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REVIEW

Acute heart failure: mechanisms and pre-clinical models—a Scientific Statement of the ESC Working Group on Myocardial Function

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Abstract

While chronic heart failure (CHF) treatment has considerably improved patient prognosis and survival, the therapeutic management of acute heart failure (AHF) has remained virtually unchanged in the last decades. This is partly due to the scarcity of pre-clinical models for the pathophysiological assessment and, consequently, the limited knowledge of molecular mechanisms involved in the different AHF phenotypes. This scientific statement outlines the different trajectories from acute to CHF originating from the interaction between aetiology, genetic and environmental factors, and comorbidities. Furthermore, we discuss the potential molecular targets capable of unveiling new therapeutic perspectives to improve the outcome of the acute phase and counteracting the evolution towards CHF.

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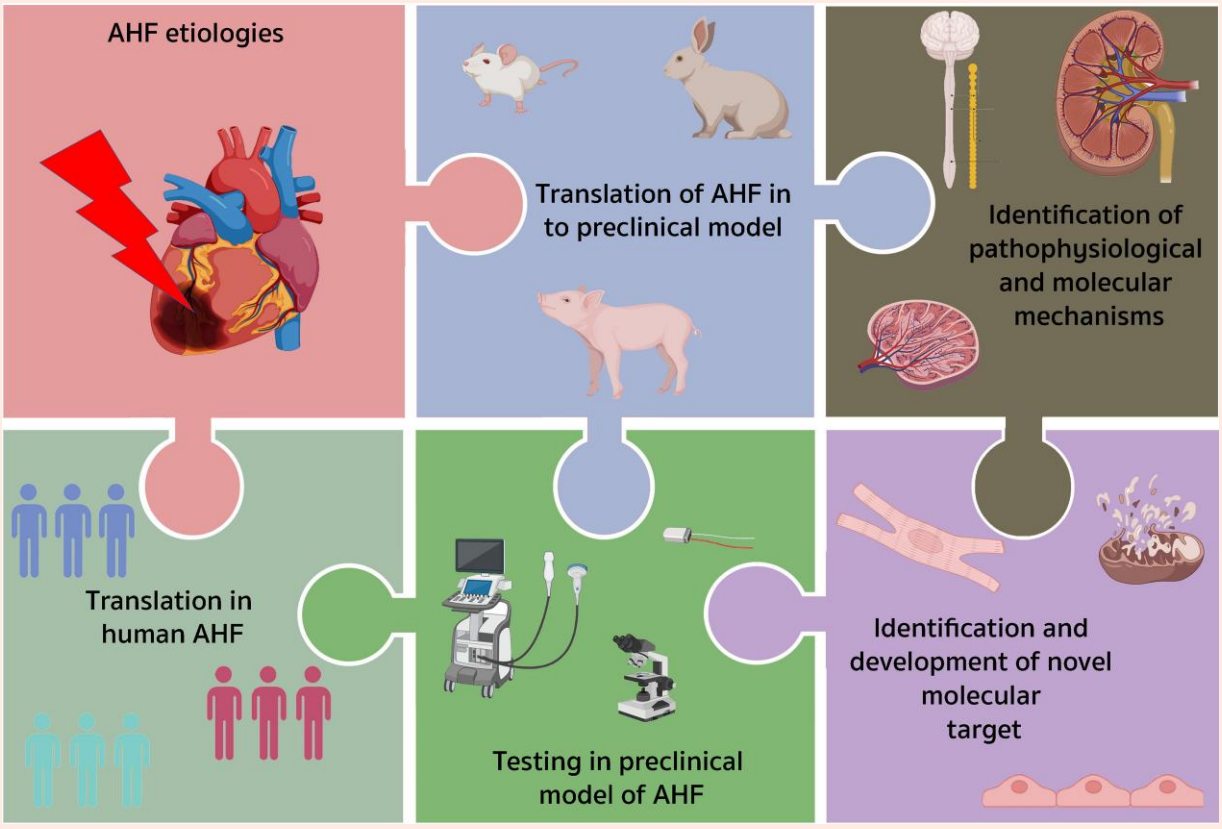
Graphical Abstract



Assembling the acute heart failure (AHF) in a translational view. Different causes of AHF can be reproduced in pre-clinical models to unveil novel pathophysiological and molecular mechanisms. Identifying novel molecular targets amongst organelles and cellular compartments can be tested again in the pre-clinical models. Effective strategies can be exploited in human scenarios. Image was partially created with BioRender.com.

Keywords Acute heart failure • Phenotypes • Trajectories • Pre-clinical models • Therapeutic management • Scientific statement • New strategies

1. Introduction

The management of chronic heart failure (CHF) has significantly improved over the last three decades, due to a better understanding of the underlying molecular and pathophysiologic mechanisms and to the consequent advancement of pharmacologic and device therapies, able to arrest, or at least delay, the disease progression.[1–5]

In contrast, the management of acute heart failure (AHF) has remained mostly unchanged over the decades and is based on the standard loop diuretics, vasodilators, vasopressors, and inotropes.[5,6]

AHF is a complex clinical syndrome that arises from the rapid onset or worsening of a pre-existing cardiac dysfunction that impairs the ability of the ventricle to fill and eject blood, producing signs and symptoms of HF, and a need for acute admission to the emergency department and unplanned hospitalizations.[5] Nonetheless, hospital admissions herald poor prognosis with a high risk of readmissions and deaths post-discharge, as evidenced by several AHF registries.[7–11] This article is the result of a science retreat held in September 2019 by the ESC Working Group on Myocardial Function, starting from a proposal of Prof Michele Ciccarelli and discussed with the other Nucleus Members.

The complexity of AHF is demonstrated by the finding that acute cardiac dysfunction may arise from several aetiologies and include a multitude of comorbidities, making this a complex set of HF syndromes.[12] Specifically, a significant challenge in classifying AHF as a single entity is the heterogenicity in its clinical presentation: patients admitted with AHF span from those with severe left ventricular (LV) systolic dysfunction and low cardiac output to those with normal or near-normal LV systolic function and severe hypertension.[13] In addition, worsening haemodynamic profile in a major feature of patients with reduced left ventricular ejection fraction (LVEF). In contrast, in patients with preserved LVEF a precipitating factor can be worsening of comorbidities.[13] Here we classify AHF as (i) New-onset or *de novo* AHF, which occurs in patients without a previous history of HF and (ii) acute worsening HF[14] or acutely decompensated HF,[15] which occurs in patients with pre-existing CHF.[15,16] The degree of the physiologic response is typically different between the two conditions, being more pronounced in *de novo* AHF cases and subtler in chronic cases because of previously activated adaptive mechanisms. In acutely decompensated HF, symptoms increase in individuals with previously diagnosed chronic HF;[15] it can be defined as the sudden or gradual onset of HF symptoms or signs requiring hospitalization, emergency room visits, or unplanned office visits.[17] Despite the causal precipitant of the exacerbation, pulmonary and systemic congestion due to augmented right- and left-heart filling pressures is a nearly universal finding in acutely decompensate HF.[17] Precisely, in acute worsening HF, structural abnormalities of the heart are considered irreversible, and the pharmacological approach in the stable phase aims to arrest or delay the progression of the disease by inhibiting the

pathophysiological and molecular mechanisms involved in cardiac remodelling.[15] *De novo* AHF occurs in subjects without previous history of heart disease with an apparently normal cardiac substrate, in which the establishment and progression towards irreversible cardiac damage rely on the crosstalk between aetiology (ischaemic and non-ischaemic), demographic factors (age, sex), presence of comorbidities (e.g. diabetes, chronic kidney disease, anaemia, chronic obstructive pulmonary disease, depression, and genetic predisposition) and timing of pharmacological and/or non-pharmacological interventions.[18] Most patients with *de novo* AHF present reduced LVEF,[11] but even in cases where LVEF is preserved, cardiac damage is mostly reversible. Often there are two events that lead to AHF: a known cardiomyopathy decompensates acutely due to rhythm disturbances, infection, fluid imbalance, ischaemia or high blood pressure; obviously, treatment will be different from primary events. Indeed, some individuals with reversible or treatable causes of HF, such as hypertensive heart disease, alcohol-induced cardiomyopathy, peripartum cardiomyopathy (PPCM), or tachycardia-induced cardiomyopathy (TIC), may even recover from HF with treatment and show resolution of HF symptoms, as well as normalization of the LVEF and cardiac structure.[19]

Moreover, the evolution of a *de novo* AHF towards CHF occurs in a relatively short time frame upon injury, when the complexity of the activated molecular pathways impacts the specific trajectory.[15,18] Overall, little is known about the possible therapeutic window and treatment targets to reverse HF or prevent the onset of CHF in *de novo* AHF patients that may improve their long-term outcomes.[20] The presence of different biology and molecular mechanism according to the aetiology and comorbidities of *de novo* AHF imposes different approaches to reduce the risk of its progression towards chronic worsening or even advanced HF.

