack are associated with elevated inflammasome activity and high IL-18 levels, which are predictors of an increased risk of new cardiovascular events and hospitalization for congestive HF [22]. Furthermore, in mice lacking interleukin-22 (IL-22), HF worsens, with significant cardiac enlargement, reduced heart function, and increased inflammation [23]. Meanwhile, it has been observed that the cytokine storm, which is partially controlled by the activation of the calmodulin-dependent protein kinase II (CaMKII)/nuclear factor kappa B (NF-κB) cascade, is closely associated with hypertrophy, reduced EF, reduced shortening fraction, and extensive inflammation around blood vessels [24].

Other key triggers of HF are immune cells (such as macrophages and dendritic cells) that release pro-inflammatory cytokines and chemokines, attracting more leukocytes to the myocardium, thereby amplifying the inflammation and tissue injury. Invasive immune cells cause oxidative stress, extracellular matrix remodeling, and cardiomyocyte dysfunction, further impairing cardiac structure and function. In this persistent inflammatory *milieu*, compensatory responses occur, especially through the activation of neurohormonal cascades, such as the RAAS and sympathetic nervous system (SNS), which perpetuate cardiac dysfunction and chronic inflammation [25]. The continuous activation of these pathways exacerbates mitochondrial dysfunction, increases ROS production, causes endothelial injury, and alters intracellular Ca^{2+} levels, establishing a vicious cycle that further worsens HF (Fig. 1, upper-right panel B and lower, central panel C).

The pan-immune-inflammation value (PIV) has recently been associated with prevalent HF in a cross-sectional analysis of NHANES data, with each one-unit increase in log-transformed PIV associated with 34% higher odds of HF. These findings suggest a potential association between systemic inflammation and HF, although longitudinal studies are needed to determine whether PIV can predict incident HF [25]. The systemic immune-inflammation index (SII), calculated from neutrophil, platelet, and lymphocyte counts, has been investigated in relation to cardiovascular disease and hypertension [26]. In addition, the pan-immune-inflammation value (PIV), which incorporates neutrophils, platelets, monocytes, and lymphocytes, has been evaluated as a prognostic biomarker in patients with non-ST-segment elevation acute coronary syndrome [27]. As PIV reflects both innate and adaptive immune responses, it can provide a broader view of the inflammatory burden related to cardiovascular problems. Similarly, the neutrophil-to-lymphocyte ratio (NLR) is an easy and reliable inflammatory marker for HF. The NLR integrates two key elements of the immune response: lymphopenia, often linked to poor immune regulation and prognosis, and neutrophilia, which indicates increased systemic inflammation. Thus, an elevated NLR is a predictor of worsening HF and adverse cardiovascular outcomes [20]. In addition to its association with HF, an elevated NLR is also linked to serious cardiovascular events, HF-related hospitalizations, and chronic kidney disease in elderly patients [28]. Additionally, this index correlates positively with known inflammatory and cardiac markers, including IL-6 and N-terminal pro-B-type natriuretic peptide (NT-pro-BNP), reinforcing its relevance as an indicator of disease severity and systemic inflammatory status in patients with HF [18] (Fig. 1 upper-right panel B and lower-central panel C). Thus, both inflammatory biomarkers suggest changes in mitochondrial function, oxidative stress, and Ca^{2+} homeostasis in the heart. Given that inflammation is closely linked to MERCSs/-MAMs signaling, these biomarkers may indirectly indicate impaired communication between the mitochondria and ER during HF progression. However, further studies are required to confirm this hypothesis.

The interplay between energy metabolism and the immune response hinges on MAMs dysfunction, which in turn influences the reprogramming of immune cells and the intensity of the inflammatory response [29]. This inflammatory response promotes abnormal Ca^{2+} transfer, mitochondrial Ca^{2+} overload, and enhanced oxidative stress, leading to mitochondrial dysfunction and cardiomyocyte death [26]. It has long been established that MAMs serve as a molecular platform for the assembly of the cytoplasmic inflammasome of the NLR family containing the pyrin 3 domain (NLRP3) [30]. Mechanistically, it is recognized that Ca^{2+} transfer from the ER to the mitochondria is regulated by MAMs, along with the production of mitochondrial ROS, which serve as initiators of NLRP3 activation [31,32]. Furthermore, the disassembly of MERCSs activates IP3R, increasing the influx of Ca^{2+} into the mitochondria, causing their depolarization, leading to increased ROS production and the release of mitochondrial DNA. Both factors are detected by NLRP3, thereby initiating inflammasome formation [33] (Fig. 1, lower central panel C).

MAMs have been proposed as important platforms for NLRP3 inflammasome assembly and activation. Conversely, mitophagy contributes to mitochondrial quality control by removing damaged mitochondria and limiting

the release of mitochondrial ROS and DNA, thereby restraining NLRP3 inflammasome activation [34,35]. In fact, it has been shown that overexpression of BNIP3 induces voltage-dependent anion channel (VDAC) oligomerization, which in turn induces an increase in Ca^{2+} flux through MAMs, contributing to HF [36]. Furthermore, it has been reported that CaMKII is activated in cardiomyocytes, leading to the subsequent activation of the NLRP3 inflammasome, which triggers macrophage recruitment, fibrosis, and myocardial dysfunction [37]. Recent studies have indicated an interrelationship between mitochondrial dynamics and the function of MAMs in macrophages, which regulate their immunometabolism reprogramming. Interestingly, MAMs influence macrophage polarization toward a pro-inflammatory or anti-inflammatory phenotype, which determines the outcome of cardiovascular diseases, such as atherosclerosis [29]. Collectively, inflammation-induced changes in MERCSs/MAMs constitute a key link between immune activation, bioenergetic failure, and impaired ECC during the progression of HF (Fig. 1).

