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REVIEW

The scientific targets: the myocardium, the vasculature and the body's response to heart failure

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Abstract

Heart failure (HF) is a common but complex clinical syndrome associated with a reduced ability of a heart to pump and/or fill with blood. We now appreciate the more complex picture involving metabolic derangements, changes in fetal gene expression and abnormalities in the periphery as forming part of the HF syndrome. Therapeutic targets include the failing myocardium, the vasculature, and peripheral mechanisms. The pathophysiology of HF is currently being intensively investigated, with the identification of new relevant mechanisms, some of them emerging as potential therapeutic targets.

Key words heart failure, therapeutic targets.

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Introduction

Heart failure (HF) is a common but complex clinical syndrome associated with a reduced ability of a heart to pump and/or fill with blood. HF may be defined patho-physiologically as a cardiac output inadequate to meet metabolic demands, or an adequate cardiac output secondary to excessive compensatory neurohormonal activation (generally manifested as increased left ventricular filling pressures).[1]

The theories explaining the origin of the HF syndrome are rapidly evolving, moving from the concept of hypervolemia due to pump failure and consequent neurohormonal activation to a more complex picture involving metabolic derangements, changes in fetal gene expression and abnormalities in the periphery to name but a few. These other features of the HF syndrome are currently the object of much basic and clinical research (Figure 1).

The failing myocardium as a scientific target

When the heart starts to fail, a number of intrinsic mechanisms are invoked in order to increase cardiac output and thereby maintain adequate tissue perfusion. Initially, through the Frank-Starling mechanism, preload can be increased by ventricular chamber dilation and volume expansion can thereby enhance cardiac output. This mechanism, however, becomes deleterious if maintained long-term.[2] There are two general models that attempt to unify and explain the origin of HF: heart damage (*e.g.* infarction, myocarditis) leading to stiffness, myocardial remodeling and ventricular dilatation,[3] and heart hypertrophy (*e.g.* due to hypertension or other pressure or volume overload syndromes), where a myocardial hypertrophic response precedes later wall thinning and cavity remodeling.

When gathering evidence concerning the pathophysiology of HF, an explicit separation between heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF) seems arbitrary. The vast majority of patients with HF undergo the following steps in the progression of HF: i) heart damage (of differing types in terms of etiology, time and magnitude); ii) myocardial stiffness (with early changes in hemodynamics); iii) myocardial remodeling (local and/or global) with a preceding phase of hypertrophy in some cases – along with structural and functional pathologies – quantitative and qualitative changes on the histological and molecular level (including deranged cardiomyocytes, cardiofibroblasts, and other cell types); iv) further advanced changes in remodeling leading to wall thinning and ventricular/atrial dilatation with changes in geometry, desynchrony, and further metabolic and molecular changes in the myocardium.

In HFpEF – but also in the more recently defined HF with midrange (40-50%) ejection fraction (HFmrEF) – the primary functional abnormality is increased left ventricular stiffness due to a variety of processes including ischemia, insulin resistance and fibrosis, which is associated with increased left ventricular diastolic pressure, a passive increase in left atrial and pulmonary venous pressure, that in turns causes signs and symptoms of pulmonary venous congestion. Pressure overload is associated with a parallel replication of myofibrils and thickening of individual cardiomyocytes as well as an activation of cardiofibroblasts with resulting changes in the extracellular matrix.

In HFrEF (but also to some extent in HFmrEF), there are marked changes in left ventricular (LV) shape and geometry with the LV becoming more globular or spherical. Volume overload leads to a replication of sarcomeres in series and an elongation of myocytes, that proceed to a stretching of the mitral valve ring and consequent functional mitral regurgitation. This pathology significantly increases the load on the failing ventricle, and contributes to another *vicious cycle*, that can drive a cycle of deterioration and a progression of the manifestations of HF. An initial stress-induced increase in sarcomere length can maintain a near optimal overlap between myofilaments, but severe hemodynamic overload eventually yields to a depression of myocardial contractility.[3]

Along with dilatation and an altered geometry of the cardiac chambers, another phenomenon is the presence of dyssynchrony, seen at the interventricle, interatrium and atrio-ventricular levels, the mechanical dyssynchrony is usually associated with electrical dyssynchrony, which usually appears first, particularly in a form of left bundle branch block on the electrocardiogram.

