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Review

Mitochondrial pathophysiology of heart failure with reduced ejection fraction: From quality control failure to emerging therapies

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Received: 18 October 2026 | Approved: 02 November 2026 | Online: 02 November 2026

Abstract

Chronic heart failure with reduced ejection fraction (HFrEF) is increasingly understood as a disorder of cardiac energy conversion in which mitochondria fail both as the principal source of ATP and as regulators of calcium handling, redox balance, cell survival and sterile inflammation. This narrative review synthesizes evidence published between 2021 and 2026 on mitochondrial pathophysiology in HFrEF, with emphasis on human myocardium and cardiovascular aging. Human studies converge on a reproducible energetic signature: a 20% reduction in the phosphocreatine to ATP ratio, depletion of the adenine nucleotide pool, a collapse of creatine kinase flux, reduced fatty acid import and oxidation, glycolysis uncoupled from glucose oxidation, increased ketone and lactate consumption, defective branched-chain amino acid catabolism, hyperacetylation of mitochondrial enzymes and myocardial iron deficiency. These lesions are coupled to failure of mitochondrial quality control (fragmentation, cristae

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disruption, defective canonical and alternative mitophagy, blunted biogenesis and unfolded protein response), to calcium mishandling at the uniporter and the Na^+/Ca^{2+} exchanger, to permeability transition, and to release of mitochondrial DNA that activates cGAS-STING and inflammasome signaling. Most of these processes are also hallmarks of cardiac aging, which explains the vulnerability of the older HFrEF heart. Foundational therapies such as sodium-glucose cotransporter 2 inhibitors and intravenous iron act in part through mitochondria, whereas direct mitochondrial therapies (ketone esters, elamipretide, NAD^+ precursors, coenzyme Q10, mitophagy inducers, gene therapy and mitochondrial transfer) range from negative phase 2 trials to a first regulatory approval. We discuss why translation has lagged and propose priorities for mitochondria-directed trials in HFrEF.

Keywords: Heart failure with reduced ejection fraction, mitochondrial quality control, mitophagy, cardiac energy metabolism, cardiolipin, cardiovascular aging, sodium-glucose cotransporter 2 inhibitors, mitochondrial calcium

INTRODUCTION

The adult human heart hydrolyzes and resynthesizes its entire ATP pool many times per min, and more than 90% of this ATP is generated by oxidative phosphorylation in mitochondria that occupy roughly one third of cardiomyocyte volume[1,2]. Heart failure (HF), a syndrome defined by the inability of the heart to meet metabolic demand at normal filling pressures, has therefore long been described as an “engine out of fuel”. What has changed over the past five years is the quality of the evidence. Integrated metabolomic, proteomic and ultrastructural studies of explanted human hearts, large meta-analyses of phosphorus magnetic resonance spectroscopy, and mechanistic work with cardiomyocyte-specific genetic models have moved mitochondrial dysfunction in HFrEF from a plausible correlate to a quantified and mechanistically dissected component of the disease[3-5].

Mitochondrial quality control (MQC) denotes the network of processes that maintains a functional mitochondrial population in the cardiomyocyte. It comprises the balance between fission, executed by dynamin-related protein 1 (Drp1), and fusion, mediated by mitofusin 1 and 2 (Mfn1, Mfn2) and optic atrophy 1 (OPA1), which allows damaged segments of the network to be segregated; the selective removal of damaged

organelles by mitophagy through PINK1/Parkin-dependent and receptor-mediated (BNIP3, NIX, FUNDC1) pathways; the generation of new organelles by biogenesis under the control of peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α), nuclear respiratory factors 1 and 2 (NRF1, NRF2) and mitochondrial transcription factor A (TFAM); and the maintenance of proteostasis by mitochondrial chaperones and proteases[5,6]. When MQC fails, dysfunctional organelles accumulate, ATP production falls, reactive oxygen species (ROS) are generated in excess, and mitochondrial DNA (mtDNA) and cardiolipin escape into the cytosol, where they activate the NLRP3 inflammasome and the cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING) pathway[6]. These three consequences, energetic deficit, oxidative stress and sterile inflammation, connect MQC and metabolism to the pathogenesis of HF and form the organizing framework of this review.

The clinical framing of HFrEF has also moved. The 2026 European Society of Cardiology (ESC) guidelines for the management of heart failure abandoned the category of HF with mildly reduced ejection fraction and now define HFrEF as symptomatic HF with a left ventricular ejection fraction (LVEF) below 50%, adopt the stage A to D classification, and build pharmacotherapy around a foundational regimen of a mineralocorticoid receptor antagonist and a sodium-glucose cotransporter 2 inhibitor (SGLT2i) for all patients, with a renin-angiotensin system inhibitor or angiotensin receptor-neprilysin inhibitor and a beta-blocker added in HFrEF[7]. The guideline runs to 112 pages, and the words mitochondria, mitochondrial and energetics do not appear in it. The omission is instructive, because several foundational therapies modify mitochondrial biology, yet no drug has entered the HFrEF armamentarium on the basis of a mitochondrial mechanism, and the only mitochondria-targeted agent to reach regulatory approval, in September 2025, did so for an ultra-rare cardiolipin disorder rather than for common HFrEF[8,9].

This review addresses that gap. We synthesize the literature on mitochondrial pathophysiology in chronic HFrEF published from January 2021 to October 2026, prioritizing studies in human myocardium and clinical trials, and using experimental work to explain mechanism. We cover the energetic and substrate signature of the failing heart, the failure of MQC, calcium and redox handling, mitochondria as signaling hubs of inflammation and cell death, the convergence of these processes with

cardiac aging, mitochondrial disease in skeletal muscle, and, in a dedicated section, current and emerging therapies. Because the Journal of Cardiovascular Aging has recently published a complementary review of mitochondrial homeostasis in HF with preserved ejection fraction (HFpEF)[10], we draw contrasts with HFpEF where they inform the understanding of HFrEF, but we do not review HFpEF in detail.

METHODOLOGICAL NOTE

This is a narrative review. We searched PubMed, Crossref and the Perplexity academic index for articles published between January 2021 and October 2026 using combinations of the terms heart failure, reduced ejection fraction, mitochondria, mitochondrial dynamics, mitophagy, biogenesis, calcium uniporter, permeability transition, reactive oxygen species, cardiolipin, mitochondrial DNA, cGAS-STING, metabolism, ketone, branched-chain amino acid, iron, SGLT2, elamipretide, nicotinamide riboside, coenzyme Q10, urolithin, gene therapy and mitochondrial transplantation. Priority was given to studies using human myocardium, human imaging or randomized trials, and to mechanistic studies with cardiomyocyte-specific genetic tools. A small number of earlier landmark articles were retained where they remain the primary source for a statement. Every reference was verified against PubMed and Crossref metadata before inclusion.

THE ENERGETIC SIGNATURE OF THE FAILING HUMAN HEART

High-energy phosphates and creatine kinase flux

Phosphorus-31 magnetic resonance spectroscopy (^{31}P-MRS) is the only noninvasive technique that quantifies myocardial high-energy phosphates *in vivo*. A 2026 meta-analysis of 176 studies and 7,843 examinations reported a pooled phosphocreatine to ATP ratio (PCr/ATP) of 1.96 in healthy volunteers compared with 1.54 in HFrEF (a 21% reduction) and 1.60 in HFpEF, with further reductions in valvular disease and diabetes, and with field strength, pulse sequence and voxel location all influencing the absolute values[4]. A second meta-analysis restricted to HF versus controls found a pooled odds ratio of 7.62 (95% confidence interval [CI] 4.90 to 11.85) for the association between reduced PCr/ATP and HF, with all 26 eligible studies being observational[11]. The energetic deficit is therefore reproducible, but it is not specific to reduced ejection fraction.