2.3 Bioenergetic Aspects

The heart sustains continuous contraction by producing large amounts of adenosine triphosphate (ATP). Approximately 95% of this energy is derived from mitochondrial oxidative phosphorylation (OxPhos), whereas the remaining ~5% is derived from glycolysis. Therefore, even short breaks in ATP production can seriously affect cardiac function [38]. The main processes in cardiomyocytes that use ATP include actomyosin ATPase activity in myofibrils, SERCA2a, plasma membrane Ca^{2+}-ATPase (PMCA), and Na^{+}/K^{+}-ATPase at the sarcolemma. Despite the enormous energy demand from these processes, a healthy heart maintains intracellular ATP levels of approximately 10 mM, reflecting the tight coupling between energy production and consumption [39].

The energetic shortage observed in patients with HF is linked to problems with mitochondrial metabolism, changes in how the heart uses energy sources, and a gradual drop in heart efficiency. As the heart uses ATP very quickly, the lack of ATP replenishment would lead to contractile failure in seconds, demonstrating the crucial role of continuous mitochondrial ATP production in heart function. In addition to producing ATP, mitochondria are vital for intracellular Ca^{2+} signaling and ECC, connecting the energy status with the heart's mechanical performance. This situation is more complicated in HFpEF when combined with obesity, diabetes mellitus, and metabolic syndrome, *a.k.a.*, the cardiometabolic phenotype. In these cases, the heart undergoes significant metabolic remodeling, relying more on fatty acid (FA) oxidation and altering glucose use. This eventually leads to mitochondrial inefficiency, oxidative stress, and reduced heart function, which are linked to poor clinical outcomes [40].

These metabolic processes also affect how cells handle intracellular Ca^{2+} ($[Ca^{2+}]_{int}$) and mitochondrial signaling, which further contributes to HF progression, as these processes are closely linked (Fig. 1, lower-central panel C). In addition to producing ATP, mitochondria constantly detect and react to changes in $[Ca^{2+}]_{int}$, ensuring that the energy supply meets contractile demand. Consequently, problems in mitochondrial metabolism can directly impact Ca^{2+} cycling, while issues with cation handling may hinder ATP production and worsen energy failure. This two-way relationship is crucial in cardiac dysfunction and disease progression in HF. Efficient matching of energy demand with ATP production requires coordinated communication between intracellular organelles, especially the SR/ER and mitochondria, where local Ca^{2+} microdomains regulate cellular metabolism, signaling, and survival. Mitochondrial Ca^{2+} uptake serves as a key metabolic signal that activates important dehydrogenases of the Krebs cycle and aligns ATP synthesis with the contractile workload. Thus, disruptions in organelle crosstalk and Ca^{2+} transfer pathways are increasingly considered major contributors to the energy deficits found in both HFpEF and HFrEF, linking metabolic dysfunction to impaired cardiac performance [41,42].

The healthy heart is omnivorous and uses different energy sources, such as FA, lactate, glucose, ketone bodies, and amino acids from the blood, as it cannot store much energy in its cells. Typically, most ATP is produced from FA, and the heart can adjust to changes in the available energy fuels to function normally [43]. Studies have shown differences in substrate utilization among different HF types. In patients with HFpEF, approximately 85.9% of ATP comes from FA oxidation, while ketone bodies, amino acids, and lactate contribute 6.4%, 4.6%, and 2.8%, respectively. In HFrEF, FAs comprise nearly 71.4% of ATP production, with ketone bodies, amino acids, and lactate contributing approximately 16.4%, 6.7%, and 5%, respectively [38]. In this vein, a recent systematic review found that HFpEF hearts can exhibit two distinct metabolic states: increased FA uptake and oxidation with decreased glucose utilization or decreased FA uptake and oxidation with impaired glucose oxidation [40] (Fig. 1, lower central panel C).

A possible explanation for this shift is that insulin stimulation of glucose oxidation is significantly reduced, whereas the oxidation rates of FA increase. The rates of cardiac ketone oxidation and glycolysis were similar to those in the hearts of healthy controls. This disrupts the balance between glucose and FA oxidation, contributing to overall ATP production. HFpEF hearts rely more on FA as the main fuel source for ATP production, compensating for the reduced ATP from glucose oxidation [44]. However, research methods need to be improved to better understand the role of metabolism in HF [45]. In addition to differences in HF types, sex also affects the metabolic heterogeneity of these diseases, especially in HFpEF. In the "3-Hit" model, which includes aging, a high-fat diet, and L-NAME administra-

tion, female mice show different mitochondrial changes and energy use patterns compared to males [45,46]. These findings emphasize the need to consider both age and sex as critical biological variables when studying heart metabolism and energy remodeling in HF.