These structural and functional changes in HFpEF, HFmrEF and HFrEF translate into an adaptation (to a new hemodynamic status) of volumes and pressures within the atria and ventricles.

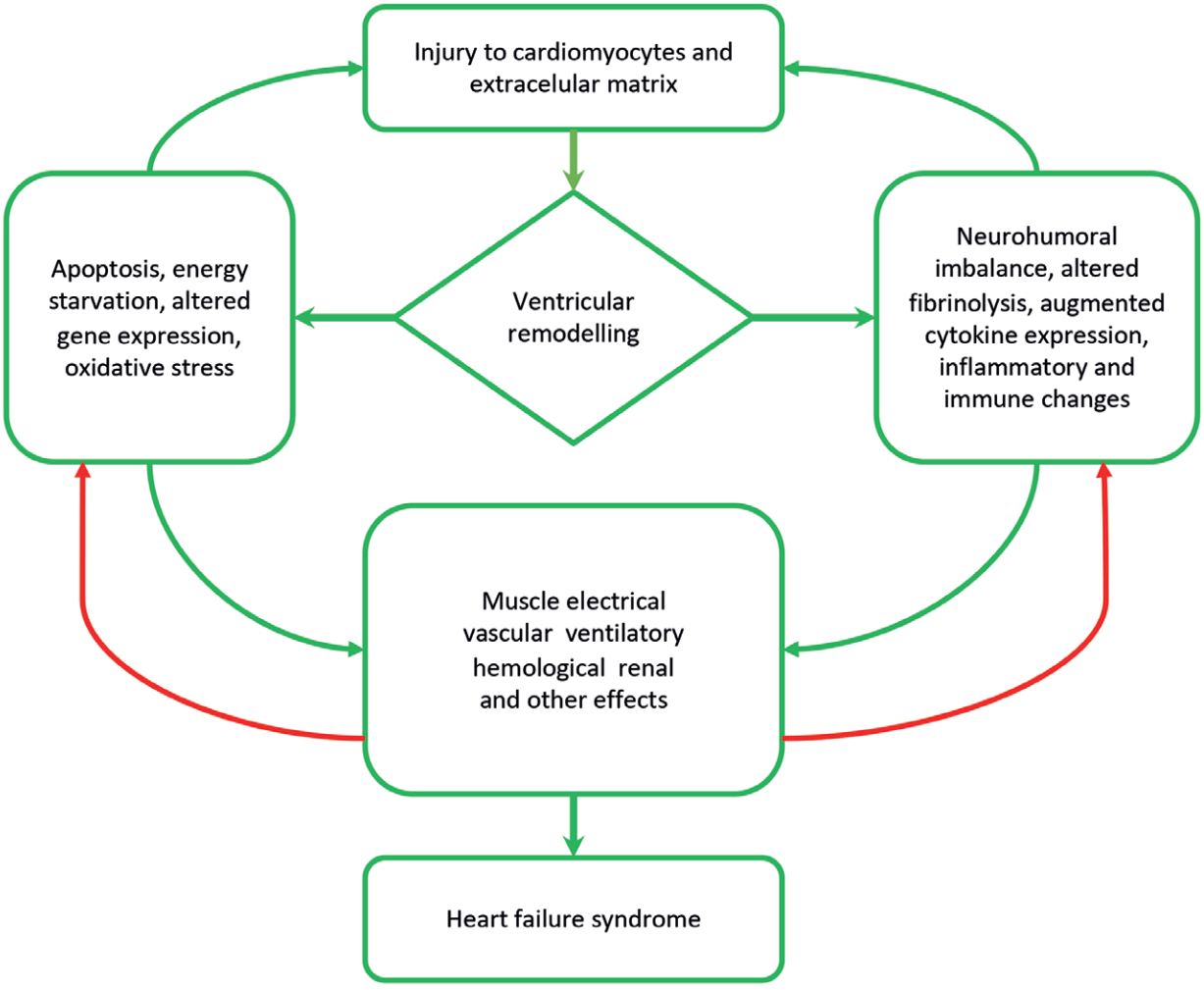

Figure 1. Pathophysiology of heart failure (HF) as a result of left ventricular systolic dysfunction. Damage to the cardiomyocytes and extracellular matrix leads to changes in the size, shape, and function of the left ventricle and heart more generally (remodeling). These changes, in turn, lead to electrical instability, systemic processes resulting in many effects on other organs and tissues, and further damage to the heart. These vicious cycles, along with intercurrent events, such as myocardial infarction or hypertensive crisis, are believed to cause progressive worsening of the syndrome of HF over time.

