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New kids on the block to treat heart failure

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Abstract

In the last decades, important advancements were made in our understanding of heart failure (HF) pathophysiology, revealing that the failing heart is characterized by deficient energy production, alterations in ion handling and mitochondrial dysfunction. However, drugs targeting these derangements are not routinely used for HF treatment, which remains largely unsatisfactory. New promising therapeutic approaches currently tested in clinical trials are aimed at improving contractile function, restoring nitric oxide signaling, and targeting mitochondrial reactive oxygen species. Furthermore, sodium/glucose cotransporter 2 inhibitors substantially reduce HF hospitalization and cardiovascular mortality in patients with diabetes, and their pleiotropic effects on the heart and kidneys are likely beneficial also for HF patients without diabetes. Finally, preclinical studies indicate that restoring deranged cardiac ion handling positively affects mitochondrial energetics, and therefore targeting altered sodium and calcium dynamics may represent a viable strategy for treating HF. ■ *Heart Metab*. 2018;77:13-18

Keywords: mitochondria-targeted drug; myosin activator; soluble guanylate cyclase activator

Introduction

In spite of existing medical and interventional therapies, many patients with heart failure (HF) remain symptomatic and fail to achieve an acceptable quality of life. In the last decades, a wealth of experimental and clinical evidence has revealed that HF is characterized by an energy deficit, derangements in cellular ion handling, and mitochondrial dysfunction. So far, however, agents routinely used for HF treatment are mainly aimed at inhibiting neuroendocrine activation and reducing myocardial oxygen consumption,[1] whereas other pathogenic mechanisms have not been successfully targeted. Here, we outline experimental and clinical evidence supporting novel therapeutic options for chronic HF with reduced ejection fraction (HFREF).

Myosin activator: omecamtiv mecarbil

Independent of its etiology, decreased systolic function is a hallmark of HFREF, and agents targeting inotropy are routinely used in patients with acute decompensated HF. However, treatment with classic positive inotropic drugs, such as dobutamine and noradrenaline has been associated with adverse outcomes,[2] likely because these agents act by increasing calcium (Ca^{2+}) concentrations and consequently myocardial oxygen consumption within cardiac myocytes, creating a favorable substrate for arrhythmias and ac-

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Abbreviations

cGMP: cyclic guanosine monophosphate; **GTP:** guanosine triphosphate; **HF:** heart failure; **[Na^+]i:** intracellular sodium concentration; **NADPH:** nicotinamide adenine dinucleotide phosphate; **NCLX:** mitochondrial Na^+/Ca^{2+} exchanger; **NHE:** sodium/hydrogen exchanger; **NO:** nitric oxide; **ROS:** reactive oxygen species; **sGC:** soluble guanylate cyclase; **SGLT:** sodium/glucose cotransporter; **SS-31:** Szeto-Schiller peptide 31

tivating signaling pathways to promote maladaptive cardiac remodeling. Therefore, new inotropes directly targeted to sarcomeric proteins were developed to enhance contractility without elevating intracellular Ca^{2+} levels. A promising new inotrope is the myosin activator omecamtiv mecarbil *(Figure 1)*, which increases the amplitude and duration of contraction by favoring the transition of myosin to its force-generating state. Importantly, omecamtiv mecarbil achieves its effect without increasing oxygen consumption or cytosolic Ca^{2+} concentrations.[3] In contrast with conventional inotropic agents, which shorten the duration of systole, omecamtiv mecarbil enhances systolic function, mainly by prolonging systolic ejection time.[4] In dose-finding clinical studies, cardiac troponin release was observed in a few patients receiving high doses of omecamtiv mecarbil, which may have been related to an impairment in coronary perfusion and cardiac filling.[4] In the more recent ATOMIC-AHF study (Acute Treatment with Omecamtiv Mecarbil to Increase Contractility in Acute Heart Failure), omecamtiv mecarbil did not meet the primary end point, but improved dyspnea in the higher dose group as a supplemental predefined analysis.[5] At the lower doses used in this trial, no correlation between very small troponin increases and omecamtiv mecarbil plasma concentrations was observed.[5] While the detailed mechanisms of omecamtiv mecarbil on myofilaments[6] and their hemodynamic and energetic consequences[7] are not yet fully resolved, the compound has currently advanced to a phase 3 clinical trial in patients with stable (not acute) HFREF (NCT02929329).