Cardiomyocytes have a very high energy demand, as shown by their structure, where approximately 30–40% of the cell volume is composed of mitochondria [47]. These organelles sustain the heart's exceptionally high and continuous energy demand. The adult human heart has an estimated ATP turnover equivalent to approximately 30 kg per day; extrapolated over an 80-year lifespan, this would amount to nearly 880 metric tons of ATP [8]. The rest of the cell is mostly myofibrils, which change their arrangement during HF and affect contractile efficiency. Mitochondrial function worsens in HF due to several factors, including reduced mitochondrial biogenesis, increased ROS production, changes in mitochondrial dynamics, faulty mitophagy, and ongoing autophagic stress, all of which lead to energy shortage and cardiomyocyte dysfunction. For instance, complex I deficiency harms OxPhos and accelerates HF by blocking *Ndufs4*-dependent pathways [48]. In addition, mitochondria from failing hearts, regardless of the EF phenotype, show reduced membrane potential ($\Delta\Psi m$), indicating a global decline in bioenergetic capacity and metabolic flexibility.

Importantly, these alterations should not be viewed as isolated events but rather as interdependent components of a self-reinforcing network that drives and amplifies mitochondrial dysfunction during HF progression. Impaired electron transport chain (ETC) efficiency, primarily associated with dysfunction of respiratory complexes I and III and disruption of respiratory supercomplex organization, compromises the coupling between electron transfer and OxPhos, thereby limiting the mitochondrial capacity to meet the high energetic demands of the myocardium [49]. Concomitantly, increased electron leakage promotes the premature reduction of molecular oxygen and superoxide formation, fostering a sustained mitochondrial oxidative stress. The resulting accumulation of ROS induces oxidative modifications of key components of the bioenergetic machinery, including ETC proteins, ATP synthase, and Krebs cycle enzymes, further impairing ATP production and establishing a feed-forward loop between respiratory dysfunction and oxidative stress. This process is further amplified by the peroxidation of inner mitochondrial membrane lipids, particularly cardiolipin, whose oxidation disrupts cristae architecture, destabilizes respiratory complexes and supercomplexes, and compromises membrane integrity and function [50]. Collectively, these perturbations disrupt $\Delta\Psi m$ homeostasis and increase susceptibility to mitochondrial permeability transition pore (mPTP) opening. Sustained permeability transition can precipitate $\Delta\Psi m$ collapse, uncouple OxPhos, and facilitate the release of pro-apoptotic factors, thereby mechanistically linking bioenergetic failure to cardiomyocyte death [51]. Thus, the reciprocal interplay among ETC dysfunction, excessive ROS production, oxidative membrane remodeling, and loss of mitochondrial homeostasis establishes a vicious cycle that promotes progressive cardiomyocyte loss and contributes to myocardial dysfunction and HF progression.

Mitochondrial energetic failure is not an isolated event; it is closely linked to problems in handling $[Ca^{2+}]_{int}$. The breakdown of MAMs integrity and Ca^{2+} transfer efficiency is a key factor connecting mitochondrial dysfunction, energetic collapse, and contractile issues in HF [41,42]. Besides energy coupling issues, mitochondrial dysfunction is also tied to structural remodeling and redox imbalance. In HFpEF models, higher ROS levels are associated with severe ultrastructural abnormalities, such as disrupted mitochondrial cristae and loss of mitochondrial integrity, leading to cardiomyocyte death. These structural defects reflect a deeper failure of mitochondrial quality control, which is regulated by mitochondrial dynamics and stress-responsive proteolytic pathways. Notably, removing mitochondrial AAA protease-1 (OMA1), which processes dynamin-related guanosine triphosphate optic atrophy 1 (OPA1) under stress, stops the harmful effects related to HFpEF, emphasizing the importance of inner mitochondrial membrane (IMM) changes in disease progression [52]. Similarly, Cox-deficient mice develop early and lethal dilated cardiomyopathy with impaired OxPhos, lysosomal dysfunction, abnormal mitochondrial shape, and stress response activation, all dependent on OMA1 [53] (Fig. 1, lower central panel C). Recently, it was shown that OPA1-mediated formation of mitochondrial contact sites is controlled by activating transcription factor 4 (ATF4) during mitochondrial stress, further linking stress signaling to the structure of mitochondria-ER interfaces [8]. These findings support the idea that mitochondrial dysfunction in HF goes beyond reduced ATP production. They also involve changes in mitochondrial structure, redox state, and interorganellar communication. Mitochondrial stress not only affects bioenergetics but also reshapes MAMs, which alters Ca^{2+} transfer areas crucial for balancing the energy supply with contractile needs (Fig. 1, lower-central panel C).

3. Ca^{2+} Handling in HF

3.1 Cytosolic Calcium

Beyond oxidative stress, contractile dysfunction, and pathological remodeling, HF is strongly associated with impaired Ca^{2+} handling. This cation serves as a common second messenger in a wide range of cellular processes and is central to controlling both systolic and diastolic cardiac functions, making it essential for cardiomyocyte performance [54]. The balance of Ca^{2+} is maintained by a carefully controlled gradient across the SR, created by the coordinated action of Ca^{2+} channels, ATP-dependent pumps, transporters, and various Ca^{2+}-binding and regulatory proteins (Fig. 2, upper left panel A).