In HFrEF, the major abnormality will be a reduced left ventricular ejection fraction (LVEF), associated with reduced stroke volume and increased LV end diastolic and LV end systolic volumes (LVEDV and LVESV).

The underlying causes of myocardial remodeling are the target of many established life-saving therapies for patients with HFrEF, such as renin angiotensin aldosterone system (RAAS) blockers (angiotensin converting enzyme inhibitors, angiotensin receptor type 2 blockers, also in combination with neprilysin inhibitors, and mineralocorticoid receptor antagonists), and β-blockers.[4,5] Therapeutic options to treat functional mitral regurgitation are currently also under investigation with different types of mitral devices,[6] as well as cardiac resynchronization therapy (CRT).[7,8] CRT has been designed primarily for counteracting different types of dyssynchrony, but importantly the consequences of effective resynchronization include improvements in left ventricular filling time and contractility, a decrease in mitral regurgitation and an increase in cardiac output.[7,8]

An important pathophysiological element of HFrEF in particular is impaired cardiac contractility seen at the molecular, cellular and structural levels.[9] Based on this paradigm, drugs increasing cardiac contractility (positive inotropes) were developed for the treatment of HF. The first generation of positive inotropes, including phosphodiesterase-inhibitors (milrinone) and catecholamine derivates (dobutamine, dopamine, norephinephrine), although used still in some circumstances, have several limitations due to serious side-effects. However, development continues in this area, and the novel positive inotropes (levosimendan, omecamtiv mecarbil) have a better safety profile with some potential regarding their efficacy.[10,11] Importantly, cardiac contractility modulation represents a device-based intervention aiming to improve cardiac contractility and global myocardial function through the application of nonexcitatory electrical signals during the absolute refractory period, adjusted to and synchronized with the electrical action in the cardiac cycle.

The current understanding of molecular and metabolic mechanisms behind the aforementioned macroscopic changes remains limited. These changes may be localized after myocardial infarction, but more diffuse in patients with idiopathic dilated cardiomyopathy and/or myocarditis.[12] They comprise myocyte loss by necrosis and apoptosis, alterations in excitation-contraction coupling, alterations in composition and architecture of the extracellular matrix and deranged functioning of cardiac fibroblasts.[13] Apoptosis results from the induction of a genetic program that leads to the degradation of nuclear DNA, which is induced due to angiotensin II, reactive oxygen species, nitric oxide, pro-inflammatory cytokines.[13] Changes in the extracellular matrix usually manifest with an increase in collagen content though the imbalance between degradation and synthesis (along with the changed activity of enzymes governing these processes).[14] Some drugs counteracting these processes are in development, *e.g.* anti-apoptotic agents or anti-matrix metalloproteinases.[15]

In myocardial tissue, within the set of expressed genes, certain genes representing sarcomere and mitochondrial components and other transcripts are abundantly expressed in the cardiomyocytes. The molecular profiling of the failing heart shows widespread changes in splicing of sarcomere genes with a transition from α-myosin to β-myosin expression, a titin isoform switch, a lower expression of key calcium channels including *SERCA2a* and *RYR2*, an up-regulation of natriuretic peptides, a switch from expression of enzymes involved in fatty acid oxidation to glycolysis as well as a switch from enzymes involved in oxidative reactions towards anaerobic processes with augmented production of reactive species.[16]

Of special importance for the origin of HF is the presence of specific profiles of microRNA (miRNA) expression. These miRNAs are short, highly conserved, anti-sense RNA strands that target mRNA in a complementary manner and reduce protein expression by inhibiting mRNA translation and by targeting their breakdown. Many of them are described in HF as a potential therapeutic target, *i.e.* some drugs could promote the degradation of some detrimental miRNAs or *vice versa*.[17]