The PCr/ATP ratio captures only part of the energetic lesion. In HFrEF, the forward flux through creatine kinase (CK) is reduced by about 50%, a much larger change than the 15 to 20% fall in PCr/ATP, and it is CK flux rather than PCr/ATP that tracks outcome[12]. In 37 patients with nonischemic cardiomyopathy studied by ^{31}P-MRS at 3 T, baseline CK flux was higher in those who later recovered to HF with improved ejection fraction than in those who remained in HFrEF, whereas PCr/ATP did not discriminate the groups[13]. Pathologic left ventricular hypertrophy and dilatation in 27 HF patients correlated closely with reduced CK energy metabolism, and in mice cardiac-specific overexpression of mitochondrial CK, but not of myofibrillar CK, attenuated maladaptive hypertrophy after pressure overload[14]. These observations suggest that the capacity to transfer energy from the mitochondrial matrix to the myofibril, and not only the size of the phosphagen pool, determines the trajectory of the failing ventricle.

Two caveats matter for interpretation. Chronic reductions in PCr/ATP may reflect loss of total creatine as much as a fall in the ATP/ADP ratio[15]. Among 38 surgical patients, PCr/ATP measured by ^{31}P-MRS did not correlate with ADP-stimulated or maximally uncoupled respiration of mitochondria isolated from atrial tissue, which indicates that the *in vivo* energetic marker and *ex vivo* respiratory capacity report different aspects of mitochondrial biology[16].

Metabolomic and proteomic profile of explanted hearts

The most complete picture of metabolism in the failing human heart comes from an integrated analysis of 87 explanted hearts from 39 patients with end-stage nonischemic dilated cardiomyopathy and 48 nonfailing donors, combining tissue and plasma metabolomics (678 metabolites), RNA sequencing and proteomics[3]. Failing tissue showed selective depletion of adenylate purines, substantial reductions in fatty acids and acylcarnitines despite elevated plasma levels, which points to defective import of fatty acids into cardiomyocytes, elevated tissue glucose, de-repression of pyruvate dehydrogenase with increased lactate and pyruvate oxidation, reduced tricarboxylic acid (TCA) cycle intermediates, and a profound reprogramming of bioactive lipids with loss of ceramides and accumulation of lysoglycerophospholipids. Arteriovenous metabolomics across the coronary circulation of failing and nonfailing human hearts had earlier shown that the failing heart consumes more ketones and lactate and has

higher rates of proteolysis, while fatty acids remain the dominant substrate[17]. Combined proteomic and phosphoproteomic profiling of failing human left ventricle identified more than 5,000 proteins and 13,000 phosphosites and revealed etiology-specific perturbations in dilated and ischemic cardiomyopathy[18].

The gateway for carbohydrate carbon into mitochondria is also compromised. Protein and transcript levels of the mitochondrial pyruvate carrier subunits MPC1 and MPC2, together with sirtuin 3 (SIRT3), were reduced in left ventricular tissue from patients with ischemic HFrEF, although not significantly in idiopathic dilated cardiomyopathy[19]. In Tgαq*44 mice the transition to overt HF was marked by increased reliance on glucose, impaired MPC-mediated pyruvate utilization and redirection of glycolytic intermediates into the hexose monophosphate shunt, glycogenesis and serine biosynthesis, and the key findings were confirmed in a small human HF cohort[20]. Earlier work established that cardiac MPC deficiency drives hypertrophy and that redirecting pyruvate toward oxidation attenuates it[21].

Myocardial iron deficiency

Iron is indispensable for heme and iron-sulfur cluster proteins of the respiratory chain and TCA cycle. In 138 failing and 46 nonfailing explanted human hearts, left ventricular iron content was lower in HF (median 121 versus 137 µg/g dry weight) and 23% of HF patients fell below a threshold defining myocardial iron deficiency; these hearts had a higher New York Heart Association (NYHA) class, worse left ventricular function, suppressed respiratory chain and Krebs cycle enzyme activities that correlated with iron depletion, impaired antioxidant defenses, and defective sarcolemmal iron uptake, and cardiac magnetic resonance $T2^*$ captured myocardial iron status noninvasively[22]. A dedicated review has summarized how cellular iron dyshomeostasis impairs mitochondrial function in the failing heart[23]. These data give a mitochondrial rationale to the clinical trials of intravenous iron discussed below.

Table 1 summarizes the human evidence for mitochondrial and metabolic alterations in the myocardium and skeletal muscle of patients with HFrEF published in the review period.

Table 1. Human evidence (2021-2026) for mitochondrial and metabolic alterations in the myocardium and skeletal muscle of patients with heart failure with reduced ejection fraction.

Domain	Key finding in human HFrEF	Material and method	Ref.
High-energy phosphates	Pooled PCr/ATP 1.54 in HFrEF versus 1.96 in healthy volunteers (21% reduction); reduced PCr/ATP associated with HF (OR 7.6)	^{31}P-MRS meta-analyses (176 studies, 7,843 examinations; 26 studies)	[4,11]
Energy transfer	CK flux reduced by about 50%; higher baseline CK flux predicts later LVEF recovery whereas PCr/ATP does not	^{31}P-MRS in nonischemic cardiomyopathy (*n* = 37)	[12,13]
Substrate landscape	Adenylate depletion; reduced tissue fatty acids and acylcarnitines despite high plasma levels; elevated glucose; de-repressed PDH; reduced TCA intermediates; loss of ceramides	Explanted hearts (39 DCM patients, 48 donors); metabolomics, RNA sequencing, proteomics	[3]
Fuel consumption	Failing heart consumes more ketones and lactate and has higher proteolysis; fatty acids remain the dominant fuel	Coronary arteriovenous metabolomics	[17]
Pyruvate entry	MPC1, MPC2 and SIRT3 reduced in ischemic HFrEF; not significant in idiopathic DCM	LV tissue; immunoblot and qPCR	[19]

Domain	Key finding in human HFrEF	Material and method	Ref.
Iron	LV iron 121 versus 137 µg/g dry weight; 23% with myocardial iron deficiency; suppressed respiratory chain and Krebs cycle enzyme activities; $T2^*$ detects myocardial iron	138 failing versus 46 nonfailing explanted hearts	[22]
Ultrastructure	Smaller, rounded mitochondria; disrupted SR-mitochondria apposition; fewer lipid droplets in contact with mitochondria; conserved across DCM, HCM and ICM	Transmission electron microscopy of explanted hearts	[24]
UPRmt	Reduced HSP10, CLPP, LONP1, OMA1 and SPG7; low expression associated with earlier transplantation or LVAD	DCM and ICM myocardium; immunoblot	[25]
Calcium uniporter	MCU increased in LV of HF patients in proportion to remodeling and reduced after LVAD; MCU rises in adaptive hypertrophy and falls in failure	LV tissue; immunoblot	[26,27]
Mitophagy and redox regulators	PDE4D upregulated (suppresses PINK1/Parkin mitophagy); GSNOR suppressed (ANT1 nitrosylation)	Failing human hearts; immunoblot	[28,29]
Proteome	More than 5,000 proteins and 13,000 phosphosites quantified; etiology-specific perturbations in DCM versus ICM	LV proteomics and phosphoproteomics	[18]
Systemic mtDNA	Lower leukocyte mtDNA copy number predicts incident HF (HR 1.34 per SD); pooled RR 1.43 for lowest versus highest category	Population cohort (n = 2,508); meta-analysis of 22 studies	[30,31]

Domain	Key finding in human HFrEF	Material and method	Ref.
Skeletal muscle	Electron transport capacity correlates with peak VO2 (*r* up to 0.64); mitochondrial gene sets downregulated in men but not women with HFrEF	Pectoralis and limb muscle biopsies; respirometry, RNA sequencing	[32,33]

ANT1: adenine nucleotide translocase 1; CK: creatine kinase; DCM: dilated cardiomyopathy; GSNOR: S-nitrosoglutathione reductase; HCM: hypertrophic cardiomyopathy; HF: heart failure; HFrEF: heart failure with reduced ejection fraction; HR: hazard ratio; ICM: ischemic cardiomyopathy; LV: left ventricle; LVAD: left ventricular assist device; LVEF: left ventricular ejection fraction; MCU: mitochondrial calcium uniporter; MPC: mitochondrial pyruvate carrier; mtDNA: mitochondrial DNA; OR: odds ratio; PCr: phosphocreatine; PDE4D: phosphodiesterase 4D; PDH: pyruvate dehydrogenase; RR: relative risk; SD: standard deviation; SIRT3: sirtuin 3; SR: sarcoplasmic reticulum; TCA: tricarboxylic acid; UPRmt: mitochondrial unfolded protein response; VO2: oxygen uptake; ^{31}P-MRS: phosphorus-31 magnetic resonance spectroscopy.