Soluble guanylate cyclase activators

Nitric oxide (NO) is a gaseous signaling molecule predominantly produced by endothelial cells, which mediates pleiotropic effects on the vasculature and the myocardium via soluble guanylate cyclase (sGC) activation. Active sGC catalyzes the conversion of guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP), an intracellular second messenger with multiple downstream targets *(Figure 1)*. The NO-sGC-cGMP axis plays a key homeostatic role in the cardiovascular system, whereby its activation leads to vasodilation, modulates capillary permeability, and inhibits platelet aggregation and leukocyte adhesion to the endothelium. HF is accompanied by derangements in the NO-sGC-cGMP signaling axis, leading to systemic and pulmonary vasoconstriction and impairment of the renal and coronary vasomotor responses (reviewed in reference 8). Although the role of NO signaling in the vasculature has been the subject of extensive investigation, its effects on cardiac myocytes were initially overlooked. In fact, the concept that sGC activation may represent a valuable therapeutic approach in HF mainly resulted from studies reporting favorable effects of NO on left ventricular relaxation[9] and myocardial energetics.[10,11] These results rebutted the misconception that increasing NO bioavailability may negatively impact cardiac function because of its purported negative inotropic effect[11] and paved the way for clinical trials testing sGC stimulators and activators in HF patients. Based on their mechanism of action, it has been suggested that these agents may be particularly effective in HF subpopulations presenting with markers of endothelial dysfunction.[8] Although, in a phase 2 clinical trial, the sGC stimulator vericiguat failed to meet the primary end point of reducing N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels in patients with HFREF, a trend toward lower NT-proBNP levels was observed in patients treated with the highest dose of the drug.[12] A phase 3 clinical trial with vericiguat is currently in the recruiting stage (NCT02861534).

Targeting mitochondrial ROS production

Oxidative stress is considered a major driver of maladaptive ventricular remodeling and HF progression.[13] However, treatment with global antioxidative agents, such as vitamin C and E, failed to show any benefit in patients at high cardiovascular risk,[14] possibly because these agents are not specifically targeted to the primary pathological sources of reactive oxygen species (ROS), but, on the contrary, they also interfere with

the adaptive function played by physiological ROS production.[13] On this basis, specifically targeting mitochondrial ROS may represent a viable therapeutic approach for HF. The Szeto-Schiller peptide 31 (SS-31), also known as elamipretide, is a mitochondria-targeted tetrapeptide and one of the most promising agents in this regard *(Figure 1)*. Although its mechanism of action is not completely resolved, elamipretide may prevent ROS formation by interacting with cardiolipin, a phospholipid that is almost exclusively present in the inner mitochondrial membrane.[15] Due to its unique structure, cardiolipin is pivotal in shaping the morphology of mitochondrial cristae and promoting efficient electron transfer at the respiratory chain. By binding cardiolipin, elamipretide may preserve mitochondrial morphology and prevent electrons from "slipping" from the respiratory chain complexes to oxygen, giving rise to superoxides.[15] Treatment with elamipretide was proven beneficial in animal models of HF,[16] and phase 2 clinical trials are currently underway to test its efficacy in patients with systolic or diastolic HF (NCT02814097, NCT02914665, NCT02788747).