There is emerging evidence indicating that epigenetic regulation may play an important role in the pathogenesis of HF, namely in the phenotypic response of a failing heart.[18] Epigenetics refers to the changes in the regulation of gene activity and its expression that are not related to the gene sequence. These epigenetic modifications affecting DNA methylation, ATP-dependent chromatin remodeling, histone modifications, and microRNA-related mechanisms are considered sufficient factors contributing to adverse cardiac remodeling and preceding overt cardiac dysfunction (Figure 2).[19] In the future epigenetic modifications of cardiomyocytes and/or cardiac fibroblasts could be a target for personalized management and more effective tools for the prevention of HF.[20]

The vasculature as a scientific target

Abnormalities within vasculature occur in the course of HF, across the whole spectrum of LVEF. However, these pathophysiological changes in the vasculature are of special importance in patients with HFpEF.[21,22]

Microvascular dysfunction

Numerous pathophysiological mechanisms have been proposed for coronary microvascular dysfunction, as well as for peripheral microvascular dysfunction, contributing for example to the limitation of exertion-related perfusion of exercising muscles, and reduced global perfusion during episodes of decompensation. These changes include endothelial, smooth muscle, and sympathetic dysfunction, microvascular spasm, extramural rarefaction, and luminal obstruction, and all are potential targets for treatment interventions.[23]

Vascular remodeling and vasoconstriction

Patients with HF develop vascular remodeling that is related to hyperplasia of vascular smooth muscle cells, driven mainly

by the activation of the RAAS. Additionally systemic as well as pulmonary vasoconstriction are fundamental features of HF progression and are thought largely to be due to neurohormonal activation, inflammation and insulin resistance, with a resultant imbalance between vasoconstrictive and vasodilative mediators with resulting endothelial dysfunction. These structural and functional abnormalities translate into increased systemic and pulmonary vascular resistance and are now considered as key pathophysiological mechanism of HF, which have to date not been effectively therapeutically targeted.[24-26]

Peripheral mechanisms as scientific targets

Neurohormonal activation

Neurohormonal overactivity constitutes a fundamental pathophysiological mechanism involved in the origin and progression of HF. It remains the key therapeutic target, already underpinning multiple life-saving therapies for HFrEF worldwide.[10,27] Both the sympathetic nervous system (SNS) and the RAAS are activated reflexly during the onset of myocardial damage (due to reducing cardiac pumping shortly after the onset of myocardial infarction, myocarditis, *etc*.). These changes are thought to be adaptive during the initial stages and help to maintain acceptable cardiac output and tissue perfusion of critical vital organs such as the kidney and brain. Importantly, the features of neurohormonal activation are demonstrated at the systemic and peripheral level, namely molecular features of augmented aldosterone and adrenergic pathways have been demonstrated in the myocardium, but also in numerous peripheral tissues and organs, contributing to the progression of HF (*e.g.* vasculature, skeletal muscle, kidneys). However, a sustained chronic activation of RAAS and SNS translates into significant adverse consequences leading to progression of the HF syndrome, including peripheral vasoconstriction, sodium retention, hemodynamic alterations, skeletal dysfunction and renal dysfunction to name but a few.