SUBSTRATE REMODELING AND ITS SIGNALING CONSEQUENCES

Fatty acids, glucose and ketones

Two recent reviews in Nature Reviews Cardiology and Cardiovascular Research provide the current consensus on substrate remodeling[34,35]. In HFrEF, mitochondrial oxidative capacity falls, fatty acid oxidation declines as disease progresses, glucose uptake and glycolysis increase while glucose oxidation decreases so that glycolysis becomes uncoupled from mitochondrial oxidation, and ketone oxidation increases and partially compensates[2,34]. In HFpEF with obesity or diabetes the picture is one of substrate oversupply rather than failed oxidation, with preserved or increased fatty acid oxidation and accumulation of lipotoxic intermediates[10,34,36]. This distinction has therapeutic implications, because strategies that increase fuel delivery may help the fuel-starved HFrEF heart and harm the oversupplied HFpEF heart.

The role of ketones remains debated. The failing heart increases its capacity to oxidize 3-hydroxybutyrate, and ketones have been proposed as an efficient “thrifty” substrate as well as signaling molecules that modulate histone acetylation, inflammasome activity and oxidative stress[37,38]. Whether increased ketone oxidation in HFrEF is adaptive or a marker of fuel insufficiency has not been resolved[2]. The hemodynamic

trials of exogenous ketones reviewed later address the therapeutic question directly, but not the mechanistic one.

Branched-chain amino acids

Impaired catabolism of branched-chain amino acids (BCAA) is a recognized metabolic hallmark of HF. *In vivo* isotope infusions in mice showed, contrary to the prevailing assumption, that cardiac BCAA oxidation increases rather than decreases in HF, that cardiac-specific activation of BCAA oxidation does not protect, and that systemic activation protects by lowering blood pressure through reduced vascular resistance to adrenergic constriction, a finding supported by Mendelian randomization linking plasma BCAA to blood pressure in humans[39]. In a complementary approach, cardiomyocyte-specific inactivation of the branched-chain α-ketoacid dehydrogenase E1α subunit was sufficient to cause systolic dysfunction and chamber dilation, whereas cardiomyocyte-specific activation of the enzyme did not alter baseline function or the response to pressure overload[40]. The cardiomyocyte therefore requires intact BCAA catabolism, but pharmacological enhancement acts mostly outside the heart.

Acetylation, NAD+ and sirtuin 3

Substrate remodeling feeds back on the mitochondrial proteome through post-translational modification. Pressure overload HF in mice is accompanied by global hyperacetylation, particularly of TCA cycle enzymes, as a result of SIRT3 downregulation, with loss of enzyme activity, ATP depletion and ultrastructural damage[41]. SIRT3 is also reduced in human ischemic HFrEF myocardium[19], and mitochondrial SIRT3 protects against doxorubicin-induced dilated cardiomyopathy by modulating protein acetylation[42]. The relationship between NAD^+ and acetylation is not one-directional, however. In mice with established pressure overload dysfunction, nicotinamide riboside improved mitochondrial function and blunted HF progression to the same extent in wild-type and SIRT3-deficient animals, and the benefit was traced to improved function of NAD(H) redox-sensitive short-chain dehydrogenase/reductase proteins rather than to deacetylation[43]. NAD^+ repletion thus acts on multiple mitochondrial nodes, which is relevant to the clinical trials of NAD^+ precursors discussed below.

FAILURE OF MITOCHONDRIAL QUALITY CONTROL

The four arms of MQC introduced above, dynamics, mitophagy, biogenesis and proteostasis, are each altered in the failing heart. Protein-level surveillance is provided by the mitochondrial unfolded protein response (UPRmt), a retrograde transcriptional program that induces matrix chaperones and proteases, and by ubiquitin-dependent degradation of outer membrane proteins. The accumulation of dysfunctional mitochondria in cardiomyocytes is a hallmark of both aging and HF, and impaired MQC is a major driver of that accumulation[5,6].

Dynamics and ultrastructure

Transmission electron microscopy of cardiomyocytes from patients with dilated, hypertrophic and ischemic cardiomyopathy showed smaller, rounded mitochondria compared with nonfailing controls, disrupted apposition between sarcoplasmic reticulum (SR) and mitochondria, altered expression of proposed molecular tethers, and fewer lipid droplets in contact with mitochondria; these changes were conserved across etiologies[24]. The mechanistic literature on Drp1-dependent fission and Mfn1-, Mfn2- and OPA1-dependent fusion in the heart has been reviewed recently[44,45]. Of the primary studies, two illustrate the therapeutic logic. Loss of the outer membrane ubiquitin ligase MITOL in cardiomyocytes allows Drp1 to accumulate, producing mitochondrial fragmentation, reduced ATP production, increased ROS, myocardial senescence and chronic HF, and adeno-associated virus (AAV) delivery of MITOL after infarction improved cardiac function[46]. Conversely, cardiomyocyte-specific overexpression of the methyltransferase SMYD1a increased OPA1 expression, cristae density and respiratory supercomplex stabilization, and reduced infarct size by more than half[47]. Cristae architecture is tightly linked to respiratory efficiency: complexome profiling of mouse hearts four weeks after infarction revealed reorganization of supercomplex-associated subunits of the electron transport chain and decreased abundance of α-ketoglutarate dehydrogenase components[48]. The relationship between mitochondrial fragmentation and dysfunction in human HF is reviewed in detail elsewhere[1].

Mitophagy: Canonical and alternative pathways

Removal of depolarized mitochondria proceeds through canonical PINK1/Parkin-dependent mitophagy, receptor-mediated mitophagy (BNIP3, NIX and FUNDC1) and a

more recently described alternative pathway that depends on Ulk1 and Rab9 rather than on Atg7 and LC3[49,50]. In pressure overload, mitophagy is activated early through an Atg7-dependent mechanism that peaks within a day and then more strongly and with a delayed course through an Ulk1-dependent mechanism characterized by Rab9 phosphorylation at Ser179; cardiomyocyte-specific deletion of Ulk1 abolished the delayed response and produced more severe dysfunction, hypertrophy and fibrosis[51]. The same alternative pathway protects the heart against obesity-associated cardiomyopathy, and knock-in mice with a non-phosphorylatable Rab9 S179A develop impaired mitophagy and worse dysfunction on a high-fat diet[52].

Canonical mitophagy is suppressed in failing hearts by at least two mechanisms. PINK1 expression declines after transverse aortic constriction, and PINK1 deficiency promotes release of mtDNA into the cytosol and overactivation of cGAS-STING signaling, whereas cardiac PINK1 overexpression limits hypertrophy; the inflammatory arm was confirmed in PINK1/STING double-knockout mice[53]. Phosphodiesterase 4D is upregulated in failing human and murine hearts, and its overexpression suppresses PINK1/Parkin-mediated mitophagy through inhibition of cAMP-PKA-CREB-SIRT1 signaling, whereas silencing or inhibition with roflumilast restored mitophagy and attenuated hypertrophy and HF[28]. Pharmacological Parkin activation is now feasible: the small molecule PR-364 given after myocardial infarction reduced mortality, preserved ejection fraction and increased mitophagy, mitochondrial biogenesis and TCA cycle ATP production[54].