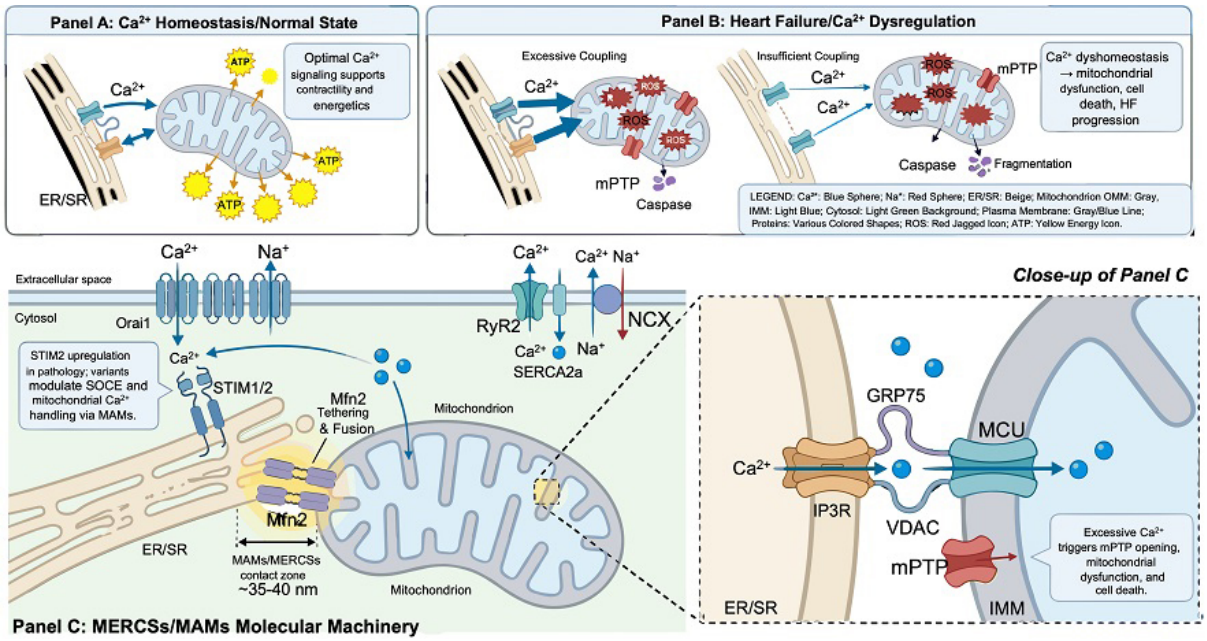


Fig. 2. Ca^{2+} handling by MAMs/MERCSs in cardiomyocytes under physiological conditions and HF. Panel A in the upper-left illustrates the physiological conditions in which balanced mitochondrial-SR/ER coupling ensures optimal mitochondrial Ca^{2+} signaling, efficient ATP production, and preservation of contractile performance. Panel B illustrates pathological remodeling of MAMs during HF, resulting in either excessive coupling, leading to mitochondrial Ca^{2+} overload, ROS generation, mPTP opening, and apoptosis, or insufficient coupling, characterized by impaired mitochondrial Ca^{2+} uptake, reduced ATP synthesis, energetic failure, and defective ECC. The molecular machinery involved in intracellular Ca^{2+} transfer between the SR/ER and mitochondria through MERCSs/MAMs. On the lower-left panel C: Under physiological conditions, Ca^{2+} entry through SOCE mediated by STIM1/2 and Orai1 contributes to intracellular Ca^{2+} homeostasis and excitation–contraction coupling. Cytosolic Ca^{2+} is recycled through the coordinated activity of RyR2, SERCA2a, and NCX. At MAMs, Mfn2 contributes to ER/SR–mitochondrial tethering, maintaining the close inter-organelle distance required for efficient Ca^{2+} transfer. The close-up view in panel C depicts the canonical Ca^{2+} transfer axis composed of IP3R, GRP75, VDAC, and MCU, which collectively regulate mitochondrial Ca^{2+} uptake and ATP production. Excessive mitochondrial Ca^{2+} accumulation promotes mPTP opening, mitochondrial depolarization, and activation of cell death pathways. Abbreviations: IMM, inner mitochondrial membrane; OMM, outer mitochondrial membrane; Orai1, Ca^{2+} release-activated calcium channel protein 1; STIM, stromal interaction molecule; ECC, excitation–contraction coupling; GRP75, glucose-regulated protein 75; MCU, mitochondrial calcium uniporter; Mfn2, mitochondrial fusion protein mitofusin-2; mPTP, mitochondrial permeability transition pore; VDAC, voltage-dependent anion channel; RyR2, ryanodine receptor/calcium release channel; SOCE, store-operated calcium entry; IP3R, inositol 1,4,5-triphosphate receptor; ROS, reactive oxygen species. Created using FigureLabs; Silva-Palacios, A (2026), FL-PUB-20260706-CAW6II.

Cardiomyocyte contractile function is governed by the ECC process, which causes quick and temporary changes in intracellular Ca^{2+} concentration, driving systole and diastole. During systole, an action potential triggers sarcolemma depolarization, allowing a small amount of extracellular Ca^{2+} to enter the cytosol via L-type voltage-dependent Ca^{2+} channels (LTCCs). This initial Ca^{2+} entry activates RyR2, leading to massive Ca^{2+} release from the SR into the cytosol via Ca^{2+}-induced calcium release (CICR). This results in approximately a ten-fold increase in cytosolic Ca^{2+} concentration ($[Ca^{2+}]_{cyt}$), which activates calcium-sensitive contractile proteins, such as troponin C, driving ATP-dependent cross-bridge cycling and force generation. During relaxation, cytosolic Ca^{2+} is rapidly removed via coordinated extrusion and reuptake. Nearly 30% of Ca^{2+} is expelled from the cell via NCX and plasma membrane Ca^{2+}-ATPase (PMCA), whereas the remaining ~70% is taken back into the SR by SERCA2a, restoring basal Ca^{2+} levels and enabling diastolic relaxation [55].