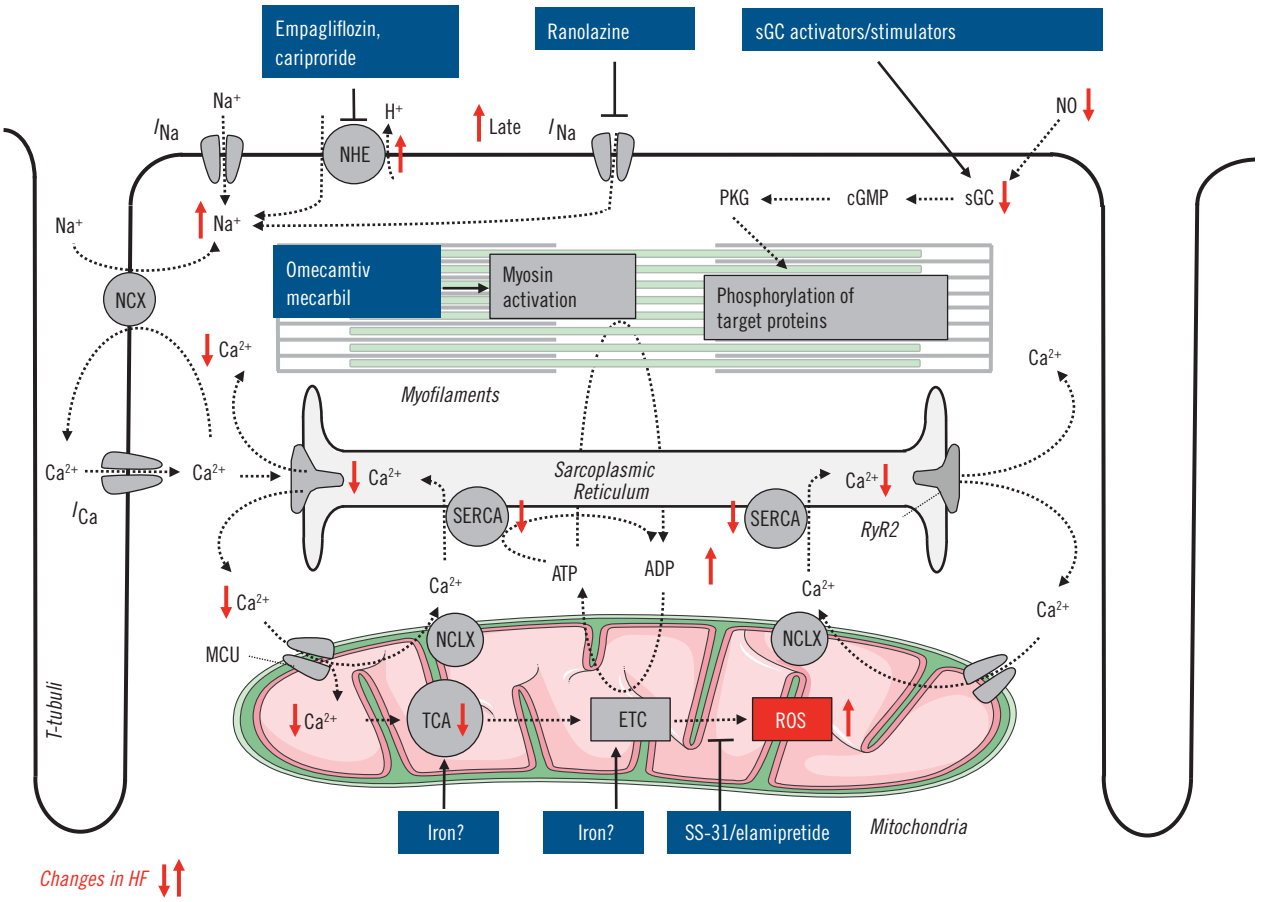

Fig. 1 *Novel therapeutic targets in heart failure. Deranged ion handling, impaired NO signaling, and mitochondrial dysfunction are promising therapeutic targets in HF. Independent of the underlying mechanism, impaired contractile function is a hallmark of HFREF. New positive inotropic agents, such as omecamtiv mecarbil, enhance systolic function by directly interacting with sarcomeric proteins and without increasing intracellular Ca^{2+} or myocardial oxygen consumption. Furthermore, the NO-sGC-cGMP axis is disrupted in HF, and restoring its activity via pharmacological stimulation of sGC positively affects both vascular and myocardial function. Another well-established feature of HFREF is increased intracellular sodium concentration ($[Na^+]i$), which has adverse bioenergetic consequences because it accelerates Ca^{2+} efflux from the mitochondria via NCLX. By inhibiting NHE, which is known to contribute to elevated $[Na^+]i$, empagliflozin and cariproride may restore ion homeostasis and thereby improve the bioenergetic feedback response. A similar effect may be obtained by inhibiting the late Na^+ current (late INa) with ranolazine. Moreover, mitochondria are a predominant source of ROS in HF, and increased oxidative stress contributes to maladaptive ventricular remodeling and arrhythmogenesis. Therefore, mitochondria-targeted drugs preventing ROS emission, such as the SS-31 may prevent HF progression and sudden cardiac death. Finally, myocardial iron deficiency decreases the activity of the Krebs cycle and mitochondrial antioxidative enzymes, and thus the beneficial effects of iron supplementation in HF patients may partly result from improved mitochondrial function.*

Abbreviations: *ADP, adenosine diphosphate; ATP, adenosine triphosphate; cGMP, cyclic guanosine monophosphate; ETC, electron transport chain; MCU, mitochondrial Ca^{2+} uniporter; NCLX, sarcolemmal Na^+/Ca^{2+} exchanger; NHE, sarcolemmal Na^+/hydrogen (H^+) exchanger; PKG, protein kinase G; ROS, reactive oxygen species; RyR2, ryanodine receptor 2; SERCA, sarcoendoplasmic reticulum Ca^{2+} ATPase; sGC, soluble guanylate cyclase; SS-31, Szeto-Schiller peptide 31; TCA, tricarboxylic acid cycle.*