Receptor-mediated mitophagy behaves differently in HFrEF. BNIP3 has been implicated in myocardial remodeling and progression to HFrEF, and a multiomics analysis in an experimental HFrEF model showed that BNIP3 knockdown improved glycolysis, pyruvate metabolism, BCAA catabolism and oxidative phosphorylation, restored endoplasmic reticulum-mitochondrial calcium homeostasis and relieved BNIP3-mediated downregulation of SERCA2a and phospholamban phosphorylation[55]. In this setting BNIP3 therefore acts less as a protective mitophagy receptor than as a mediator of organelle dysfunction.

Biogenesis and the mitochondrial unfolded protein response

PGC-1α remains the master regulator of mitochondrial biogenesis. It coactivates NRF1 and NRF2, which drive the expression of TFAM and thereby couple nuclear transcription of respiratory chain subunits to replication and transcription of mtDNA; its upstream regulators, signaling partners and transcriptional targets have been comprehensively reviewed[6,56]. Suppression of this axis reduces the capacity to replace damaged organelles and is a recurrent finding in experimental pressure overload and in the aging heart[5]. In human myocardium, the UPRmt is impaired at the protein level: expression of HSP10, CLPP, LONP1, OMA1 and SPG7 was reduced in dilated and ischemic cardiomyopathy, myocardial ROS were increased, and patients with lower expression of HSP10, HSP60, HTRA2, OMA1, SPG7 and YME1L underwent transplantation or left ventricular assist device implantation earlier in life, which identifies UPRmt failure as a determinant of disease pace[25]. In spontaneously hypertensive rats, metformin induced heat shock factor 1 and the UPRmt (ATF5, LONP1, HSP60), restored the mtDNA/nuclear DNA ratio and complex I to V levels and attenuated hypertrophy and fibrosis[57]. Restoring the capacity to oxidize fatty acids is another entry point: AAV-mediated cardiac overexpression of carnitine palmitoyltransferase 1B attenuated hypertrophy, fibrosis and systolic dysfunction after pressure overload[58].

CALCIUM, REDOX BALANCE AND THE PERMEABILITY TRANSITION

Mitochondrial ATP production is matched to cytosolic demand by the parallel activation of oxidative phosphorylation by calcium and ADP: during workload transitions, calcium accumulates in the matrix and stimulates TCA cycle dehydrogenases, which regenerates NADH for the respiratory chain and NADPH for antioxidant systems[59,60]. In HF, elevated cytosolic sodium accelerates calcium extrusion through the mitochondrial Na^+/Ca^{2+} exchanger (NCLX), blunting matrix calcium accumulation, oxidizing the pyridine nucleotide pool and increasing emission of ROS[59,61]. Excess ROS oxidize mtDNA, peroxidize cardiolipin and other membrane lipids and modify respiratory chain proteins, which impairs supercomplex assembly and further increases electron leak, so that oxidative damage and energetic failure reinforce each other[1,6].

The mitochondrial calcium uniporter (MCU) shows a biphasic behavior. In both human and murine hearts, MCU levels rise in the adaptive phase of hypertrophy and fall in the

failing stage; viral downregulation of MCU accelerated contractile dysfunction and fibrosis after aortic constriction, whereas MCU overexpression prolonged the adaptive phase through retrograde Akt signaling[27]. In angiotensin II-induced HF, however, MCU upregulation drove calcium overload, ROS production and nuclear factor κB-dependent hypertrophic and proinflammatory signaling, MCU was increased in the left ventricle of HF patients in proportion to remodeling, and MCU expression fell after left ventricular assist device implantation[26]. These apparently contradictory results are compatible with a model in which matrix calcium must be sufficient to drive oxidative metabolism but not so high as to trigger permeability transition, and in which the therapeutic direction depends on disease stage.

Efflux is equally important. Cardiomyocyte overexpression of NCLX preserved contractile function and prevented hypertrophy and fibrosis in chronic pressure overload, but unexpectedly reduced survival under severe combined neurohormonal stress[62]. The inner membrane protein TMEM65 was identified as a binding partner required for NCLX-dependent calcium efflux, and its knockdown caused matrix calcium overload, cell death and cardiac dysfunction in mice[63]. The structure of NCLX has now been resolved[64], which opens the way to rational modulators.

Sustained matrix calcium overload and oxidative stress converge on the mitochondrial permeability transition pore, whose molecular identity remains debated but whose opening dissipates the membrane potential, releases mtDNA and cytochrome c, and commits the cell to death[65]. Redox regulation of the adenine nucleotide translocase is one relevant mechanism: S-nitrosoglutathione reductase (GSNOR) is suppressed in cardiac tissue from HF patients, mitochondrial GSNOR denitrosylates adenine nucleotide translocase 1, and restoration of mitochondrial GSNOR in cardiac-specific knockout mice improved mitochondrial function and remodeling after pressure overload[29]. The physical coupling between SR and mitochondria that shapes calcium microdomains, which depends on tethering complexes such as those containing Mfn2, is itself remodeled. Loss of SR-mitochondria apposition in human HF has been documented ultrastructurally[24], enhanced tethering in mice triggered adaptive muscle remodeling[66], and the biology of mitochondria-associated membranes in HF has been reviewed[67].

MITOCHONDRIA AS HUBS OF STERILE INFLAMMATION AND CELL DEATH

Mitochondrial DNA, cGAS-STING and the inflammasome

Mitochondria carry a bacterial-like genome with hypomethylated CpG motifs, and its release into the cytosol or extracellular space is sensed by cGAS-STING and Toll-like receptor 9[68]. Oxidized mtDNA and cardiolipin that has been externalized to the outer membrane also serve as ligands for the NLRP3 inflammasome, so that a single damaged organelle can engage both the interferon and the interleukin-1β arms of sterile inflammation[6]. Pressure overload is a potent stimulus for this pathway. Inducible nitric oxide synthase promoted mtDNA release and cGAS-STING activation in pressure-stressed hearts; iNOS deletion abrogated mtDNA release and sterile inflammation and improved function, while cardiomyocyte-specific STING deletion or AAV9-mediated suppression of the cascade was protective[69]. As noted above, defective PINK1-dependent mitophagy is a proximal cause of mtDNA leakage in hypertrophy[53]. In patients, the mitochondrial contribution to inflammation can be tracked systemically: in the 30-participant nicotinamide riboside trial, individual increases in whole-blood NAD^+ correlated with increased respiration of peripheral blood mononuclear cells and with decreased NLRP3 expression[70]. A detailed account of mitochondria-inflammation coupling in human HF is available[1].

Mitochondrial DNA as a circulating biomarker

Leukocyte mtDNA copy number (mtDNA-CN) is an accessible readout of systemic mitochondrial reserve. In 2,508 middle-aged Swedish women followed for a median of 17 years, each standard deviation decrease in baseline mtDNA-CN was associated with a 34% higher incidence of HF (hazard ratio 1.34, 95% CI 1.11 to 1.63), and the lowest versus the highest quartile carried a hazard ratio of 2.04[30]. A meta-analysis of 22 observational studies found a pooled relative risk of 1.43 (95% CI 1.15 to 1.79) for HF in the lowest compared with the highest mtDNA-CN category, with parallel associations for coronary disease, stroke and all-cause mortality[31]. Inherited and acquired mtDNA variants, and heteroplasmy that accumulates with age, add a further layer to the mitochondrial substrate for HF[71,72].