Notably, patients with HF have defects in both systolic and diastolic functions due to disruptions in Ca^{2+} cycling, which affect HF phenotypes differently. In HFpEF, the main issue is poor relaxation, which is linked to faulty Ca^{2+} reuptake and increased myocardial stiffness. In HFrEF, both systolic Ca^{2+} release and diastolic Ca^{2+} clearance are compromised, causing problems in both systolic and diastolic dysfunction. As mentioned earlier, as the disease progresses, profound structural and functional remodeling occurs, including increased chamber dimensions, thinner ventricular walls, and major changes in cardiomyocyte ultrastructural alterations, such as increased cell length/size, disorganized sarcomeres, and myofibrillar disarray. These

changes are often linked to disturbances in Ca^{2+} balance due to altered expression or function of regulatory proteins, such as channels, pumps, and binding proteins. Therefore, the heart in HF shows multiple defects in energy supply and demand, resulting in an energy-deprived and dysfunctional organ system.

Importantly, Ca^{2+} handling abnormalities are not identical in all HF phenotypes [56]. Studies have shown that cardiomyocytes isolated from HFrEF models have diminished Ca^{2+} transients and impaired Ca^{2+} cycling, whereas HFpEF cardiomyocytes may have enhanced intracellular Ca^{2+} levels even with a preserved EF [2]. However, this concept remains debatable, as other studies have found similar calcium transient rates between sham and HFrEF animals [2], indicating that changes in Ca^{2+} handling may depend on the disease stage, model, and underlying etiology. Mechanistically, these findings show that HF is not merely a disorder of Ca^{2+} concentration but rather a disease characterized by disrupted Ca^{2+} compartmentalization and signaling. Although altered Ca^{2+} levels are a hallmark of HF and play a critical role in contractile dysfunction and arrhythmogenesis, HF also involves extensive remodeling of other ion channels and transporters. For example, failing cardiomyocytes exhibit profound functional and structural alterations in Na^+ and potassium (K^+) channels, which collectively destabilize the cardiac action potential and promote the onset of lethal arrhythmias [57].

In summary, ionic remodeling in HF encompasses changes in Na^+ channels, such as (a) the late sodium current (INaL), which is upregulated in failing hearts, causing a continuous inward flow during the plateau phase; (b) prolongation of the action potential, as increased I_{NaL} extends repolarization, raising the risk of early post-depolarization; and (c) intracellular ionic overload due to the ongoing influx of Na^+, which alters NCX, causing secondary Ca^{2+} overload and delayed afterdepolarizations [58]. For K^+ channels, remodeling includes: (a) reduction of outward currents due to a significant reduction in key repolarizing currents, notably the inward rectifying K^+ current (I_{K1}) [59]; (b) destabilization of the resting membrane potential, caused by the loss of I_{K1}, affecting the stability of the resting membrane potential, causing ectopic activity; and (c) heterogeneity in duration due to changes in transient outward (I_{t0}) and delayed rectifier (I_{Kr}, I_{Ks}) potassium channels, which increase the dispersion of refractoriness and vulnerability to reentry [60]. These changes are connected through signals such as oxidative stress and kinases such as CaMKII [61], creating a feedback loop that simultaneously affects Na^+, K^+, and Ca^{2+} ions, showing the complexity of ion channels in HF. Thus, mitochondrial ATP production and intracellular Ca^{2+} cycling are tightly linked, and disturbances in local Ca^{2+} microdomains (as those of other ions) can simultaneously impact contractile performance, energy homeostasis, and cell survival (Fig. 2, panels B and C).

3.2 Mitochondrial Calcium

Calcium ions are critical signaling molecules that link the heart's workload to energy production in the mitochondria. Normally, the uptake of calcium by mitochondria ($[Ca^{2+}]_{mit}$) adjusts the oxidative metabolism to meet the energy demands of the heart muscle. In addition, temporary increases in $[Ca^{2+}]_{mit}$ stimulate key enzymes in the Krebs cycle, including pyruvate dehydrogenase, isocitrate dehydrogenase, and α-ketoglutarate dehydrogenase. This boosts the production of NADH and $FADH_2$, promoting ATP synthesis through OxPhos [62]. Thus, mitochondrial Ca^{2+} signaling is essential for matching the energy supply to the heart's demands. However, disturbances in its homeostasis are increasingly recognized as major contributors to mitochondrial dysfunction, energy failure, and cardiomyocyte death in HF [63,64]. Excess mitochondrial Ca^{2+} can increase ROS generation, impair OxPhos, and facilitate the opening of the mPTP, causing mitochondrial swelling, membrane depolarization, and cell death [41]. Conversely, insufficient mitochondrial Ca^{2+} uptake can compromise ATP production and reduce the ability of cardiomyocytes to adapt to an increased workload, highlighting the need for tight regulation of mitochondrial Ca^{2+} flux.

Several molecular components orchestrate mitochondrial Ca^{2+} transport. The VDAC in the outer mitochondrial membrane (OMM) is the primary gateway for Ca^{2+} diffusion into the intermembrane space of the mitochondria. Meanwhile, the mitochondrial calcium uniporter (MCU) in the IMM allows Ca^{2+} entry into the mitochondrial matrix. Together, these channels manage mitochondrial Ca^{2+} cycling, which is crucial for maintaining metabolic flexibility and homeostasis. Problems with either component can lead to mitochondrial Ca^{2+} overload and cardiac dysfunction. For example, increased MCU expression is observed in pathological left ventricular hypertrophy in HF. In contrast, blocking MCU with drugs or genetics attenuates cardiac remodeling and promotes cardioprotection, partly by boosting autophagy and maintaining mitochondrial integrity [63]. Specifically, mitochondrial Ca^{2+} transport does not occur in isolation but within specialized microdomains called MERCSs. These areas create local Ca^{2+} nanodomains that efficiently move cations from inside the cells to the mitochondria. This process ensures rapid metabolic adaptation and prevents cytosolic Ca^{2+} overload. Consequently, changes in the architecture and function of these microdomains can contribute to defective Ca^{2+} signaling and energy impairment during HF development [65].