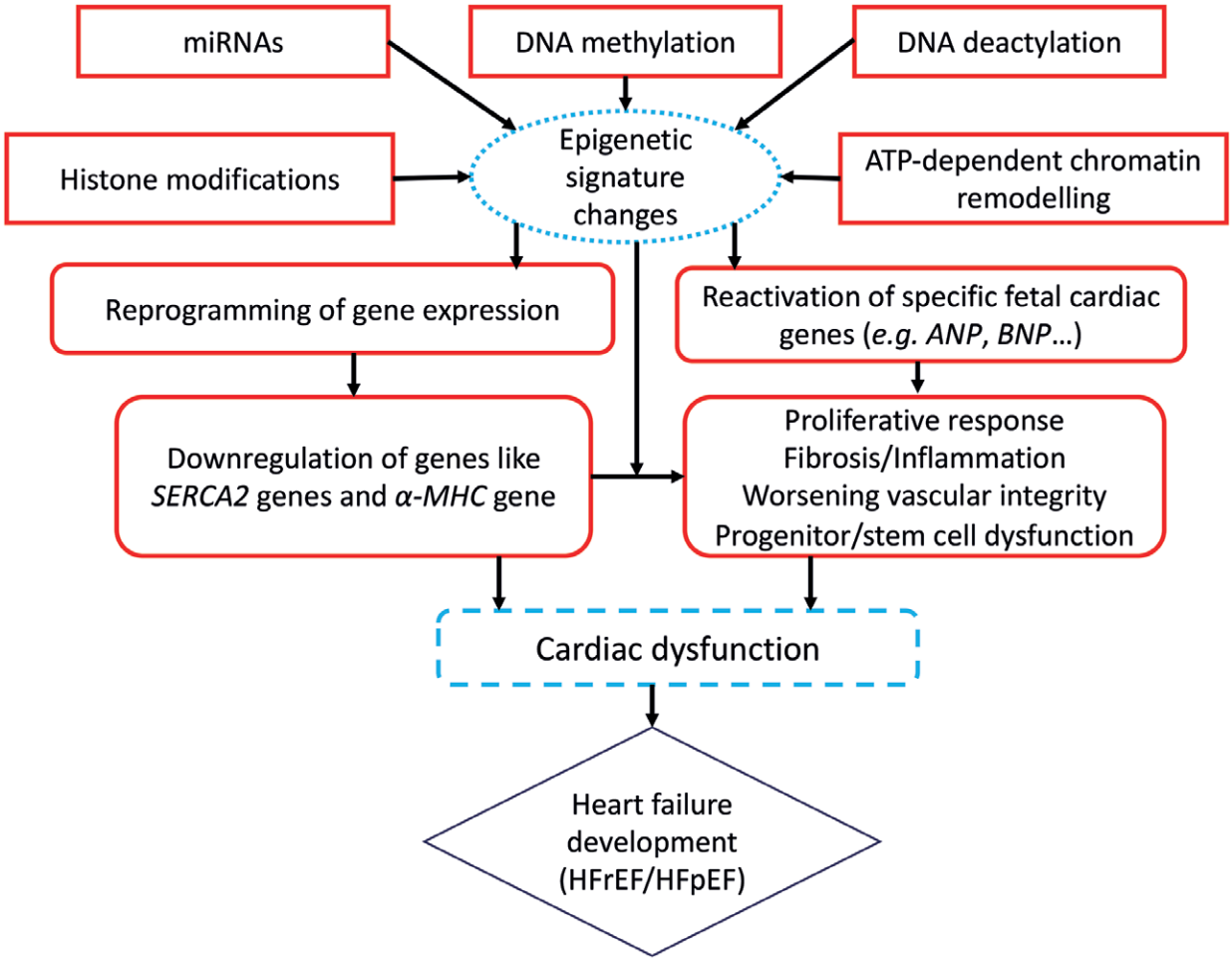

Figure 2. Epigenetic regulations in heart failure development.
α-MHC, α-myosin heavy chain gene; *SERCA2*, sarcoplasmic reticulum Ca2+ ATPase gene; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

Along with SNS and RAAS activation, there are adaptive and later maladaptive changes within the system of endogenous natriuretic peptides, which physiologically promote urinary sodium and water excretion, produce vasodilation, and inhibit pathological growth (*e.g*. hypertrophy and fibrosis).[28] In patients with HF, the response of overproduced natriuretic peptides is limited, therefore suggesting instead the therapeutic possibility of either administration of exogenous natriuretic peptide analogues or the inhibition of natriuretic peptide degradation (*e.g.* inhibition of neprilysin which degrades natriuretic peptides).

The clinical effects of parenteral administration of exogenous natriuretic peptides (nesiritide, carperitide, ularitide) have not been conclusive, and further studies are ongoing, whereas the administration of the combination of an angiotensin receptor blocker (valsartan) with the neprilysin inhibitor sacubitril has been successful in improving symptoms and clinical outcomes in patients with HFrEF.[28]

Autonomic imbalance and abnormal reflex control

Along with neurohormonal activation, autonomic imbalance with abnormal reflex control constitutes another fundamental pathophysiological mechanism contributing critically to the origin and progression of HF. Autonomic imbalance is related to activation of the SNS and concurrent depression of parasympathetic nervous system.