Regulated cell death

Mitochondrial dysfunction feeds several death pathways in cardiomyocytes. Beyond apoptosis and necrosis gated by permeability transition, iron-dependent lipid peroxidation (ferroptosis) has emerged as a mitochondria-linked mechanism in cardiomyopathies[73]. In mice with cardiomyocyte-specific mitochondrial dysfunction, NAD^+ depletion impaired lysosomal acidification and autophagy, lysosomal iron accumulation triggered ferroptosis, and nicotinamide mononucleotide administration improved lysosomal rather than mitochondrial function, reduced HF and extended lifespan[74]. This finding indicates that the effective target of a nominally mitochondrial intervention may lie in a neighboring organelle.

MITOCHONDRIAL AGING AND THE OLDER HFREF HEART

HFrEF is predominantly a disease of older adults, and almost every mitochondrial lesion described above is also a hallmark of cardiovascular aging. The proposed hallmarks of cardiovascular aging include disabled macroautophagy, loss of proteostasis, genomic instability, epigenetic alterations, mitochondrial dysfunction, cell senescence, dysregulated neurohormonal signaling and inflammation[75], and a 2025 roadmap sets out how organ-specific and cell-specific aging mechanisms in the circulatory system could be targeted by gerotherapeutics and how markers of biological aging could be built into clinical trials[76]. The accumulation of dysfunctional mitochondria with age reflects a progressive failure of the same quality control systems that fail in HF[5], and age-related changes in mitochondrial structure, dynamics, calcium handling and redox state have been reviewed in detail[77,78].

Two concepts from the Journal of Cardiovascular Aging are particularly relevant. One is cardiomyocyte senescence, driven in part by mitochondrial ROS and mtDNA damage, which produces a senescence-associated secretory phenotype that promotes fibrosis and inflammation and which senolytic strategies aim to remove[79]. The other is the observation that aging erodes the coordination between mitochondria, the SR, lysosomes and the nucleus, and this “dysfunctional interorganellar network” has been proposed as a hallmark of subcellular aging and a therapeutic target in HF[80]. The loss of SR-mitochondria apposition in explanted failing human hearts[24] and the Drp1-dependent senescence and chronic HF of MITOL-deficient mice[46] can both be read as experimental instances of this concept. Chronic HF in the older patient may thus be

understood as accelerated organ-specific mitochondrial aging on which neurohormonal and hemodynamic stress is superimposed.

BEYOND THE MYOCARDIUM: SKELETAL MUSCLE MITOCHONDRIA AND EXERCISE INTOLERANCE

Symptoms in HFrEF correlate poorly with LVEF and strongly with the periphery. In patients with HF, *in situ* respiration of pectoralis major biopsies through complexes I, II and IV and total electron transport system capacity correlated with peak oxygen uptake, lactate threshold and peak circulatory power (r 0.40 to 0.72), and a model combining age, hemoglobin, LVEF and electron transport capacity explained 52% of the variability in peak oxygen uptake and 80% of the variability in the lactate threshold[32]. The structural and metabolic remodeling of skeletal muscle in HFrEF, including fiber type shift, capillary rarefaction, mitochondrial loss and activation of catabolic programs, has been reviewed recently[81], and sex modifies the phenotype: RNA sequencing of skeletal muscle biopsies from 22 men and 16 women with moderate HFrEF identified 5,629 differentially expressed genes between the sexes, with catabolic terms upregulated and mitochondrial terms downregulated in men, whereas women showed a pro-oxidative phenotype with more type I fibers and higher capillarity[33].

These peripheral mitochondrial lesions are therapeutically accessible. Exercise training is the best-established intervention, and the peripheral determinants of exercise reserve that it modifies, including mitochondrial density, biogenesis and respiratory capacity in skeletal muscle, have been reviewed[81,82]. For older, frail or deconditioned patients who cannot exercise at an effective intensity, peripheral muscle electrostimulation offers a way to load the muscle; a systematic review of eight controlled trials in 387 cardiac patients aged 65 years and older found consistent improvement in lower-extremity function and walking distance with an acceptable safety profile[83]. Whether such interventions change myocardial mitochondrial function is unknown, but their effect on the symptomatic burden of HFrEF is mediated largely through the mitochondria of skeletal muscle.

THERAPEUTIC PERSPECTIVES

This section proceeds from established to experimental interventions. It begins with the mitochondrial actions of guideline-directed therapies and continues with substrate-level

interventions, membrane and redox agents, modulators of MQC, calcium handling and gene therapy, and mitochondrial transfer. Table 2 summarizes the strategies, their mitochondrial target and the stage of evidence reached by October 2026. Figure 1 places the therapeutic entry points on an integrated model of mitochondrial pathophysiology in HFrEF.

Table 2. Therapeutic strategies that act on mitochondria in heart failure with reduced ejection fraction: status of the evidence in October 2026.

Strategy (agent)	Mitochondrial target or mechanism	Highest level of evidence in HF	Key result	Ref.
SGLT2 inhibitors	Nutrient deprivation signaling (SIRT1, AMPK, PGC-1α); NHE1-NO axis; Na^+ and Ca^{2+} handling; ketone utilization; mitophagy	Guideline class I for outcomes; mechanistic RCT (EMPA-VISION, *n* = 72)	Outcome benefit independent of LVEF; no change in PCr/ATP after 12 weeks	[7,84,85]
Intravenous iron (ferric carboxymaltose, ferric derisomaltose)	Iron supply for heme and iron-sulfur proteins of the respiratory chain and Krebs cycle	Large RCTs and meta-analyses; ESC class I (symptoms), IIa (hospitalization)	RR 0.81 for cardiovascular death or HF hospitalization, driven by recurrent hospitalizations	[7,86-89]

Strategy (agent)	Mitochondrial target or mechanism	Highest level of evidence in HF	Key result	Ref.
Exogenous ketones (ketone ester, 1,3-butanediol)	Substrate supply (3-hydroxybutyrate); vasodilation	Randomized crossover trials (n = 24; n = 12); meta-analysis	Cardiac output +0.3 to +0.9 L/min; wedge pressure -3 mmHg; LVEF +3 points; NT-proBNP -18% (exploratory)	[90-92]
Trimetazidine	Partial fatty acid oxidation inhibition; glucose oxidation; mitophagy	Meta-analysis of 28 small, mostly open-label RCTs (2,552 patients)	Cardiovascular mortality OR 0.33; HF hospitalization OR 0.42; low certainty	[93,94]
Elamipretide	Cardiolipin binding; cristae and supercomplex stabilization	Phase 2 RCT in HFrEF (PROGRESS-HF); accelerated approval in Barth syndrome (2025)	No change in LVESV or LVEF at 4 weeks in HFrEF; sustained functional and cardiac improvement in Barth syndrome	[8,95,96]
NAD^+ precursors (nicotinamide riboside; intravenous NAD^+)	NAD^+ redox pool; short-chain dehydrogenase/reductase proteins; sirtuins	Phase 1 safety study (n = 30); single-center RCT (n = 180)	Whole-blood NAD^+ doubled; LVEF 45.4 versus 42.4% at 1 month	[70,97]

Strategy (agent)	Mitochondrial target or mechanism	Highest level of evidence in HF	Key result	Ref.
Coenzyme Q10	Electron carrier; antioxidant	Meta-analysis of RCTs; 6-month RCT	All-cause mortality RR 0.64; HF hospitalization RR 0.50; improved GLS and 6MWD	[98,99]
Urolithin A	Mitophagy induction	Crossover RCT (n = 10)	No change in echocardiographic indices or natriuretic peptides	[100]
Parkin activator (PR-364); PDE4 inhibition (roflumilast)	Restoration of canonical mitophagy	Preclinical (post-infarction and pressure overload models)	Reduced mortality, preserved ejection fraction, improved mitochondrial biogenesis	[28,54]
Gene therapy (AB-1002; DWORF; CPT1B; MITOL)	SR-mitochondria calcium coupling; fatty acid oxidation capacity; Drp1 clearance	Phase 1 (AB-1002, n = 11); preclinical for the others	No treatment-related adverse events; preliminary improvement in NYHA class and LVEF	[46,58,101,102]
Mitochondrial transfer (mitochondria-rich extracellular vesicles; MitoCatch)	Organelle replacement	Preclinical	Restored ATP and contractility in hypoxic cardiomyocytes and post-infarction mice; cell-type-targeted delivery	[103,104]