Bearing this in mind, it is necessary to conceive and implement novel preclinical models of AHF, as well as deepen our understanding of the specific molecular mechanisms to define the specificity of each AHF phenotype. Here, we describe the clinical scenario and molecular mechanisms through which AHF can evolve to remission or to persistent/advanced HF, the available animal models of AHF, and potential molecular targets that could be exploited to develop novel therapeutic strategies.

2. Trajectories of AHF: how *de novo* AHF evolves into persistent or worsening HF

The natural history of HF includes progressive modifications in the clinical risk of hospitalization and death over time, with risk increasing from 'pre-HF' to 'new-onset/*de novo* HF,' and further increasing with each episode of 'worsening HF'.[21] It is, therefore, pivotal to recognize the stage of the patient's natural history, and to identify the patient's specific trajectory heading to HF remission, persistent or worsening HF.[22] Noteworthy, a condition of AHF is not necessarily associated with a LV dysfunction in terms of morphological changes and/or systolic function;[23] instead, we focused on how mechanisms activated after a cardiac insult and the next evolution towards remission, persistent and advanced HF. The transition from one stage to another, particularly from *de novo* AHF to worsening HF, is dictated by a series of pathophysiological and molecular events that reflect the specific combination of aetiology, comorbidities, and environmental factors.

Overall, long-term-trajectories are defined as reversible HF/HF in remission, persistent HF, and advanced HF[24] and are mainly affected by the establishment and extension of irreversible cardiac damage (*Figure 1*: Crosstalk between aetiology and comorbidities in the long-term trajectory of *de novo* AHF).[25]

Conditions that often evolve to remission of HF are stress-induced cardiomyopathy [Takotsubo (TTS)], PPCM, or thyroid disease[26] (*Figure 1*). In addition, temporary cardiac systolic impairment can be observed before or near complete restoration of LVEF. Still, this dysfunction is not associated with macroscopic fibrotic myocardial areas akin to those seen in post-acute ischaemia, and cardiac function often recovers within days, weeks, or months after the acute onset. Nevertheless, it can ease evolution to persistent or even advanced HF in case of pre-existing structural or genetic damage or comorbidities.[27]

Myocarditis may present as AHF and is an example of how a persisting injury, when not entirely resolved in the acute phase, prompts progression to a persisting or advanced HF, with a dilated cardiomyopathy (DCM) as a typical functional and morphological cardiac phenotype.[28,29]

Similarly, acute coronary syndrome (ACS) leads to AHF in about half of cases[8] and often evolves towards a persistent/advanced HF due to extensive scar tissue replacement of the necrotic myocardium.[30] Myocardial infarction (MI) can acutely occur either because of sudden occlusion of a coronary vessel (Type 1 MI) or as a consequence of increased oxygen demand by the cardiac muscle (Type 2 MI, e.g. during uncontrolled hypertension in combination with anaemia or respiratory failure in pulmonary oedema). As for most forms of AHF, also in AHF due to myocardial ischaemia, comorbidities negatively affect prognosis.[5,31–33] Anaemia and impaired renal function have probably the worst impact on outcomes.[5,34] However, remission of HF can potentially occur and strongly depends on the timing of treatment when the heart function can be restored, thanks to prompt treatment of myocardial ischaemia and precipitating factors. Specifically, in the stunned myocardium, the severity and duration of myocardial ischaemia are not prolonged enough to kill cardiomyocytes or induce extensive cardiac damage. When the ischaemia is relieved by reperfusion, the myocardium is viable but stunned, showing transient post-ischaemic contractile and biochemical dysfunction.[30]

The effectiveness of a prompt and early intervention is particularly evident in AHF due to TIC.

TIC is generally reversible if it can be treated successfully with medications, surgery or catheter ablation,[35] and cardiac function is often restored in weeks or months after.[36]

More complexity is observed in genetic cardiomyopathies, in which gene-environmental crosstalk and comorbidities have a significant influence on the development of the cardiac remodelling, which spans from DCM, to hypertrophic (HCM) or arrhythmogenic cardiomyopathy (AC).[37] Direct causes of these cardiomyopathies include pathogenic gene variants (known mutations; DCM up to 30%, HCM 50–60%, AC 70%) and acquired causes such as toxins, auto-immunity, storage diseases, infections, and tachyarrhythmias.[38] Disease modifiers aggravating or triggering a cardiomyopathy include age, gender, pregnancy, lifestyle, and most cardiovascular comorbidities[39,40] that often lead to a persistent/advanced HF (*Figure 1*).

3. Translational research for developing new strategies in AHF

3.1 Molecular and pathophysiological mechanisms involved in AHF

The molecular mechanisms leading to cardiac remodelling and the transition from acute to chronic HF activate immediately after an insult, and from a cellular point of view, involve the cardiomyocyte population and other cell types. Endothelial cell dysfunction, neurohormonal activation, inflammation, defective microcirculation, mitochondrial dysfunction, and oxidative stress produce cardiac damage, increasing the chance of developing persistent HF. These processes are variably represented and interconnected in the different AHF aetiologies, and initiate a series of adverse pathologic mechanisms following a myocardial injury that triggers fibrosis, progressive LV dysfunction, and remodelling, by involving the cardiovascular system, splanchnic bed, and renal function (*Figure 2*). Moreover, although underlying causes are heterogeneous, most AHF patients have symptoms of pulmonary congestion that lead to compromised gas exchange and arterial hypoxaemia, with dyspnoea presenting as the key manifestation.[41] The primary causal mechanism for pulmonary congestion in AHF is high LV filling pressure resulting in increased pulmonary capillary wedge pressure and pulmonary hypertension.[42]