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Targeting deranged ion handling

Increased formation of ROS at the respiratory chain is not the only mechanism potentially leading to ROS emission from mitochondria, but it can also arise from a depletion of mitochondrial antioxidative defenses. In fact, whereas superoxide is efficiently converted to hydrogen peroxide (H_2O_2) by mitochondrial superoxide dismutase (SOD2), H_2O_2 is detoxified by three systems (glutathione peroxidase, peroxiredoxin, and glutaredoxin), which are regenerated in their active form by NADPH. In turn, the maintenance of the reduced (active) NADPH pool depends on the Krebs cycle activity and its stimulation by Ca^{2+}.[17] Experimental studies demonstrated that, in the failing heart, elevated cytosolic sodium (Na^+) concentrations ($[Na^+]i$) impair Ca^{2+}-dependent stimulation of the Krebs cycle by accelerating Ca^{2+} efflux from the mitochondria via the mitochondrial Na^+/Ca^{2+} exchanger (NCLX).[18] Therefore, restoring abnormal Ca^{2+} handling may reduce ROS emission by preserving the mitochondrial antioxidative capacity. Although this approach has not been tested in clinical trials so far, promising results came from a guinea pig model of pressure overload-induced HF, in which restoring mitochondrial Ca^{2+} accumulation via pharmacological NCLX inhibition ameliorated ventricular remodeling and prevented sudden cardiac death.[19] Alternatively, reducing $[Na^+]i$ may be a viable approach to improve the bioenergetics feedback response, which can be achieved by inhibiting the late Na^+ current (late INa) with ranolazine or inhibiting the sodium (Na^+)/hydrogen exchanger (NHE) with cariporide, which may both account for elevated $[Na^+]i$ in patients with HFREF (reviewed in reference 20) *(Figure 1)*.