Strategy (agent)	Mitochondrial target or mechanism	Highest level of evidence in HF	Key result	Ref.
Exercise training; peripheral muscle electrostimulation	Skeletal muscle mitochondrial biogenesis and oxidative capacity	Systematic reviews; guideline recommendation for rehabilitation	Improved functional capacity and walking distance	[7,81-83]

6MWD: six-min walk distance; AMPK: AMP-activated protein kinase; CPT1B: carnitine palmitoyltransferase 1B; Drp1: dynamin-related protein 1; DWORF: dwarf open reading frame; ESC: European Society of Cardiology; GLS: global longitudinal strain; HF: heart failure; HFrEF: heart failure with reduced ejection fraction; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; MITOL: mitochondrial ubiquitin ligase; NHE1: sodium-hydrogen exchanger 1; NO: nitric oxide; NT-proBNP: N-terminal pro-B-type natriuretic peptide; NYHA: New York Heart Association; OR: odds ratio; PCr: phosphocreatine; PDE4: phosphodiesterase 4; PGC-1α: peroxisome proliferator-activated receptor γ coactivator 1α; RCT: randomized controlled trial; RR: relative risk; SGLT2: sodium-glucose cotransporter 2; SIRT1: sirtuin 1; SR: sarcoplasmic reticulum.

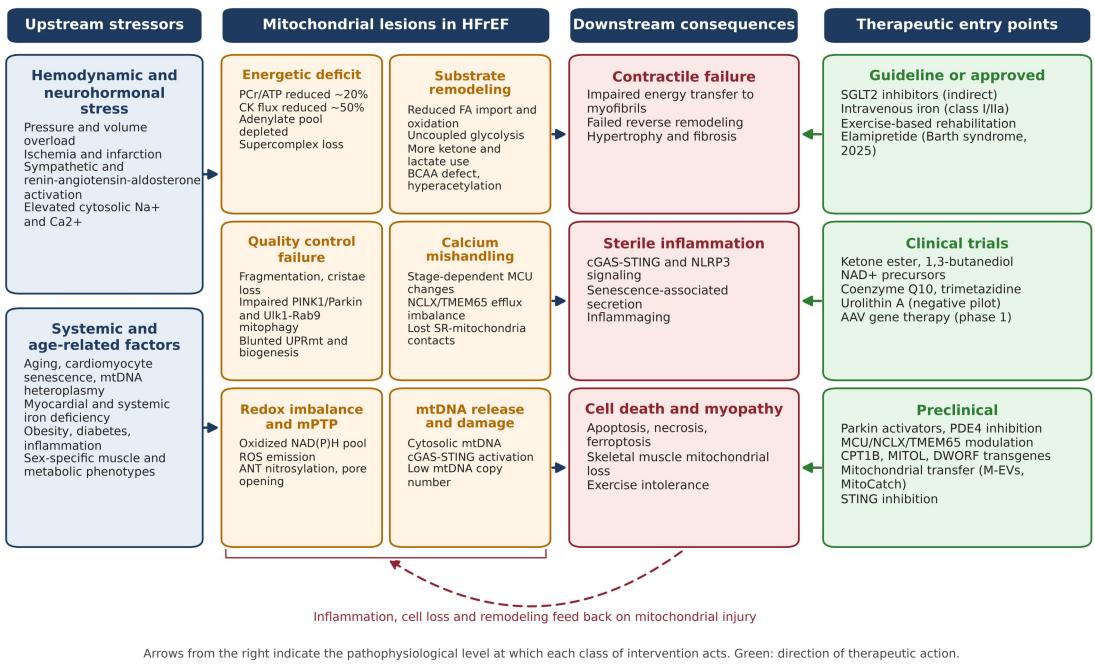


Figure 1. Integrated model of mitochondrial pathophysiology in heart failure with reduced ejection fraction (HFrEF) and the level at which current and emerging therapies act. Hemodynamic, neurohormonal, systemic and age-related stressors (left)

produce six interrelated mitochondrial lesions (center left) that drive contractile failure, sterile inflammation, cell death and skeletal muscle myopathy (center right). These consequences feed back on mitochondrial injury (dashed arrow). Therapeutic entry points (right) are grouped by the stage of evidence reached in October 2026. ANT: adenine nucleotide translocase; BCAA: branched-chain amino acids; CK: creatine kinase; CPT1B: carnitine palmitoyltransferase 1B; DWORF: dwarf open reading frame; FA: fatty acid; MCU: mitochondrial calcium uniporter; M-EVs: mitochondria-rich extracellular vesicles; MITOL: mitochondrial ubiquitin ligase; mPTP: mitochondrial permeability transition pore; mtDNA: mitochondrial DNA; NCLX: mitochondrial Na^+/Ca^{2+} exchanger; PCr: phosphocreatine; PDE4: phosphodiesterase 4; ROS: reactive oxygen species; SGLT2: sodium-glucose cotransporter 2; SR: sarcoplasmic reticulum; UPRmt: mitochondrial unfolded protein response.

Mitochondrial actions of guideline-directed therapy

Sodium-glucose cotransporter 2 inhibitors

SGLT2i reduce HF hospitalization and cardiovascular death and are now foundational therapy irrespective of LVEF[7]. Because cardiomyocytes express little or no SGLT2, the cardiac benefit must involve indirect or off-target mechanisms, and mitochondria figure prominently in the proposed explanations[105,106]. The nutrient deprivation hypothesis holds that SGLT2i mimic fasting, activating SIRT1, AMPK and PGC-1α signaling, promoting autophagy and mitophagy, and reducing oxidative stress and inflammation[85,107]. Empagliflozin prevented HF in a pressure overload and mineralocorticoid excess model equally in wild-type and SGLT2-knockout mice, the protection was mimicked by the NHE1 inhibitor cariporide and abolished by nitric oxide synthase inhibition, which places the NHE1-nitric oxide axis upstream of the mitochondrial effects[108]. In diabetic cardiomyopathy, ertugliflozin lowered a more than two-fold elevation of intracellular sodium, restored phosphocreatine and PCr/ATP measured by ^{31}P nuclear magnetic resonance and improved contractile function[109]. In isolated hearts, empagliflozin increased incorporation of 3-hydroxybutyrate carbon into TCA cycle intermediates and improved ATP, phosphocreatine and the free energy of ATP hydrolysis during ischemia and reperfusion[110]. Human tissue data are emerging: empagliflozin modulated PGC-1α, NRF1 and NRF2 expression in human atrial slices subjected to tachypacing[111], and it improved sarcomere organization, contractility and mitochondrial respiration and ATP production in patient-derived induced pluripotent

stem cell cardiomyocytes carrying a dilated cardiomyopathy variant[112]. Several groups have reported activation of FUNDC1- or PINK1/Parkin-dependent mitophagy by gliflozins in experimental cardiomyopathy[113,114].

The most direct human test was nevertheless neutral. In the randomized EMPA-VISION trial, 12 weeks of empagliflozin in 36 patients with HFrEF and 36 with HFpEF did not change cardiac PCr/ATP at rest in HFrEF (adjusted treatment difference -0.25, 95% CI -0.58 to 0.09) or HFpEF, nor during dobutamine stress, and did not change a targeted set of circulating metabolites[84]. The most parsimonious interpretation is that the clinical benefit of SGLT2i in HFrEF does not depend on a measurable improvement in myocardial energetics over this time frame, and that the mitochondrial effects documented in experimental systems may be modest in magnitude or occur in compartments not captured by PCr/ATP.