Besides VDAC and MCU, mitochondrial Ca^{2+} uptake is controlled by auxiliary proteins forming the mitochondrial Ca^{2+} uptake machinery. Among these, the mitochondrial calcium uptake (MICU)1/MCU/MICU2 complex, located at the IMM and intermembrane space, acts as a molecular gatekeeper that finely tunes mitochondrial Ca^{2+} entry according to cellular demand [66]. This complex uses

phosphorylation-dependent regulation to prevent excessive Ca^{2+} accumulation at rest while allowing rapid mitochondrial Ca^{2+} uptake during increased activity. Notably, these pathways are highly susceptible to oxidative stress, which may alter MCU gating properties and contribute to mitochondrial dysfunction in cardiovascular diseases [67,68]. Recent evidence has identified MICU3 as a novel regulator of mitochondrial Ca^{2+} homeostasis in the heart. Roman et al. [64] demonstrated that cardiac overexpression of MICU3 promotes mitochondrial Ca^{2+} overload, cardiomyocyte hypertrophy, and activation of cell death pathways, even without other harmful stimuli. Interestingly, the same study found reduced MICU3 expression in failing human hearts, suggesting that MICU3 downregulation may represent a compensatory response that limits mitochondrial Ca^{2+} overload during HF progression. These findings are particularly intriguing because both excessive and insufficient mitochondrial Ca^{2+} uptake appear to be detrimental to the cardiac function. Impaired mitochondrial Ca^{2+} accumulation is linked to energy adaptation issues, reduced ATP production, and faster HF development, emphasizing the need to maintain a narrow physiological range of mitochondrial Ca^{2+} signaling [69]. The significance of these findings is underscored by the fact that MICU3's role in heart physiology was largely unexplored until recently. Earlier studies have mainly associated MICU3 with neuronal tissues, while its contribution to mitochondrial Ca^{2+} regulation in cardiomyocytes remains unclear [70]. Overall, these findings suggest that the regulatory machinery controlling mitochondrial Ca^{2+} uptake extends beyond the MCU pore and involves a complex network of modulators, whose dysregulation may lead to bioenergetic failure, maladaptive remodeling, and HF progression.

Remarkably, the ECC process is also influenced by β-adrenergic signaling, which is a central pathway that acutely regulates cardiac performance in response to physiological stressors. Upon activation by catecholamines such as epinephrine and norepinephrine, β-adrenergic receptors trigger adenylyl cyclase, which boosts cyclic AMP (cAMP) production and activates protein kinase A (PKA). This signaling cascade coordinates a wide phosphorylation network that enhances the frequency and strength of cardiomyocyte contractions [71]. Downstream of PKA activation, phospholamban (PLB) is phosphorylated, reducing its inhibition of SERCA2a, which accelerates Ca^{2+} reuptake into the SR and aids cardiac relaxation. Simultaneously, phosphorylation of L-type calcium channel (LTCC) raises Ca^{2+} influx, augmenting the systolic Ca^{2+} transients and contractile force. Moreover, troponin I phosphorylation decreases myofilament Ca^{2+} sensitivity, facilitating its release and improving diastolic relaxation. Together, these coordinated effects enhance both inotropy and lusitropy, thereby optimizing cardiac output during acute physiological demands. However, long-term β-adrenergic signaling activation, as seen in HF, leads to maladaptive remodeling, energetic imbalance, and altered Ca^{2+} handling. Ongoing PKA activity may exacerbate Ca^{2+} cycling instability and increase energy demand, thereby adding stress to mitochondrial ATP production and Ca^{2+} buffering capacity. This is crucial because of the close link between cytosolic Ca^{2+} transients and mitochondrial Ca^{2+} uptake, which are required for metabolic adaptation. Besides these groundbreaking discoveries, other aspects of Ca^{2+} regulation have been studied in depth. Recently, the scientific community has focused on organelle interactions because they play a role in various cellular processes that can be disturbed in disease conditions.

4. Ca^{2+} Handling by MERCSs/MAMs in HF

In the past 20 years, the concept of inter-organelle communication has become fundamental in cell biology because of its critical role in maintaining cellular homeostasis. Organelles inside cells do not function as isolated entities; they establish highly organized physical and functional interactions through specialized structures called membrane contact sites (MCSs). Among these, MERCSs and their functional platforms, known as MAMs, have gained considerable attention because they can coordinate multiple cellular processes, including Ca^{2+} signaling, lipid trafficking, mitochondrial dynamics, autophagy, apoptosis, and cellular bioenergetics [70,72].