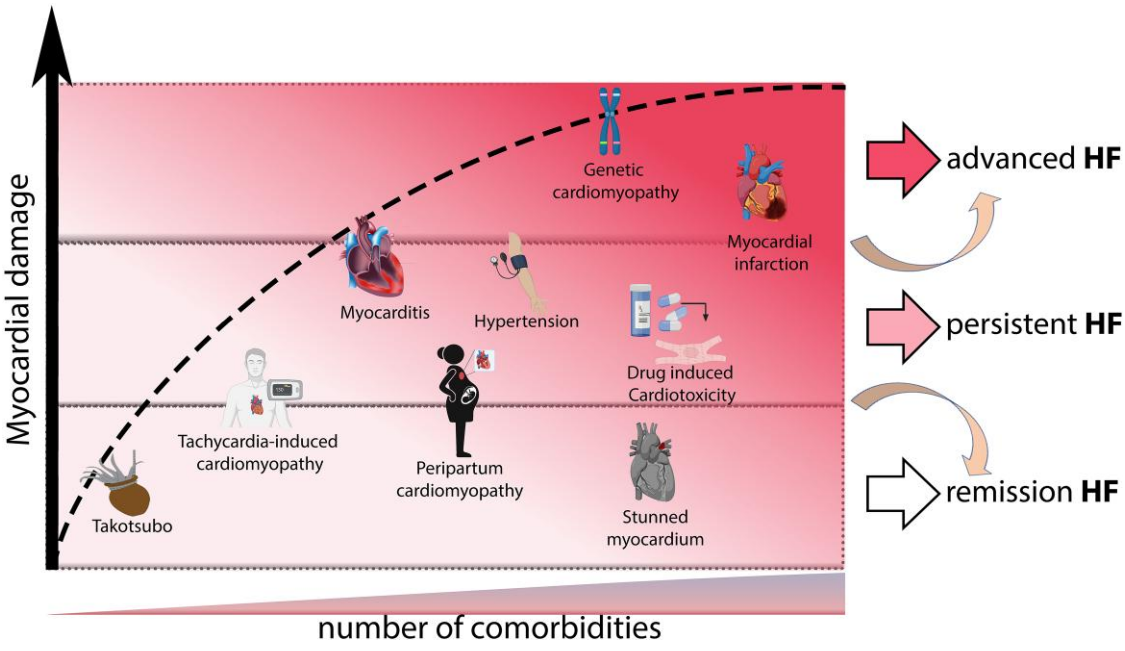


Figure 1 Trajectories of AHF. The figure displays the possible remission of the different AHF phenotypes. As shown, each phenotype owns a distinct possibility of recovery from the systolic and diastolic dysfunction in the acute phase; specifically, three different trajectories are possible: remission, persistent and advanced. The evolution of AHF relates to aetiology and environmental factors such as comorbidities and the earliness of therapy.

3.2 Endothelial dysfunction and microvascular dysfunction in AHF

Endothelial dysfunction is characterized by nitric oxide (NO) dysregulation, inflammation, and oxidative stress, which compromise the ability of the vascular endothelium to perform its several functions, such as regulation of vascular tone, anti-fibrinolysis, and inflammatory processes.[43]

These events are recognized in several conditions like sepsis and PPCM, where endothelial dysfunction results from various adaptive mechanisms following decreased cardiac output, neurohumoral activation, vasoconstriction, increased oxidative stress, and imbalance of NO generation and metabolism. In PPCM, for example, oxidative stress promotes cleavage of the hormone prolactin into a smaller antiangiogenic subfragment, 16 kDa prolactin, driving endothelial damage.[44,45] During sepsis, the endothelial barrier is primarily damaged by bacterial components by activating toll-like receptors.[46]

Moreover, acute inflammation involving the coronary microvascular endothelium leads to impaired nitric oxide (NO) bioavailability for adjacent cardiomyocytes and dysregulates the cyclic guanosine monophosphate (cGMP)-protein kinase G signalling. The reduced phosphorylation state of the giant sarcomere protein titin may foster LV stiffness, further exacerbating diastolic dysfunction and increasing the risk of triggering AHF.[47]

Diastolic dysfunction is often observed in patients prone to hypertensive AHF, where acute fluid redistribution due to increased neurohormonal activity, NO insensitivity, and arterial/ventricular stiffening associated with physiological stressors are critical determinants of the development of the phenotype.[48]

3.3 Inflammation and neurohormonal activation in AHF

Inflammation is well recognized as the key pathophysiological mechanism in AHF phenotypes like myocarditis and non-infectious diseases like TTS. In myocarditis, AHF is associated with severe neurohormonal, inflammatory, and immunological changes.[49] Typically, the infection of the myocardium occurs in three phases: Phase 1 includes viral entry into myocytes and activation of innate immunity; during Phase 2, viral replication and activation of acquired immune responses occur; and Phase 3 is either resolution with recovery or development of DCM.[50] Cardiac decompensation following myocarditis relates to a systemic pro-inflammatory environment[42,51] due to the activation of innate immunity, as observed in Phase 2. In particular, high levels of cytokines, tumour necrosis factor (TNF), IL-1 α, IL 1 ß, IL 2, and IFN γ, together with antibodies to viral and cardiac proteins, can further increase cardiac damage and compromise systolic function through derangement of the contractile apparatus and/or interstitial cells and matrix proteins.[50] TNF-α and IL-1ß have a direct negative inotropic effect on cardiomyocytes by downregulating the expression of $Ca2^{+}$-regulating genes,[52] triggering cardiomyocyte apoptosis,[53,54] and enhancing the activity of cardiac fibroblasts.[55,56] Pro-inflammatory cytokines also induce endothelial cells apoptosis,[57] generate oxygen-centred free radicals, facilitate transendothelial migration,[58] increase adhesion molecule expression,[59] and following adhesion of immune cells to the endothelium.[60]

Whether the systemic inflammatory response in AHF contributes to the pathophysiology of decompensation leading to hospitalization (i.e. causality) has yet to be established.[61] However, acute administration of cytokines in the pre-clinical model has been shown to induce a pathophysiological scenario typical of AHF with ventricular dysfunction, increased diastolic stiffness, and pulmonary oedema.[62]

Likewise, SARS-CoV-2 may contribute to myocarditis and other myocardial involvement by multiple mechanisms, comprising direct virus invasion, microvascular angiopathy, and host inflammatory or immune responses.[63–66]

COVID-19 produces an intensely pro-inflammatory state, as suggested by high levels of C-reactive protein, ferritin, lactate dehydrogenase, interleukin-6, and D-dimer. The cytokine hyperproduction in COVID-19 comprises TNF, IL-6, IL-7, and inflammatory chemokines (CCL2, CCL3, and soluble IL-2 receptors).[67] This so-called 'cytokine storm' stimulates thrombosis through several mechanisms, including activation of monocytes, neutrophils, and endothelium, finally inducing vascular injury.[68]