Intravenous iron

The mitochondrial rationale for iron repletion is strong, and the clinical evidence has matured. IRONMAN randomized 1,137 patients with HF, LVEF of 45% or less and iron deficiency to ferric derisomaltose or usual care; the primary endpoint of recurrent HF hospitalization and cardiovascular death occurred at 22.4 versus 27.5 events per 100 patient-years (rate ratio 0.82, 95% CI 0.66 to 1.02), with a rate ratio of 0.76 in the prespecified COVID-19 sensitivity analysis[86]. HEART-FID randomized 3,065 ambulatory patients to ferric carboxymaltose or placebo and found an unmatched win ratio of 1.10 (99% CI 0.99 to 1.23) for the hierarchical composite of death, HF hospitalization and six-min walk distance, which did not meet the prespecified significance threshold[87]. FAIR-HF2 randomized 1,105 patients and observed a hazard ratio of 0.79 (95% CI 0.63 to 0.99) for cardiovascular death or first HF hospitalization, a rate ratio of 0.80 for total HF hospitalizations, and did not formally meet its hierarchical testing criteria[88]. Pooled analyses are consistent: an individual patient data meta-analysis of three ferric carboxymaltose trials (4,501 patients) found a rate ratio of 0.86 (95% CI 0.75 to 0.98) for total cardiovascular hospitalizations and cardiovascular death[115], and a systematic review of intravenous iron trials reported a relative risk of 0.81 (95% CI 0.63 to 0.97) for the composite over complete follow-up, driven by recurrent HF hospitalizations, with treatment effects greatest during the first year when dosing is highest[89]. The 2026 ESC guidelines give a class I recommendation for

intravenous iron to improve symptoms and quality of life in symptomatic HFrEF with iron deficiency, and a class IIa recommendation to reduce HF hospitalization[7]. Iron repletion is therefore the first widely adopted therapy for HFrEF whose rationale is explicitly mitochondrial, even though no trial has yet shown that it reverses the myocardial energetic deficit.

Substrate-level interventions

Exogenous ketones

Oral ketone ester has produced the clearest short-term signal. In a randomized, double-blind crossover trial, 14 days of ketone ester in 24 patients with HFrEF increased resting cardiac output (5.2 versus 5.0 L/min) and lowered pulmonary capillary wedge pressure (8 versus 11 mmHg) at trough drug levels, reduced exercise wedge pressure by 3 mmHg and increased exercise cardiac output by 0.5 L/min, and in exploratory analyses lowered N-terminal pro-B-type natriuretic peptide by 18% and increased LVEF from 34 to 37%[90]. The ketogenic precursor 1,3-butanediol raised circulating 3-hydroxybutyrate by 1,400 µmol/L and increased cardiac output by 0.9 L/min, stroke volume by 15 mL and LVEF by 3 percentage points over six h in 12 patients with HFrEF, with reduced afterload and lower free fatty acids and glucose[91]. A meta-analysis of ketone interventions in HF found standardized mean differences of 0.52 for LVEF, 0.84 for cardiac output and -0.92 for systemic vascular resistance, with no change in mean arterial pressure[92]. These acute hemodynamic effects combine substrate provision with vasodilation and possibly direct inotropy, and the biology supporting them has been reviewed[37,38]. Whether they translate into reverse remodeling or outcome benefit requires trials of months rather than days.

Partial fatty acid oxidation inhibition

Trimetazidine shifts substrate preference toward glucose oxidation and improves coupling between glycolysis and oxidation. A systematic review of 28 randomized studies (2,552 patients, almost exclusively HFrEF) found reductions in cardiovascular mortality (odds ratio 0.33, 95% CI 0.21 to 0.53) and HF hospitalization (odds ratio 0.42, 95% CI 0.29 to 0.60) together with improvements in NYHA class and six-min walk distance, but the studies were small (median 58 patients), short (mean follow-up 6 months) and mostly open label[93]. An earlier meta-analysis restricted to nonischemic HF reached similar conclusions[116]. In a post-infarction HF model, trimetazidine

promoted PINK1/Parkin-mediated mitophagy[94], which suggests that its benefit may extend beyond substrate switching. An adequately powered, blinded outcome trial on top of contemporary foundational therapy remains to be done.

Membrane and redox agents

Elamipretide

Elamipretide (SS-31) is a cell-permeable tetrapeptide that binds cardiolipin in the inner membrane, stabilizes cristae and respiratory supercomplexes and reduces electron leak[117,118]. In the PROGRESS-HF phase 2 trial, 28 days of elamipretide at 4 or 40 mg daily did not reduce left ventricular end-systolic volume or improve LVEF compared with placebo in patients with stable HFrEF (mean LVEF 31%), although the drug was well tolerated[95]. Subsequent development has diverged. In Barth syndrome, an X-linked cardiolipin remodeling disorder with cardiomyopathy, the 168-week open-label extension of TAZPOWER showed a cumulative 96 m improvement in six-min walk distance, improved three-dimensional left ventricular volumes and improvement in the monolysocardiolipin to cardiolipin ratio[96], and on 19 September 2025 the United States Food and Drug Administration granted elamipretide accelerated approval to improve muscle strength in patients with Barth syndrome weighing at least 30 kg, on the basis of knee extensor strength as an intermediate endpoint and with a confirmatory placebo-controlled trial required[8,9]. It is the first approved therapy that acts directly on mitochondria. The contrast between a negative four-week trial in genetically heterogeneous HFrEF and sustained benefit in a monogenic cardiolipin disease illustrates a general lesson: mitochondria-targeted drugs are most likely to succeed where the mitochondrial lesion is primary and measurable.

NAD+ precursors and coenzyme Q10

Nicotinamide riboside at 1,000 mg twice daily was safe, approximately doubled whole-blood NAD^+ and improved mononuclear cell respiration in a 30-participant HFrEF study[70]. A single-center randomized trial of 180 patients with ischemic cardiomyopathy (LVEF 45% or less, NYHA II to III) compared seven days of intravenous NAD^+ with placebo on top of guideline-directed therapy and reported a higher LVEF at one month (45.4 versus 42.4%) with nonsignificant trends toward lower natriuretic peptide, fewer HF hospitalizations and better NYHA class at six months[97]. The preclinical demonstration that nicotinamide riboside acts on established

dysfunction and independently of SIRT3[43] supports moving to adequately powered trials with functional endpoints.

Coenzyme Q10 is the mobile electron carrier of the respiratory chain. A meta-analysis of randomized trials reported lower all-cause mortality (relative risk 0.64, 95% CI 0.48 to 0.85) and HF hospitalization (relative risk 0.50, 95% CI 0.37 to 0.67) with coenzyme Q10, with moderate-quality evidence for these endpoints and low-quality evidence for small improvements in LVEF and NYHA class[98]. A recent six-month randomized trial of 120 mg daily found improvements in global longitudinal strain, natriuretic peptides and six-min walk distance without a significant change in LVEF[99]. Most of the mortality signal, however, derives from trials conducted before contemporary foundational therapy was established, and the place of coenzyme Q10 in HF management remains unsettled[98,119]. Coenzyme Q10 is inexpensive and safe, and a contemporary outcome trial would resolve a question that has remained open for a decade.

Modulators of mitochondrial quality control

Pharmacological induction of mitophagy is attractive but has not yet produced clinical benefit in HFrEF. The gut microbial metabolite urolithin A, a mitophagy inducer, had no effect on LVEF, ventricular dimensions, tricuspid annular plane systolic excursion or natriuretic peptides in a small randomized crossover trial of 500 mg twice daily for four weeks in 10 patients with HFrEF[100], although in 50 healthy middle-aged adults it increased mitochondrial biogenesis and fatty acid oxidation capacity in $CD8^+$ T cells in a four-week placebo-controlled trial[120]. The Parkin activator PR-364[54] and phosphodiesterase 4 inhibition[28] are promising experimental approaches to restore canonical mitophagy, and the recognition of Ulk1-Rab9 alternative mitophagy as a protective program in pressure overload[51] suggests a second, mechanistically distinct target. Pharmacological inhibition of fission with Mdivi-1 has been widely used experimentally, but the compound has off-target effects on ion channels and complex I that complicate interpretation and limit translation[121]. Metformin, which induces the UPRmt and biogenesis in hypertensive hearts[57], is already in wide clinical use and could be tested for cardiac mitochondrial endpoints in HFrEF with diabetes. Broader reviews of MQC as a therapeutic target are available[5,122,123].