The close apposition between the mitochondria and ER/SR enables highly efficient and spatially restricted Ca^{2+} transfer through the MAMs (Fig. 2, upper-left panel A). In cardiomyocytes, the average distance of 35–40 nm between these organelles helps create local Ca^{2+} microdomains that aid in mitochondrial Ca^{2+} uptake and metabolic coupling [73,74,75]. Both excessive and insufficient SR/ER-mitochondrial coupling can be detrimental. Disruption of MAM integrity impairs mitochondrial Ca^{2+} uptake and ATP production, whereas excessive tethering can lead to mitochondrial Ca^{2+} overload, oxidative stress, and activation of cell death pathways. Supporting this, sustained enhancement of MAMs formation exacerbates renal reperfusion injury by promoting pathological Ca^{2+} transfer and mitochondrial dysfunction [75,76]. These observations suggest that maintaining an optimal degree of ER/SR-mitochondrial communication is crucial for cellular homeostasis and raise the possibility that aberrant MAM remodeling may contribute to HF progression (Fig. 2, upper right panel B).

In general, Ca^{2+} signaling at MERCSs is tightly regulated by a functional axis comprising the inositol 1,4,5-trisphosphate receptor (IP3R) in the ER and VDAC in the OMM. This physical and functional coupling is facilitated by glucose-regulated protein 75 (GRP75), which acts as a molecular chaperone bridging IP3R and VDAC and facilitates Ca^{2+} exchange at MERCs/MAMs [77] (Fig. 2, close-up of panel C). In addition, MAMs coordinate Ca^{2+} transfer from IP3R to MCU, whose overflow induces cation over-

load, leading to mPTP opening, mitochondrial inflammation, and ultimately cell death. This process represents a critical mechanism linking Ca^{2+} dyshomeostasis to cardiomyocyte injury and HF progression [76,78]. On the other hand, store-operated calcium entry (SOCE) is another important pathway for intracellular Ca^{2+} signaling, mediated by stromal interaction molecule 1 (STIM1) and Ca^{2+} release-activated calcium channel protein 1 (Orai1), the pore-forming subunit of the calcium release-activated calcium (CRAC) channel. STIM1 is an ER-resident single-pass transmembrane protein that senses luminal Ca^{2+} depletion and activates Orai1 channels at the plasma membrane to maintain intracellular Ca^{2+} homeostasis. Various STIM isoforms are expressed in the heart, with STIM2 being particularly relevant in pathological conditions [79].

Specifically, STIM2 expression increases in pressure-overload mouse models, whereas the *Stim2.1* splice variant is downregulated in end-stage failing human ventricles and cardiac fibroblasts [80,81]. Recent evidence indicates that the *Stim2.2* variant, enriched in neonatal cardiomyocytes, negatively affects Orai1-mediated SOCE and modulates mitochondrial Ca^{2+} uptake through the STIM2/IP3R/VDAC/MCU axis, in conjunction with the mitochondrial fusion protein mitofusin 2 (Mfn2) [82]. Mfn2 has two roles in mitochondrial biology: it aids mitochondrial fusion and regulates the structural and functional regulation of MERCSs (Fig. 2, lower-left panel C). Importantly, increased Mfn2 expression and IP3R1 dephosphorylation are associated with reduced MAM formation and impaired mitochondrial Ca^{2+} homeostasis, as observed in endothelial cells after sunitinib treatment [83]. Collectively, these Ca^{2+} transients and their dysregulation are closely linked to alterations in cardiomyocyte contractility, which is a central mechanism in HF pathophysiology [84].

The multiple Ca^{2+} regulatory systems described herein, including ECC, mitochondrial Ca^{2+} uptake machinery, MAMs, and SOCE, work together to maintain cardiomyocyte Ca^{2+} homeostasis under physiological conditions [85]. These systems are interconnected, forming an integrated and dynamic network in which local Ca^{2+} microdomains coordinate energy production, contractile function, and stress responses. In HF, the finely tuned Ca^{2+} signaling network is disrupted progressively. Alterations in RyR2-mediated release, SERCA2a-dependent reuptake, NCX extrusion, and mitochondrial Ca^{2+} buffering collectively contribute to cytosolic and mitochondrial Ca^{2+} dyshomeostasis in cardiomyocytes. Additionally, dysregulation of SOCE components (STIM/Orai1), poor ER–mitochondrial coupling through MAMs, and maladaptive β-adrenergic signaling further exacerbate Ca^{2+} overload and energetic collapse in cardiomyocytes. As a result, Ca^{2+} stop being a well-regulated messenger and starts causing mitochondrial dysfunction, maladaptive remodeling, and cardiomyocyte loss. This breakdown in Ca^{2+} management represents a central integrative mechanism underlying both preserved and reduced ejection fraction heart failure phenotypes, highlighting Ca^{2+} handling machinery and inter-organelle communication as promising therapeutic targets for cardiac disease.

5. Treatments Targeting Ca^{2+} Handling in HF

New treatments for HF are focusing more on restoring intracellular Ca^{2+} homeostasis, as it plays a central role in ECC, mitochondrial bioenergetics, and survival of cardiomyocytes. Accordingly, Ca^{2+} signaling is now considered a promising target for treating contractile dysfunction, metabolic impairment, and inflammatory remodeling in the failing heart. Cannabidiol (CBD), for example, is one of the most recently explored compounds. Preclinical studies have shown that CBD administration (1 mg/kg) improves cardiac contractility, intracellular Ca^{2+} handling, and adverse remodeling in experimental HFrEF models. These effects appear to be mediated, at least in part, by the activation of PPAR-γ-dependent signaling pathways, suggesting that metabolic and inflammatory modulation converge on Ca^{2+} homeostasis as a central mechanism of action [86]. In HFpEF, CBD promotes cardioprotection by controlling inflammation, oxidative stress, and premature cellular senescence through increased communication among MERCSs (Silva-Palacios et al. [7], *in submission*). This suggests that CBD can effectively manage various cellular mechanisms and slow disease progression.