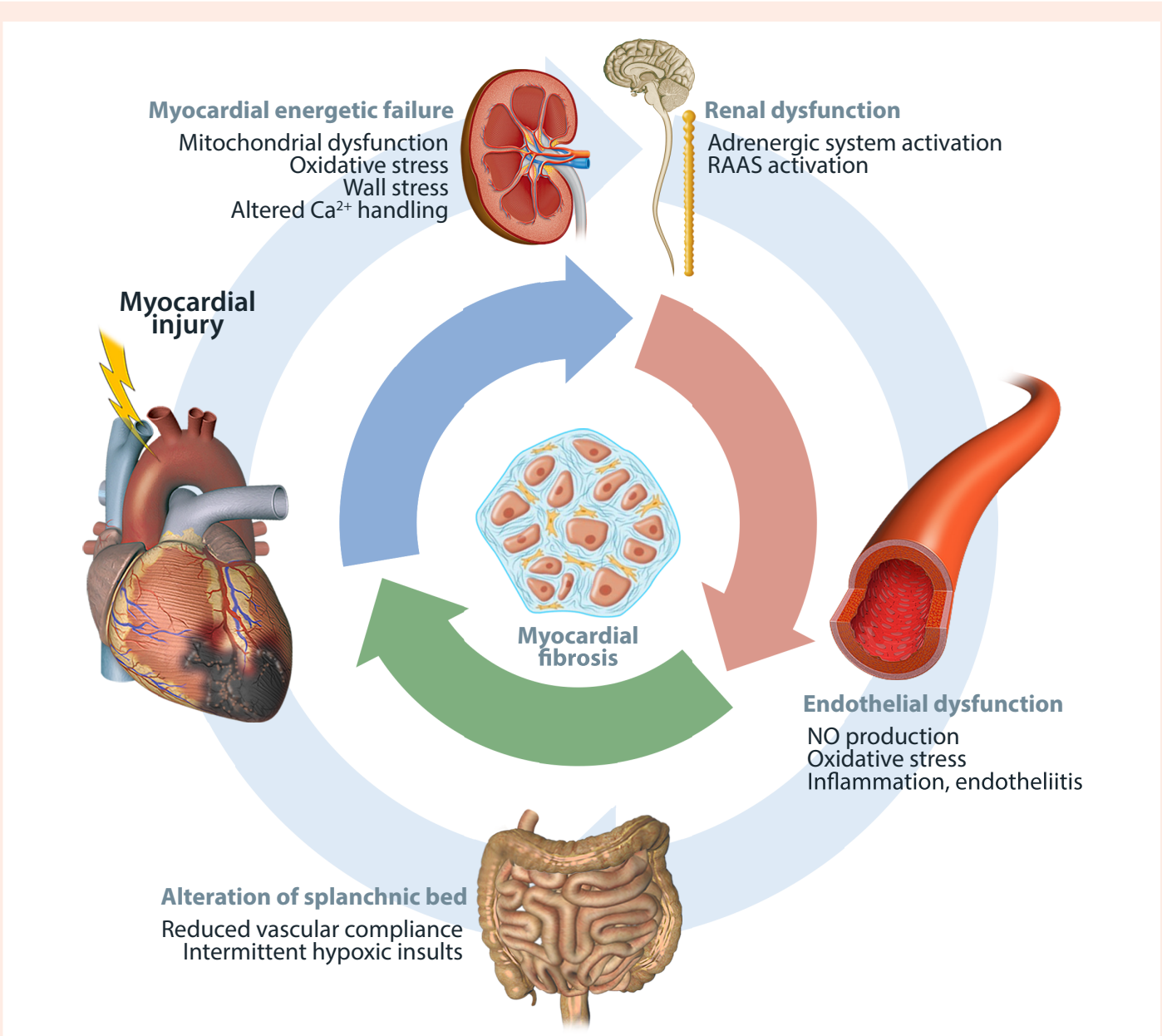


Figure 2 Common pathophysiological mechanisms in AHF phenotypes. Different causes of cardiac injury activate early pathophysiological and molecular mechanisms, including energetic cardiac failure, renal and endothelial dysfunction, and alteration of the splanchnic bed. Perpetuating these mechanisms promotes cardiac fibrosis and remodelling. NO, nitric oxide; RAAS, Renin–Angiotensin–Aldosterone System.

Similarly, in non-infectious myocarditis, the so-called cytokine release syndrome caused by anticancer CAR-T therapies and by specific antibodies such as blinatumumab is due to high levels of inflammatory cytokines released by activated CAR-T cells and other immune cells, such as macrophages, with fever and tachycardia that may be associated with hypoxia and hypotension. Additionally, the (counter-) regulatory processes following an episode of AHF also seem to involve heart-specific adaptive immunity.[69] Indeed, anti-myocardial autoantibodies have been found in patients hospitalized with AHF, probably reflecting patterns of adaptive immune responses in these patients.[70] Interestingly, impaired thymic tolerance to myosin antigens is one of the putative mechanisms of development for immune checkpoint inhibitors (ICIs, used for cancer treatment) related to cardiovascular immune adverse events.[71,72] In another model, Gil-Cruz *et al.*[73] showed that the progression of autoimmune myocarditis to severe heart disease depends on cardiac myosin-specific Th17 cells imprinted in the intestine by a peptide mimic derived from a commensal *Bacteroides* species, with a significantly high *Bacteroides*-specific CD4+ T cell and B cell responses in human myocarditis. Accordingly, antibiotic therapy led to the effective prevention of lethal disease in mice, suggesting that mimic peptides from commensal bacteria can stimulate inflammatory cardiomyopathy in genetically susceptible patients.[74]

In TTS, adrenergic signalling activates cytoadhesin expression (ICAM-1) by bone marrow cells and cardiac endothelial cells, fostering diapedesis, developing sterile inflammation, and remodelling of the failing heart.[75,76]

Additionally, neurohormonal and inflammatory alterations in AHF may impair the endothelial glycocalyx's structure and function, consisting of networks of glycosaminoglycans connected to the endothelium by adhesion

molecules. Glycosaminoglycans networks function as sodium buffer and therefore play a critical role in regulating endothelial function and interstitial fluid accumulation. Neurohumoral alterations observed in AHF can alter glycosaminoglycan density and sulfatation, resulting in amplified vascular resistance and permeability, oedema, and cardiac filling pressures.[77]

Inflammation is also accompanied by the early onset of interstitial and perivascular fibrosis.[78] Drugs that may address anti-remodelling effects through targeting multiple pathways in parallel, such as miRNA therapeutics, thus may be well suited as next-generation therapeutics. As such, preclinical and clinical evidence suggests that targeting remodelling-associated miRNA miR-132 leads to a normalization of pathological hypertrophy and fibrosis, and maybe a novel entry point to fight early pathological remodelling post-MI.[79,80]

3.4 Mitochondrial dysfunction and oxidative stress

Mitochondria are abundant in energy-demanding cardiac tissues, and mitochondrial energy production depends on factors that modulate normal mitochondrial function, such as enzyme activity and cofactor availability. In addition, oxidative stress, genetic factors, mitochondrial biogenesis, and aging may affect mitochondrial function.[81]

Energetic myocardial deficiency has been observed in TTS patients,[82] which may contribute to the development of chronic HF.[83] Recently, cardiac metabolic alterations were recapitulated in a rat model of TTS with the observation of multiple changes at all metabolic pathways. In particular, TTS displays dysregulation of glucose and lipid metabolic pathways with decreases in final glycolytic and β-oxidation metabolites and reduced availability of Krebs intermediates. The energetic deficit is accompanied by defective Ca^{2+} handling, inflammation, and upregulation of remodelling pathways, with the preservation of sarcomeric and mitochondrial integrity.[84] Although a precise mechanism reconciling the above observations has not yet been identified, it is plausible that these early alterations, together with the activation of inflammatory and fibrotic processes, may contribute to cardiac remodelling following TTS.

Defective mitochondria following acute myocardial ischaemia (AMI) contributes to the development of AHF and the following adverse cardiac remodelling, as observed in ischaemia-reperfusion injury. Significant biochemical and metabolic changes occur in the first few minutes of AMI, including mitochondrial Ca^{2+} overload, oxidative stress, rapid pH correction, and opening of the mitochondrial permeability transition pore (mPTP).[85] Reperfusion upon revascularization induces additional intracellular and mitochondrial Ca^{2+} overload due to disruption of the plasma membrane, oxidative stress-induced damage to the sarcoplasmic reticulum, and mitochondrial re-energization, which permits the recovery of the mitochondrial membrane potential to drive the entry of Ca^{2+} into mitochondria via the mitochondrial Ca^{2+} uniporter (MCU). The molecular identification of the MCU[86] and the mitochondrial Na^{+}/Ca^{2+} exchanger (NCX), which mediates mitochondrial calcium extrusion,[87] may result in the discovery of a new class of specific inhibitors for reducing acute ischaemia and reperfusion in AMI.[88] In summary, AHF is characterized by mechanisms activated in the acute phase and, if persisting, fosters the progression toward persistent/advanced HF.

3.5 Pre-clinical models of AHF

The molecular mechanisms underlying AHF evolution should ideally be reproduced in animal models. Over the years, numerous animal models of AHF have been implemented in different species (mice, rats, rabbits, pigs, dogs) to study AHF pathophysiology and develop new therapies.[89–93] Nevertheless, most of these models present significant limitations and only partially recapitulate the clinical traits of the human condition[89] (*Table 1*), which comprise: (i) impaired LV function; (ii) congestion with increased central venous, pulmonary artery, and capillary wedge pressures; (iii) pulmonary oedema and reduced respiratory exchange with systemic acidosis, and (iv) increased circulating cardiac biomarkers (cTnT, BNP, and others).

Moreover, the pattern of worsening AHF is difficult to reproduce, as an interaction of existing systemic factors and comorbidities is present in humans.[89] Thus, new animal models accurately mimicking human AHF are urgently needed to test new drugs before their clinical translation.