Sodium/glucose cotransporter 2 inhibitors

Sodium/glucose cotransporter (SGLT) 2 inhibitors are a new class of antidiabetic agents that act by inhibiting glucose reabsorption in the proximal tubule of the kidney, subsequently enhancing glucose excretion. A clinical trial investigating the effects of the SGLT2 inhibitor empagliflozin in patients with diabetes at high cardiovascular risk reported a striking risk reduction in hospitalization for HF and cardiovascular mortality, sparking an intense debate concerning the mechanisms underlying the unexpected magnitude and precocity of this effect.[21] In fact, the effects of SGLT2 inhibitors on glycemic control and their activity as osmotic diuretics are reputed insufficient to explain the outcome improvement associated with these drugs.[22-24] Furthermore, empagliflozin treatment was not associated with a reduction in the risk of myocardial infarction or stroke, and its cardioprotective activity was already evident within 3 months after randomization.[21] Several hypotheses have been subsequently put forward to explain its benefit, including a shift in myocardial metabolism away from fatty acid and glucose oxidation in favor of the more oxygen-efficient substrate β-hydroxybutyrate, a ketone body whose circulating levels are increased following SGLT2 inhibition.[22,23] Moreover, SGLT2 inhibitors were found to block the renal and cardiac sodium (Na^+)/hydrogen exchangers (NHE),[25] whose activities are abnormally enhanced in HF *(Figure 1)*.[26] Increased NHE activity in the kidney may partly account for resistance to diuretics and natriuretic peptide activities,[24] whereas, in the heart, it contributes to intracellular Na^+ overload.[26] As outlined above, increased $[Na^+]i$ in the failing heart impinges on mitochondrial Ca^{2+} accumulation, and therefore SGLT2 inhibitors may also improve myocardial energetics and oxidative stress by restoring mitochondrial Ca^{2+} dynamics.[27] Most likely, a combination of such beneficial effects of SGLT2 inhibitors on the heart and kidneys accounts for the outcome improvement observed in clinical trials, and further investigation is required to resolve the relative contribution of each mechanism to the overall effect. Clinical trials investigating the effects of SGLT2 inhibitors in nondiabetic HF patients with reduced (NCT03057977) and preserved (NCT03057951) ejection fraction are ongoing.

Iron supplementation

Recent studies revealed that iron deficiency is extremely common (30% to 50%) and portends a poor prognosis in HF patients.[28] Iron is a crucial component of several oxygen-binding proteins, such as hemoglobin, myoglobin, and the respiratory chain complexes, whose prosthetic groups include iron-sulfur clusters and heme groups. Furthermore, iron is also pivotal to the activity of key enzymes of the Krebs cycle and ROS-detoxifying systems.[29] Accordingly, reduced activity of the Krebs cycle and ROS-scavenging enzymes was observed in patients with both HF and myocardial iron deficiency compared with HF patients without an iron deficiency.[30] In an animal model of cardiac myocyte-specific cel-

lular iron deficiency, defects in the respiratory chain were associated with a reduced inotropic reserve after myocardial infarction and iron supplementation could improve this condition.[31] Therefore, iron deficiency might negatively affect cardiac energy production and may further worsen oxidative stress. With this rationale, the effects of oral and intravenous iron supplementation were investigated in patients with HF. Whereas oral iron supplementation failed to show any benefit,[32] potentially related to elevated circulating hepcidin levels limiting its intestinal absorption, intravenous iron administration improved HF symptoms independent of anemia.[33,34] However, so far, there is no signal that iron supplementation improves cardiovascular mortality.[35] Based on the results of these trials, current guidelines advise intravenous iron supplementation in carefully selected HF patients, taking into account hemodynamic stability, symptoms, left ventricular ejection fraction, and hemoglobin levels.[1,36] However, further investigation is warranted to unravel the mechanisms underlying iron depletion in HF and the beneficial effects associated with its supplementation.

Conclusions

For the last two decades, modulation of neuroendocrine activity has been the mainstay of HF therapy. Recently, our increasing comprehension of HF pathophysiology has led to the development of new promising therapeutic strategies, which are currently being tested in clinical trials. Myosin and guanylate cyclase activators are two examples of how our appreciation of disease mechanisms can translate into novel therapeutic approaches. Furthermore, the unexpected and striking effects of SGLT2 inhibitors on HF hospitalization and cardiovascular mortality paved the way for clinical trials testing their efficacy in nondiabetic HF patients. Finally, agents restoring deranged ion handling and preventing mitochondrial ROS production are promising strategies that warrant further investigation. Interestingly, the benefit associated with iron supplementation may partly result from an improvement in mitochondrial function. ■

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