The features of autonomic imbalance are demonstrated at both the systemic and peripheral levels, namely molecular features of augmented adrenergic and depleted cholinergic signaling have been demonstrated in the myocardium, but also in numerous peripheral tissues and organs, contributing to the progression of HF (*e.g*. vasculature, skeletal muscle, kidneys, brain).

Along with the progression of HF, we observe changes in the balance of reflexes controlling the function of the cardiovascular system, the pulmonary system and of skeletal muscles.

Cardio-inhibitory reflexes, such as the baroreflex, are inhibited, whereas the sympatho-excitatory reflexes, such as central and peripheral chemoreceptor reflexes and ergoreceptor reflex, are augmented.[29-31] Again, these changes are to thought to be adaptive during the early stages of HF, but when they persist chronically they become maladaptive and further contribute to the unfavorable phenotype of HF, both within the myocardium and in the peripheral organs involved in the progression of HF.[32]

Importantly, there is no consensus concerning the origin of autonomic imbalance and deranged reflex control in the course of HF, nor the parameters for effective modulation, such as dose, continuity of stimulation or blockade or selectivity as to which organs to target, which makes research in this field even more exciting, but also difficult.[33]

The area of autonomic imbalance and deranged reflex control is currently under intensive investigation, both within the context of establishing reliable and accurate diagnostic methods which would allow us to translate sophisticated pathophysiology into simplified clinical implications, and also in the context of an identification of crucial targets for therapeutic interventions (both pharmacological agents and with implantable devices). Among the therapeutic approaches under investigations are the modulation of baroreflexes via carotid baroreceptor stimulation,[34,35] carotid body ablation, renal sympathetic nerve ablation,[36] vagal nerve stimulation,[37] the activation of systemic cholinergic signaling (acetylocholinesterase inhibitors), and many more.

Inflammation

Immune activation is another prominent feature of HF, with abnormalities seen primarily within the innate immune response (*e.g.* endotoxin hypothesis) and the imbalance between pro-inflammatory and anti-inflammatory mediators and reactions (favoring the later ones). Immune activation and inflammation are demonstrated in the systemic circulation, within the failing myocardium and peripheral tissues, both contributing to the progression of HF (*e.g*. skeletal muscles, vasculature, brain, kidneys). A pro-inflammatory state unfavorably affects myocardial function, exerts a negative inotropic effect, induces abnormalities in cardiac metabolism and energetics, induces cardiomyocyte hypertrophy, necrosis and apoptosis, and promotes myocardial remodeling.[38] Additionally, the activation of immune response in patients with HF promotes the endothelial dysfunction, autonomic imbalance, general body wasting, skeletal myopathy and anorexia, all increasing the risk of cachexia.[39] Until now clinical study results with interventions interfering with immune mechanisms have been inconclusive (*e.g*. anankira and canakikumab).[40-42]

Skeletal myopathy

According to *muscle hypothesis*, an acquired skeletal myopathy contributes to the symptomatology and progression of HF. Skeletal myopathy is related to numerous changes within skeletal muscles, seen at different levels of complexity, including molecular (changed expression in structural elements of microfibrils and molecules involved in energetics and metabolic reactions); microscopic (structural and functional changes in sarcomeres, mitochondria and other organelles, abnormal regulation of the microcirculation, remodeling of extracellular matrix); and macroscopic with reduced muscle mass, increased fatigability, reflex-mediated exercise hyperventilation and impaired global exercise capacity.[43,44] The origin of these abnormalities is not completely understood, but the following factors are presumed to contribute: neurohormonal activation, inflammation, autonomic imbalance with abnormal reflex control, including the augmented ergoreflex, a deranged microcirculation, catabolic-anabolic imbalance, abnormal energy metabolism and iron deficiency.

Improvement in the function of skeletal muscles consti-

tutes a clinically relevant therapeutic target. Several attempts have been taken to least partially reverse the skeletal myopathy in HF, some of them having a general influence on skeletal muscles (exercise programs, including resistance exercise),[45] others more specifically targeting underlying pathomechanisms (*e.g*. intravenous iron supplementation, mitochondria enhancers, anabolic agents, metabolism modulators).