Several aspects should be considered when selecting the most appropriate species and animal model for AHF (*Table 1*). Ischaemia-induced HF is the most widely used approach.[91,92] However, acute coronary occlusion frequently fails to induce stable HF due to neurohormonal activation, development of collateral circulation, or LV dilation.[90] Microembolization is alternative option to promote ischaemic HF, but it generally requires numerous injections of microbeads to induce modest cardiac dysfunction.[90] Administration of anticancer cardiotoxic drugs, such as anthracyclines, are known to produce HF but require multiple invasive procedures and result in high mortality.[93,94] Doxorubicin can induce AHF shortly after high-dose injection in rodents (*Table 1*). This model has the advantage of a short modelling period and predictable time of cardiotoxicity but has high mortality and limited reproducibility.[107] Also, high-dose injections of catecholamines are known to induce cardiac dysfunction typical of transient TTS.[99] However, more recently, Ali *et al.*[98] reported that a catecholamine surge might not be mandatory to generate an episode of TTS since they demonstrated that inotropes, such as milrinone, also trigger TTS (*Table 1*). Nevertheless, TTS animal models remain challenging as they only partially reproduce the cardiac features of TTS.[108] Most studies are conducted in young male animals, contrasting with 92% of TTS patients, who are postmenopausal females. Finally, rapid-pacing-induced HF is another possible approach to induce AHF; however, it is reversible with cessation of pacing.[90,103]

Regarding the choice of the species to privilege, swine have been increasingly used due to their anatomic and pathophysiologic similarities to the human heart, making them the most translational model in biomedical research. Besides being genetically well-defined, mini-pigs weigh 30–70 kg at maturity, making them easier to handle compared to agricultural pigs that may grow to weigh over 320 kg. Some examples of AHF porcine models are depicted in *Table 1*. Rabbits are medium-sized animals that resemble many cellular (electrophysiology and Ca^{2+} homeostasis) and molecular characteristics of humans and represent a practical alternative to larger mammals. AHF can also be induced in rats after acute myocardial infarction (*Table 1*). However, the phenotype is strain-dependent, with Lewis inbred rats surviving more than Sprague-Dawley, which has been ascribed to its more uniform pattern of coronary branching and, thus, predictable infarct size.[109] Moreover, important differences in mouse strains and substrains should be considered when implementing mouse models of AHF. For instance, the C57BL/6J strain has a mutation in the nicotinamide nucleotide transhydrogenase (*Nnt*) gene, which regenerates NADPH from NADH. This mutation protects C57BL/6J mice from oxidative stress and HF post-TAC, compared to the inbred C57BL/6N strain.[110] Recently, a model of AHF developed in the BALB/C strain,[104] showed reproducible and robust pulmonary congestion that mimics patients with acute decompensated HF, thereby becoming a clinically relevant model of AHF. The most dangerous condition of AHF is cardiogenic shock, with a mortality of around 50% in patients. Very recently, a mouse model of cardiogenic shock was developed consisting of coronary ligation combined with hypoxic ventilation, recapitulating most features of cardiogenic shock after myocardial infarction, including increased lactate levels.[106] This model can better define the pathophysiology and potential therapeutic approaches for this devastating AHF syndrome.

4. Biomarker research in the setting of AHF: future directions

Biomarkers are non-invasive and highly reproducible quantitative tools that have highly improved the understanding of AHF pathophysiology.[111] The most studied and extensively recognized biomarkers in diagnosing AHF are natriuretic peptides (NPs), which help distinguish individuals with acute dyspnoea from those with non-cardiac disease.[112] The NPs comprise

Table 1 Animal models of acute heart failure

Species	Model	Features	References
Pig	AMI induced by occlusion of left anterior descending coronary artery followed by a second AMI by circumflex coronary artery occlusion 2 weeks later	• Reduced LV ejection fraction < 30%. • Increased thoracic fluid content > 35%. • Pulmonary oedema and high pulmonary capillary wedge pressure ~30 mmHg. • Increased central venous and pulmonary arterial pressures. • Respiratory acidosis with low arterial PO_2 and high PCO_2 • Increased LV end-diastolic/systolic volumes. • Increased circulating troponin T, natriuretic peptide, and adrenomedullin.	Olivari *et al.*[89]
	β-Blockade by an initial dose of Carazololin (1 mg/kg), followed by a continuous infusion of 1 mg/kg/h in German Landrasse pigs	• All measure parameters declined by 30%, including cardiac output, LV pressure, aortic blood pressure, systolic contractility (dP/dt_{max}), and systolic wall thickening fraction.	Kaczmarek *et al.*[94]
Rabbit	Radiation	• Induces acute myocardial lesions, such as pancarditis with inflammatory exudates, followed by a latent phase • Myocardial and pericardial fibrosis.	Fajardo *et al.*[95]
	Repetitive direct current shock	• Decreased cardiac output. • Increased LV end-diastolic pressure. • Raised peripheral resistance. • Decrease intestinal and renal flow.	Arnolda *et al.*[96]
Rat	Acute cardiac decompensation induced by salt-loading (1.8 g/kg) in rats with well-established HF due to coronary ligation	• Reduction in cardiac output. • Decreased myocardial perfusion. • Slight increase in pulmonary weight. • Impaired coronary relaxation. • Transient heart rate reduction improved acute decompensated HF-induced LV and coronary dysfunction.	Peschanski *et al.*[97]
Rat	Transient Takotsubo Syndrome (TTS) induced by a high-dose of catecholamines	• Acute severe ventricular systolic dysfunction. • LV apical akinesia (correlated with LVEF) and hypercontractility in the basal segments, resolving in 7 days. • Mortality rate of 33–42% (lower in females). • Localized myocardial inflammatory changes (early neutrophil followed by macrophage infiltrates). • Females need a higher triggering dose.	Ali *et al.*[98] Paur *et al.*[99]
Rat and mice	A single intraperitoneal injection of DOX (10–25 mg/kg) or a single tail vein DOX (20 mg/kg) can induce acute cardiotoxicity	• Weight loss, diarrhoea, and reduced activity. • Decreased LVEF, ±dP/dTmax and increased LVEDP. • Oxidative stress and mitochondrial damage. • Myocardial fibre distortion and rupture. • Increased myocardial necrosis and minimal fibrosis. • Increased BNP, lactate dehydrogenase and calponin T.	Hayward *et al.*[100] Al-Salam *et al.*[101] Shao *et al.*[102]
Rat and mice	Rapid pacing-induced HF		Shinbane *et al.*[103]
Mice	Coronary ligation (chronic or I/R)	• Reduced survival, systolic dysfunction, pulmonary congestion, and pleural effusion. • Cardiac rupture, and not AHF, is the most common cause of death within the first-week post-MI.	Ma *et al.*[104] Gao *et al.*[105]
Mice	Coronary ligation and hypoxic ventilation	• Recapitulates the most features of cardiogenic shock after myocardial infarction including increased lactate levels, severe systolic dysfunction, congestion, and high mortality	Wang *et al.*[106]

atrial natriuretic peptide, B-type or brain natriuretic peptide (BNP), inactive form of BNP, N-terminal pro B-type natriuretic peptide (NT-proBNP),[112] that, due to their diagnostic use, is recommended in patients with possible AHF from the European and American practice guidelines.[5,113] However, it is crucial to correctly interpret NPs levels, which can be significantly influenced by other alterations that mimic AHF, such as MI, anaemia, aortic stenosis, atrial fibrillation etc., thus making the diagnosis uncertain. Moreover, it is essential to consider that NPs are released during haemodynamic stress when the ventricles are dilated, hypertrophic, or subject to increased wall tension, linking them to specific molecular

Table 2 Biomarkers and related pathway in the setting of acute heart failure

Biomarkers	Pathway involved	References
Natriuretic peptides (BNP and NT-proBNP)	Haemodynamic stress and myocardial stretch	Rorth *et al.*[114]
Troponin	Cardiomyocites injury	Shah *et al.*[115]
Soluble suppression of tumourgenicity 2 (sST2)	Combined/unknown pathways, fibrosis	Lotierzo *et al.*[116]
Galectin-3 (Gal-3)	Extracellular matrix remodelling, fibrosis	Lok *et al.*[117]
Myeloperoxidase	Oxidative stress	Meijers *et al.*[118]
C-reactive protein (CRP), interleukin-6 (IL-6), procalcitonin, and Adrenomedullin (ADM)	Inflammation	Petersen *et al.*[119] Gaggin *et al.*[120] Cvetinovic *et al.*[121]
Sortilin, CD146, Phosphatidylcoline, and ANGPTL8	Endothelial dysfunction	Shah *et al.*[115] Di Pietro *et al.*[122] Medina-Leyte *et al.*[123]

mechanisms and physiological conditions. In addition, the circulating levels of NPs are higher in patients HFrEF than in patients with HFpEF, making the diagnosis of HFpEF difficult or falsely ruled out.