Calcium handling and gene therapy

Gene therapy has reached the clinic for HFrEF. In a phase 1 trial, AB-1002, a chimeric cardiotropic AAV delivering a constitutively active inhibitor of protein phosphatase 1 to cardiomyocytes, was given by intracoronary infusion to 11 patients with nonischemic cardiomyopathy, NYHA class III and LVEF of 15 to 35%; no adverse events were attributed to treatment, and preliminary efficacy signals included improved NYHA class and LVEF in both dose cohorts and improved peak oxygen consumption and six-min walk distance in the low-dose cohort[101]. The transgene acts on SR calcium handling rather than directly on mitochondria, but the two compartments are coupled: in mice, cardiac DWORF, a micropeptide that activates SERCA, increased mitochondrial basal and maximal respiration and spare capacity, enhanced mitochondrial calcium uptake and pyruvate dehydrogenase activation, and AAV-mediated DWORF delivery protected against pressure overload when given before or after the insult[102]. Mitochondria-directed transgenes with preclinical efficacy include CPT1B[58] and MITOL[46], and the field has been reviewed[124]. Direct manipulation of MCU or NCLX is complicated by the stage-dependent and stress-dependent effects described above[27,62], and TMEM65[63] and the resolved NCLX structure[64] offer new handles.

Mitochondrial transfer

Replacing rather than repairing mitochondria is the most radical approach. Mitochondria-rich extracellular vesicles from induced pluripotent stem cell-derived cardiomyocytes transferred functional mitochondria that fused with the recipient network, restored ATP production within three h in hypoxia-injured cardiomyocytes and improved post-infarction cardiac function in mice, whereas isolated mitochondria at far higher protein doses were ineffective[103]. In 2026, a platform termed MitoCatch used engineered protein binders displayed on donor mitochondria or target cells to direct mitochondria to specific cell types, including human and murine cardiomyocytes, with internalized mitochondria undergoing fusion and fission inside recipient cells[104]. Mechanisms, delivery routes and the possible use of mitochondrial transplantation to recondition donor hearts have been reviewed[125,126]. The approach remains preclinical for chronic HFrEF, and the durability of transferred organelles in a hostile failing myocardium is unknown.

Exercise and rehabilitation as mitochondrial therapy

Exercise-based cardiac rehabilitation remains the intervention with the broadest effect on mitochondrial biology across cardiac and skeletal muscle. Training counteracts the loss of mitochondrial density, biogenesis and respiratory capacity that characterizes skeletal muscle in HFrEF[81,82], and the correlation between muscle electron transport capacity and peak oxygen uptake[32] implies that these adaptations translate into functional capacity. For patients unable to train, electrostimulation of peripheral muscle provides a mitochondrial stimulus to the muscle that limits them most[83]. In the aging HFrEF population, in which sarcopenia and cardiac dysfunction coexist, rehabilitation can reasonably be regarded as a mitochondria-directed therapy.

CRITICAL APPRAISAL AND OPEN QUESTIONS

Several tensions run through the literature reviewed here. The first concerns causality. Energetic deficits are reproducible in human HFrEF, but the evidence that they cause rather than accompany contractile failure remains indirect, and PCr/ATP reductions are seen across the spectrum of ejection fraction and in conditions without HF[4,15]. The lack of correlation between *in vivo* PCr/ATP and *ex vivo* respirometry[16], and the neutral effect of empagliflozin on PCr/ATP despite a robust clinical effect[84], caution against using a single energetic biomarker as a surrogate for mitochondrial health or as a trial endpoint. CK flux, hyperpolarized metabolic imaging and circulating mtDNA-based markers deserve prospective evaluation as alternatives.

The second tension concerns heterogeneity. Mitochondrial lesions differ between ischemic and dilated cardiomyopathy[18,19], between men and women[33], between the adaptive and failing phases of hypertrophy[27], and between HFrEF and HFpEF[34]. The 2026 ESC redefinition of HFrEF to include LVEF up to 49%[7] will enlarge and diversify the trial population, and mitochondrial phenotyping may become a tool for enrichment rather than a universal target. The success of elamipretide in Barth syndrome after failure in unselected HFrEF[9,95] is the clearest argument for this view.

The third tension concerns the direction of intervention. Increasing mitochondrial calcium uptake, enhancing efflux, inducing fission or inhibiting it, and boosting ketone supply have each proved beneficial in some models and harmful in others[27,62,121]. Mitochondrial physiology is homeostatic, and interventions that push a variable in one

direction without regard to stage are unlikely to succeed. Adaptive programs such as alternative mitophagy[51] or the UPRmt[25] may be safer targets than core bioenergetic parameters because they are designed to be transiently activated.

The field also needs trials that are designed around mitochondria. Of the interventions reviewed, only intravenous iron has outcome data from large randomized trials, and those trials were not designed to test a mitochondrial hypothesis. Ketone esters, NAD^+ precursors, coenzyme Q10 and trimetazidine all have positive short-term or lower-quality signals and all lack a contemporary, adequately powered, blinded trial on top of foundational therapy. Including mitochondrial readouts, such as ^{31}P-MRS with CK flux, leukocyte mtDNA copy number, circulating cell-free mtDNA and skeletal muscle respirometry, in those trials would allow mechanism and outcome to be examined together.

CONCLUSION

Between 2021 and 2026 the mitochondrial pathophysiology of HFrEF has been quantified in human tissue and dissected in animal models with unprecedented resolution. The failing human heart shows a reproducible energetic deficit, defective fatty acid import and oxidation, uncoupled glycolysis, increased reliance on ketones and lactate, disturbed BCAA catabolism, protein hyperacetylation and myocardial iron depletion, coupled to fragmented mitochondria with disrupted cristae, impaired canonical and alternative mitophagy, a weakened unfolded protein response, disturbed calcium cycling and leakage of mtDNA that sustains sterile inflammation. These processes overlap substantially with the hallmarks of cardiovascular aging and extend to skeletal muscle, where they shape symptoms. Therapeutically, foundational drugs and intravenous iron act on mitochondria indirectly, exogenous ketones and NAD^+ precursors show encouraging short-term physiology, elamipretide has reached approval in a monogenic cardiolipin disease, and gene therapy and mitochondrial transfer have entered or are approaching human studies. The next phase should move from describing mitochondrial failure to selecting patients by mitochondrial phenotype and testing mitochondria-directed interventions with endpoints that measure both mechanism and outcome.

DECLARATIONS

Authors' contributions

Conceived the review, performed the literature search and reference verification, prepared the figure and tables, and drafted the manuscript: Sendrowski D;

Contributed to the conception of the review, critically revised the manuscript for important intellectual content and supervised the work: Kozłowski D;

Both authors read and approved the final version of the manuscript.

Availability of data and materials

Not applicable.

AI and AI-assisted tools statement

During the preparation of this work, the authors used Perplexity Computer (Perplexity AI) to assist with literature retrieval, bibliographic verification against PubMed and Crossref, and English language editing. The graphical abstract was prepared using AI-assisted visual planning and custom Python drawing code (model identified in the session as GPT-6 Astra). No text-to-image model, stock illustration library or synthetic microscopy was used for the graphical abstract. The platform version and exact model-build identifier were not exposed. The prompt and output record is provided in Supplementary Material 1. The authors reviewed and edited all content and accept full responsibility for the published material.

Financial support and sponsorship

None.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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