Co-morbidities

Heart failure does not exist in isolation but is commonly accompanied by numerous co-morbidities. Some of them may be just pathologies accompanying HF and occurring independently of the HF. However, some co-morbidities are related with the progression of HF, where intrinsic elements of HF pathology predispose to the development of other diseases (*e.g*. iron deficiency, insulin resistance and overt diabetes, hyponatremia), or treatment applied in patients with HF leads to other abnormalities (*e.g*. hyperkalemia).

Anemia constitutes a frequent co-morbidity, its prevalence is related with the progression of HF and is associated with increased morbidity and mortality.[46] Although the origin of anemia in HF is not comprehensively established, neurohormonal activation, pro-inflammatory mediators and renal dysfunction are presumed to contribute to its development.[47] Anemia remains a clinically important target, despite erythropoiesis-stimulating agents having failed to show an adequate safety and efficacy in HF. There are some other agents being investigated with some promising results, including intravenous iron supplementation in case of iron deficiency anemia.

Iron deficiency (ID) should be perceived as a separate common and ominous co-morbidity in patients with HF. ID, regardless of concomitant anemia, accelerates the progression of HF, significantly contributes to skeletal myopathy and predisposes to unfavorable clinical outcomes.[48,49] In spite of intravenous iron supplementation already studied in some groups of patients with HF,[50] the other molecules interfering with metabolic pathways orchestrated by iron are of special scientific and clinical interest). Among electrolyte abnormalities occurring in the course of HF, hyponatremia and hyperkalemia are of a particular clinical relevance, and hence several therapeutic approaches have been designed and investigated.[51,52]

Conclusions

The pathophysiology of HF is currently being intensively investigated, with the identification of new relevant mechanisms, some of them emerging as potential therapeutic targets. The most recent developments are briefly summarized in Table 1 and Figure 3.[52-60]

Table 1. Promising targets with some clinical data and future targets in heart failure.

Target	Therapeutic option	References
	Promising targets with some clinical data	
Hyperkalemia induced by drugs	Patiromer, sodium zirconium cyclosilicate	Jankowska *et al*.[50] Urso *et al*.[51]
SGLT-2	Inhibitors of SGLT-2 (empaglifozin, canaglifozin, dapaglifozin)	Grodin[52]
cGMP deficiency	Vericiguat, riociguat	Bakris *et al*.[53]
Pulmonary hypertension	Phosphodiesterase-5 inhibitor (Tadalafil), endothelin agonist (Macitentan)	Bakris *et al*.[53]
Cellular/mitochondrial ion homeostasis	Increasing calcium sensitivity of the myofilaments (Omecamtiv mecarbil)	Sr *et al*.[54]
Calcium handling (phosphorylation of phospholamban, upregulation of *SERCA-2A*)	Cardiac contractility modulation therapy	Kosiborod *et al*.[55]
Left atrial hypertension	Transcatheter interatrial shunt device	Lam *et al*.[56]
Autonomic nervous system	Spinal cord stimulation	McMurray[28]
	Future targets	
Systemic microvascular inflammation	Chemokine antagonists (anti-MCP1, MCP3), immuno-modulatory cytokines (IL-10, pentraxins, phosphatidylinositol 3-kinase gamma inhibitors, IL-1β blockade with canakinumab or anakinra)	Bakris *et al*.[53]
Cardiometabolic functional abnormalities	Partial adenosine A1-agonists (capadenoson and Neladenoson), carnitine palmitoyltransferase-1 inhibitors (etomoxir and perhexiline), fatty acid β-oxidation inhibitor (trimetazidine), mitochondrial enhancer (elamipretide)	Bakris *et al*.[53]
Cellular structural abnormalities (titin)	Genetic manipulation of an RNA motif leading to up-regulation of compliant titins	Bakris *et al*.[53]
Extracellular structural abnormalities (fibrosis, amyloid)	Inhibition of TGFβ-induced fibrogenesis (Pirfenidone)	Bakris *et al*.[53]
microRNA related with HF mechanisms (inflammation, microvascular complications energy imbalance, fibrosis)	microRNA inhibitors or mimicking agents	Teerlink *et al*.[57]
Genes related with HF (*SERCA2a*, *S100A1* and *IPP-1*)	Gene transfer through vector virus	Tschöpe *et al*.[58]

SGLT-2, sodium glucose cotransporter-2; HF, heart failure; MCP, monocyte chemotactic proteins; IL, interleukin; TGFβ, transforming growth factor-β.