This 'grey area' in the use of NPs has dramatically contributed to raising the interest of the scientific community in identifying new biomarkers that would be useful to take in consideration other physiological conditions and molecular pathways alteration involved in the diagnosis and prognosis of HF, in particular aiming at developing a multimarker approach composed of additional biomarkers that can be used in combination with the previously renowned NPs. Therefore, in the last two decades, pre-clinical and clinical research has moved toward identifying comprehensive biomarkers to mirror the different mechanisms of AHF pathophysiology (*Table 2*) with the object of obtaining an integral adjunctive tool for AHF management and the identification of individuals at risk of developing an advanced HF.

Galectin-3 (Gal-3) and soluble suppression of tumorigenicity 2 (sST2) emerged as good markers of cardiac remodelling and fibrosis, although the molecular mechanisms of their release are not fully elucidated.[114]

Myeloperoxidase (MPO) is a microbicidal haeme-containing enzyme of the innate immune system produced by neutrophils. It has been implicated in the pathogenesis of several inflammatory conditions, including coronary artery disease, HFpEF, chronic obstructive pulmonary disease, chronic kidney disease, and non-alcoholic steatohepatitis. In addition, elevated MPO levels are associated with advanced HF and correlate with microvascular dysfunction,[124] particularly in patients with myocarditis.[115]

Other studies have suggested the 'Cytokine Hypothesis' in the different settings of AHF. C-reactive protein (CRP) and interleukin-6 (IL-6) emerged as potential biomarkers for patients' stratification and prognosis of AHF. Pro-inflammatory markers are related to disease severity and provide important prognostic information beyond traditional clinical parameters and other markers such as BNP.

HF is also characterized by endothelial damage; thus, measuring circulating levels of endothelial cell injury markers could help determine the disease severity. A novel recent marker of endothelial damage related to high blood pressure is represented by sortilin.[122] This novel biomarker can be potentially implicated in AHF related to elevated blood pressure levels that can lead to cardiac remodelling.[122]

In conclusion, most novel HF biomarkers provide evidence of specific molecular and cellular processes, although in a non-cardiac-specific fashion. Therefore, it is still unclear whether altered plasma biomarkers can be directly associated with the degree of cardiac damage and risk of evolving toward an advanced HF.[123] Further studies focused on their additive value in the diagnosis of HF, the relationship between their measurements, and the identification of individuals at risk of developing HF is needed.

5. Strategies for AHF treatment

In contrast to CHF treatment, pharmacological treatment of AHF has remained largely unchanged over the past decades. The cornerstones of the therapy, which is mostly symptomatic and focused on short-term outcomes, is diuretics, vasodilators, inotropes, and vasopressors depending on the clinical profile.[5] Implementation of the underlying pathophysiology is incomplete: while particular triggers of AHF such as ACS, hypertension, arrhythmia, mechanical problems (e.g. acute valvular insufficiency), and pulmonary embolism have their specific treatments, other conditions are mainly tackled with general measures. The major, yet unresolved, problem is pharmacologically enhancing cardiac output in patients suffering from severely reduced LVEF and low blood pressure without life-threatening side effects. However, the management of AHF in urgent/emergency situations is extensively described in previous papers, and is beyond the purpose of this work. Still, it is necessary to underline that searching for AHF therapies that can reduce cardiac damage and improve long-term clinical outcomes is daunting.

Of notice, even after remission from an AHF event, some patients tend to have further events over time. Primary AHF events may lead to subclinical changes (molecular, epigenetics modifications, metabolic changes, etc.), which could explain this tendency to new events within of an apparent healthy heart. This is consistent with the idea that LVEF recovery does not necessarily correspond to the recovery from HF.[125] Precisely, the regression of the AHF phenotype and the accompanying return towards a more normal cardiac phenotype does not, per se, mean that the cellular/molecular biology and physiology of these hearts is functional, which may explain why reverse remodelling may be related to different clinical outcomes.[126]

Identification of these subclinical footprints, however, could be pivotal for novel therapeutic strategies to avoid new AHF events.

5.1 Potential therapeutic strategy in AHF

The lack of univocal results regarding current available molecules makes alternative innovative strategies necessary; specifically, a growing number of molecular mechanisms could theoretically be targeted through pharmacological approaches for new therapeutic strategies (*Figure 3*). As said, in the failing heart, oxidative stress plays an essential role.[127] Specifically, the research focused on drugs targeting mitochondrial function and energy supply (trimetazidine, mitoTEMPO, mitoQ, H_2S donors, mPTP inhibitor TRO40303, SS-31, mitochondrial Na^+/Ca^{2+} exchange inhibitors, PARP inhibitors), inhibitors of reactive oxygen species (ROS) sources (NOX inhibitors, MAO inhibitors, MPO inhibitors), drugs targeting NO/cGMP signalling and vasodilatation (PETN, H_2S donors, BH4, eNOS enhancer, and serelaxin), and antioxidant improving the redox balance (direct ROS scavenging or hormesis: Resveratrol, Coenzyme Q, NRF2 activators).[128]

5.1.1 Endothelial cell dysfunction

Interruption of the NO-sCG-cGMP pathway is broadly observed in individuals with HF leading to endothelial dysfunction.[129] The disruption is caused by an oxidized state resulting in low bioavailability of NO and cGMP.[129] The intensification in ROS can also result in oxidized, and subsequently haeme free, soluble guanylylcyclase (sGC) enzyme that NO is unable to stimulate, worsening the endothelial dysfunction.[129] Two novel classes of drugs, sGC stimulators and sGC activators, have become an attractive target for HF therapy. Specifically, the VICTORIA trial assessed the

efficacy and safety of the oral sGC stimulator Vericiguat, in patients with a reduced LVEF and recently decompensated CHF.[5,130]

Adrenomedullin (ADM) is a vasoactive peptide that is increased in patients with volume overload; consequently, high levels are found in HF.[131] Specifically, the main functions of ADM are vasodilatation to preserve vascular integrity and decrease vascular leakage. Accordingly, numerous pre-clinical[132–135] and small clinical[136–139] studies have recognized the effects of exogenous administration of ADM in HF. Briefly, these effects include reduction in myocardial infarct size, cardiac myocyte apoptosis, LV remodelling (in animals) and aldosterone levels (animals and humans), while haemodynamics (in both humans and animals) and survival (in animals) were improved.[131]

Accordingly, in a case series of AHF patients with dyspnoea and pulmonary congestion, the effects of long-term intravenous administration of ADM in acute decompensated HF were studied: ADM infusion reduced mean arterial pressure, pulmonary arterial pressure and systemic and pulmonary vascular resistance without altering heart rate, and improved cardiac output for most time-points compared with those at baseline.[140]

In particular, Adrecizumab is a humanized, monoclonal, non-neutralizing ADM-binding antibody with a half-life of 15 days.[131] Due to its high molecular weight, the antibody adrecizumab cannot cross the endothelial barrier and remains in the circulation.[131] The observation that adrecizumab increases plasma concentrations of ADM indicates that ADM-binding by adrecizumab is able to drain ADM from the interstithiium into the circulation. Consequently, by improving vascular integrity, adrecizumab may decrease tissue congestion and thereby may improve clinical outcomes in individuals with acute decompensated heart failure.[131]

Similarly, the calcium sensitizer/PDE inhibitor ORM-3819 produces endothelium-independent vasodilation. In animal models, Nagy *et al.*[141] demonstrated that this drug is a potent positive inotropic agent exerting its cardiotonic effect by a cTnC-dependent Ca^{2+}-sensitizing mechanism in combination with the selective inhibition of the PDE III isozyme; these two mechanisms of action led to the concentration-dependent augmentation of the contractile performance under control conditions and in the post-ischaemic failing myocardium.[141] Moreover, the results of Marton *et al.*[142] suggest that this compound is a potent vasodilating agent able to relieve coronary artery vasospasm by causing hyperpolarization of vascular smooth muscle cells through a process involving activation of voltage-gated potassium channels in isolated porcine coronary arteries.