Efforts have also been made to restore the normal cardiomyocyte Ca^{2+} cycling. A key feature of HF is reduced SR Ca^{2+} reuptake secondary to impaired SERCA2a activity, which affects both the systolic and diastolic functions. Therefore, increasing SERCA2a expression or activity through methods such as gene therapy and phospholamban inhibition has been explored as a potential treatment [87,88]. Although translating these findings into clinical practice has been challenging, there is renewed interest in SERCA2a-targeted therapies due to a better understanding of disease-specific alterations in Ca^{2+} cycling and patient stratification [89]. Another key therapeutic target is RyR2. In HF, chronic sympathetic stimulation, oxidative stress, and CaMKII activation promote RyR2 hyperphosphorylation and oxidation, resulting in pathological diastolic Ca^{2+} leakage from the SR. This abnormal Ca^{2+} release contributes to contractile inefficiency, arrhythmogenesis, mitochondrial dysfunction, and inflammatory signaling. Thus, pharmacological stabilization of RyR2 and inhibition of harmful CaMKII signaling are promising strategies for restoring normal Ca^{2+} release dynamics and reducing ventricular arrhythmias and disease progression [90].

Recently, there has been a growing interest in subcellular Ca^{2+} microdomains, particularly those governed by MERCSs/MAMs. These structures manage the spatiotemporal transfer of Ca^{2+} between organelles and criti-

cally determine mitochondrial Ca^{2+} uptake, ATP production, and the risk of cell death [91]. Therefore, dysregulation of MAM-associated Ca^{2+} flux may lead to mitochondrial dysfunction and cardiomyocyte loss in HF. In this situation, treatments aimed at normalizing MAM integrity or modulating key Ca^{2+} transport components, such as IP3R, GRP75, VDAC, and MCU, are being explored as potential disease-modifying approaches. By reestablishing the physiological Ca^{2+} coupling between the SR and mitochondria, these interventions may reduce mitochondrial Ca^{2+} overload, limit mPTP opening, attenuate oxidative stress, and ultimately suppress inflammation-driven myocardial remodeling [92,93].

Interestingly, therapies traditionally classified as metabolic modulators may exert part of their cardioprotective effects by improving intracellular Ca^{2+} handling. Sodium-glucose cotransporter-2 inhibitors (SGLT2i), now considered a cornerstone therapy in HF management, have been proposed to indirectly improve cardiomyocyte Ca^{2+} homeostasis by modulating intracellular sodium concentrations and Na^{+}/Ca^{2+} exchanger activity, thereby reducing cytosolic and mitochondrial Ca^{2+} overload [94]. Similarly, interventions targeting mitochondrial energetics and inflammatory pathways may converge on Ca^{2+} signaling as the final common pathway underlying their beneficial effects.

Finally, novel contractile therapies, such as cardiac myosin activators, offer a different approach to HF treatment. They improve systolic function without directly increasing intracellular Ca^{2+} concentration or myocardial oxygen consumption. This challenges the older idea that better contractility requires more Ca^{2+}. This suggests that future HF therapies may progressively shift from calcium amplification toward calcium optimization and organelle-specific modulation. Collectively, these findings support a conceptual shift in HF therapy from isolated hemodynamic modulation to integrated multi-organelle targeting strategies, in which Ca^{2+} handling serves as a central regulatory hub linking excitation-contraction coupling, energy metabolism, mitochondrial function, and inflammatory signaling.

6. Conclusions and Perspectives

Despite substantial advances in understanding the pathophysiology of HF, many important aspects of MERCSs/MAMs biology remain unresolved. Specifically, the determinants that define the optimal number and functional state of these structures required to preserve cellular homeostasis remain poorly understood. This is a crucial knowledge gap because excessive and insufficient ER–mitochondria coupling is associated with disrupted Ca^{2+} signaling, mitochondrial dysfunction, and cardiomyocyte injury.

MERCSs/MAMs are not fixed structures; they are highly dynamic signaling hubs that adjust to metabolic demands, stress, and inflammatory cues. In HF, this plasticity can become maladaptive, leading to Ca^{2+} overload, impaired mitochondrial bioenergetics, and the activation of cell death pathways. Therefore, understanding the regulation of MERCSs/MAMs stability and function in both physiological and pathological states is essential for grasping disease progression. Future research should aim to integrate structural, functional, and molecular approaches to characterize MAMs remodeling across HF phenotypes, including HFpEF and HFrEF. Identifying pharmacological or genetic interventions that restore balanced ER–mitochondrial communication may open new therapeutic avenues for modulating Ca^{2+} homeostasis, improving mitochondrial performance, and ultimately attenuating cardiac dysfunction. In conclusion, establishing the principles governing MERCSs/MAMs plasticity and Ca^{2+} microdomain organization may provide a unifying framework for understanding the adaptability of the failing heart and guide the development of next-generation therapies for HF.

Author Contributions

AS and AC designed the research study. AS and AC performed the research. Both authors contributed to critical revision of the manuscript for important intellectual content. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

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Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this manuscript, the authors used FigureLabs, an artificial intelligence-assisted platform, to generate the initial versions of the conceptual graphical illustrations included in this review. The authors subsequently reviewed, modified, and validated all scientific content, labels, and graphical elements to ensure their accuracy and consistency with the current scientific evidence. The authors take full responsibility for the content of the figures and the manuscript.

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