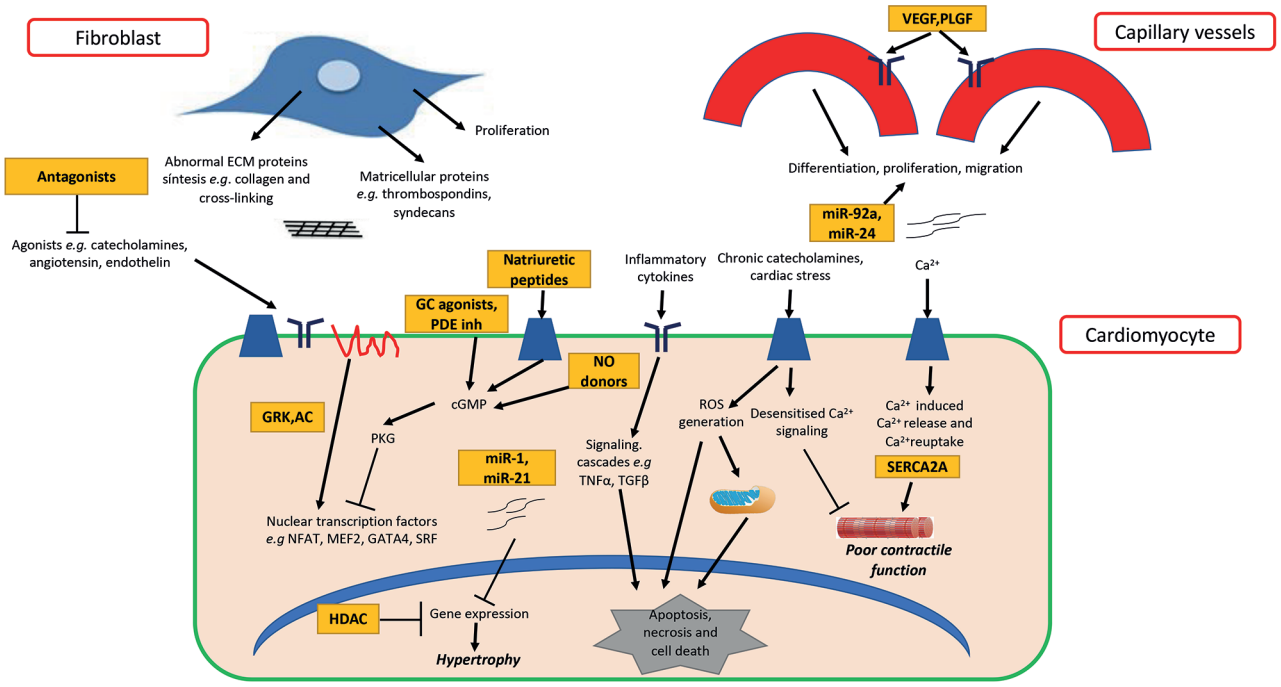

Figure 3. Pathophysiological mechanisms and key therapeutic targets (yellow boxes) in heart failure (HF). The HF phenotype involves cardiomyocyte hypertrophy, abnormalities of excitation-contraction coupling, impaired cardiomyocyte viability, abnormal protein homeostasis, oxidative stress, energetic dysfunction, arrhythmia, extracellular matrix remodelling and chamber dyssynchrony. These changes are mediated by intracellular signalling pathways and the interactions of multiple cell types within the heart including fibroblasts, endothelial cells and their associated capillary network and extracellular matrix. Some of the key signaling pathways amenable to therapeutic targeting in HF are shown in the figure.
VEGF, vascular endothelial growth factor; PLGF, placental growth factor; SERCA2A, sarcoplasmic/endoplasmic reticulum Ca2+ ATPase; HDAC, histone deacetylase; GRK, G-protein coupled receptor kinase; AC, adenylate cyclase; NO, nitric oxide; PDE, inh(phosphodiesterase inhibitors).

Contributions

The authors contributed equally.

Conflict of interest

The authors declare no potential conflict of interest.

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