Also, serelaxin, a recombinant form of human relaxin-2, has been tested in patients with AHF.[143] Serelaxin is known to have a range of pleiotropic properties, in addition to vasodilatation, including anti-fibrotic, angiogenic, anti-apoptotic, and anti-inflammatory effects.[144] Precisely, relaxin produces these effects by binding to a cognate receptor RXFP1 and activating a variety of signalling pathways including cAMP, cGMP, and MAPKs as well as by altering gene expression of TGF-β, MMPs, angiogenic growth factors, and endothelin receptors.[144] However, infusions of serelaxin did not result in a lower incidence of death in patients with AHF.[143]

5.1.2 Mitochondrial function and energy supply

The mitotrope trimetazidine blocks mitochondrial oxidation of fatty acids by the enzyme thiolase and similarly shifts metabolism towards glucose.[145] Small cohorts and open-label randomized studies suggest that trimetazidine improves myocardial performance and contractility with clinical benefits for HFrEF patients.[146–148] Breedt *et al.*[149] demonstrated that despite negligible effects on heart function during the critical AHF phase, trimetazidine had positive effects for both male and obese female mouse hearts when administered during the recovery AHF phase. Thus, trimetazidine emerges as worthy to consider for AHF treatment in normal and obese-diabetic individuals, but only when administered during the recovery phase. Nevertheless, these results have not been reproduced in appropriately sized randomized clinical trials.[150]

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are newly introduced drugs in the 2021 ESC HF guidelines.[5] There is evidence that SGLT2 inhibition improves cardiac mitochondrial function in animal models independently of the diabetes mellitus status.[151,152] Specifically, the EMPULSE trial recently demonstrated the beneficial effect of empagliflozin in both *de novo* and acute worsening HF.[153,154] Additional studies are needed to assess the possible effects of SGLT2 inhibition more comprehensively on cardiac mitochondrial function, such as mitochondrial protein levels, post-translational modifications, oxidative capacity, metabolic flux, and dynamics.[151]

The complexity and mechanistic implications of the G protein-coupled receptor kinase type 2 (GRK2) in HF are well demonstrated and documented.[155–157] The inhibition of GRK2 ameliorates cardiac metabolism and mitochondrial dysfunction.[157–159] It was demonstrated that the systemic administration of the GRK2 inhibitor cyclic peptide 'C7' corrects cardiac (lipids) metabolism and mitochondrial abnormalities (morphology, biogenesis, respiration, and ATP production) in a mouse model of HF.[160] Accordingly, previous studies, employing different strategies of GRK2 inhibition, demonstrated that by reducing the activity of this kinase, it is possible to re-establish myocardial function at biochemical and contractile level.[161,162] Some features of GRK2 inhibition make this target unique; in particular, C7 in non-failing cardiomyocytes is a direct positive inotrope and chronic infusion of GRK2 inhibitors results in metabolic and biochemical changes that could complement with adrenergic beta-blocker.[160] To date, numerous methods have been developed to inhibit GRK2 activity; most of them are far from clinical applications, but cyclic peptides are the most promising. These data support the idea that inhibition of GRK2 could be a useful strategy to restore alterations of cardiac metabolic state in AHF.

Another example is the mitochondria-targeted coenzyme Q10 (mitoQ) compound in which the direct ROS scavenger coenzyme Q is conjugated to the positively charged triphenylphosphonium, which targets mitoQ to mitochondria.[163] MitoQ has been shown to reduce ROS production at the onset of reperfusion, reducing myocardial infarct size in experimental studies of AMI and reperfusion injury.[164,165] Coenzyme Q10 (CoQ10) is a potent intracellular antioxidant generally used in cardiomyopathy;[128] moreover, MitoQ can also improve arterial endothelial function when administered to aged mice.[166] The antioxidant 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO, a spin trap) has also been conjugated to triphenylphosphonium to make mitoTEMPO and, when administered to rats, mitoTEMPO can prevent the increase in H_2O_2 levels and diaphragm muscle weakness associated with HF.[167] Recent evidence suggests that in the setting of HF, increased cytoplasmic Na^+ combined with impaired Ca^{2+} release from the sarcoplasmic reticulum alters Na^+ and Ca^{2+} gradients across the mitochondrial inner membrane, resulting in altered energy supply and demand and driving mitochondrial oxidation.[128] Accordingly, inhibition of mitochondrial Na^+/Ca^{2+} exchange with 7-chloro-5-(2-chlorophenyl)-1,5-dihydro-4,1-benzothiazepin-2(3H)-one (CGP-37157) re-establishes mitochondrial Ca^{2+} handling and protects against sudden death in a guinea pig model of HF.[168] Specifically, *in vivo* MitoTEMPO treatment of HF animals reversed HF, eliminated sudden cardiac death by decreasing dispersion of repolarization and ventricular arrhythmias, suppressed chronic HF-induced remodelling of the expression proteome, and prevented specific phosphor-proteome alterations.[169] Moreover, oxidatively inactivated proteases may be an endogenous target for mitoTEMPO treatment in pressure overload HF.[170]

Under certain (genetic) condition, catecholamines impair cardiac metabolism resulting in mitochondrial dysfunction with subsequent oxidative stress and energy depletion. For example, STAT3 deficiency and PPCM seem highly sensitive to β1-adrenergic receptor agonist stimulation.[171] Therefore, treatment of PPCM patients with β-adrenergic receptor agonists should be avoided whenever possible. In cases with cardiogenic shock complicating PPCM, when treatment with β-adrenergic receptor agonists cannot be prevented, co-medication with perhexiline might help to reduce the cardiotoxic side effects of β-adrenergic receptor stimulation.[171,172]

5.1.3 Cellular redox state

A wide variety of different pharmacological methods is under investigation as means to modulate cellular redox state. In mammalian cells, seven sirtuins (SIRT1-7) modulate distinct metabolic and stress-response pathways;

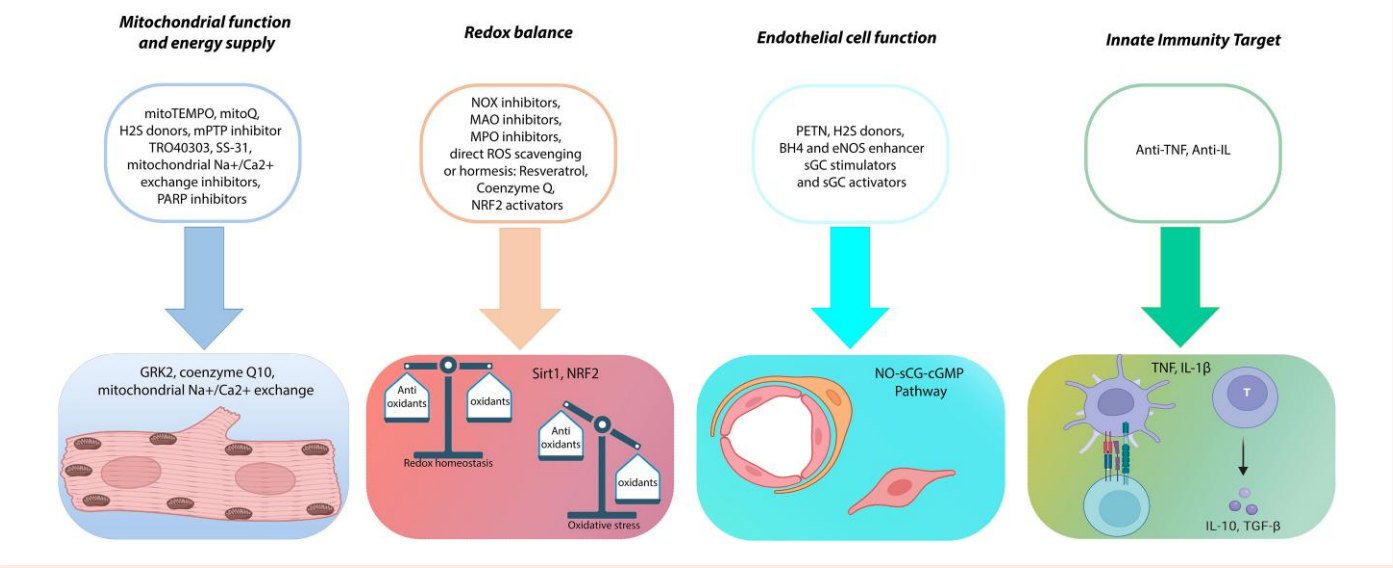


Figure 3 Summary of established and potential targets for future strategies in AHF. The coloured squares show common pathophysiological pathways between the different AHF phenotypes. NO, nitric oxide; cGMP, cyclic guanosine monophosphate; sGC, soluble guanylylcyclase; PETN, pentaerithrityl tetranitrate; H2S, hydrogen sulphide; BH4, tetrahydrobiopterin; eNOS, endothelial nitric oxide synthase; NRF2, nuclear factor-E2-related factor 2; mitoTEMPO, mitochondria-targeted 2,2,6,6-tetramethyl-1-piperidinyloxyl; mitoQ, mitochondria-targeted coenzyme Q10; mPTP, mitochondrial permeability transition pore; PARP, poly(ADP-ribose) polymerase; NOX, NADPH oxidase; MAO, monoamine oxidase; MPO, myeloperoxidase.

specifically, SIRT1 and SIRT3 have been most widely studied in the cardiovascular system.[173] The pharmacologic activation of these two sirtuins can potentially ameliorate the progression of HF because they participate in the regulation of energy production, oxidative stress, intracellular signalling, angiogenesis, autophagy, and cell death/survival.[173] The natural polyphenol, resveratrol, is of particular interest as it is believed to mediate the benefits of red wine in the cardiovascular system by activating SIRT1 via an allosteric mechanism.[174–176] On the other hand, there is a wide body of pre-clinical evidence that Nrf2 activation is extremely protective in HF models.[177] Although Nrf2 activators such as sulforaphane, dimethylfumarate, and bardoxolone are currently studied in multiple clinical trials for a broad range of indications, including chronic kidney disease and pulmonary hypertension, yet there is no clinical trial in patients with CVD.[128]

Nitroxyl (HNO), the one-electron reduction product of NO, has been shown to improve cardiac function in a redox sensitive way in experimental and clinical HF[178,179] by enhancing Ca^{2+} cycling and increasing myofilament Ca^{2+} sensitivity. The third generation HNO donor BMS-986231 (cimlanod) was recently tested in AHF. The compound rapidly and sustainably lowered pulmonary capillary pressure while improving cardiac index, without altering heart rate, or inducing arrhythmia, hypotension, or other major adverse events.[180] Ongoing Phase 2B trials are testing its clinical efficacy.[181] Unfortunately, the STAND-UP AHF Study (NCT03016325) showed that cimlanod reduced markers of congestion, but this did not persist beyond the treatment period.[182]

5.1.4 Immune modulation

Activation of innate immunity occurs in minutes upon myocardial injury, which can evolve to a chronic inflammatory state that contributes to further disease progression, under the harmful effects of sustained inflammation on cardiac myocytes and the extracellular matrix. Therefore, the modulation of pro-inflammatory mediators in the acute setting can potentially facilitate resolution.[183] Several transcriptional or translational approaches have been evaluated to antagonize pro-inflammatory mediators or by the so-called 'biological response modifiers' that bind and/or neutralize soluble cytokines (e.g. TNF or IL-1β) involved in the acute phase.[184] These approaches have produced contrasting results on the outcome in the context of CHF. However, it is possible that, given the relevance of the innate immune system in the first phase of a cardiac insult, the employment of these strategies in the acute setting can produce precise and favourable results. For instance, the IL-6 inhibitor tocilizumab can protect against major adverse cardiovascular events in CAR-T patients[185] and in severe ICI-related myocarditis unresponsive to high-dose glucocorticoid therapy.[186] In the acute myocarditis setting, if symptoms and laboratory findings do not improve with high-dose glucocorticoids, other immunosuppressant agents (e.g. mycophenolate mofetil, methotrexate, calcineurin inhibitors, intravenous immunoglobulin, anti-thymocyte globulin, rituximab, and infliximab) may be considered for management of ICIs cardiotoxicity, as reported in the consensus recommendations from the Society for Immunotherapy of Cancer Toxicity Management Working Group.[187] Recently, alemtuzumab, a humanized mAbs that binds to CD52, a protein present on the surface of mature lymphocytes, monocytes, macrophages, dendritic cells, and natural killer cells, led to a rapid cytolytic induction of immunosuppression with the resolution of cardiotoxicity in a steroid-refractory autoimmune myocarditis induced by PD-1 therapy.[188] In another case, intravenous abatacept (a cytotoxic CTLA-4 agonist used in patients with rheumatoid arthritis diseases) led to resolution of the drug-related side effect, and this was attributed to the inhibitory effects of abatacept on T cell co-stimulation upstream of the PD-1/PD-L1 pathways.[189] Recently, in a pre-clinical mouse model of ICI-associated myocarditis, the monoallelic loss of CTLA-4 in the context of complete genetic absence of Pdcd1 leads to premature death in approximately half of mice; specifically, premature death resulted from myocardial infiltration by T cells and macrophages, closely recapitulating the clinical and pathological hallmarks of ICI-associated myocarditis observed in patients.[190]

6. Conclusions

AHF represents a highly relevant clinical problem regarding short-term outcomes and subsequent evolution towards CHF. Beyond the need to use strategies for haemodynamic support in cardiogenic shock conditions, it is essential to develop new approaches to preserve vital myocardium and to counteract the evolution towards CHF. HF patients display a marked

heterogeneity in the disease evolution; however, it is possible to trace the different trajectories of AHF based on the aetiology, comorbidities and environmental factors, although aspects of the underlying molecular mechanisms need to be clarified.

In particular, timing is pivotal for an effective pharmacological or therapeutic approach to avoid transitioning from the AHF to CHF. However, the mechanisms that are early activated upon injury are poorly investigated. The improvement and/or development of new pre-clinical models, stem cell-derived models to in situ modelling of heart properties, and bioinformatic models based on large datasets, which show clinically relevant characteristics observed in patients with cardiovascular disease,[191] are needed to better understand the specific phenotypes and the potential therapeutic interventions. Thus, it becomes increasingly evident that research should focus on the specific combination of aetiology/comorbidities underlying AHF to administer an adequate therapeutic scheme which considers all the pathophysiological mechanisms underlying that specific phenotype. An effective approach to improve the outcome in AHF is to develop and validate personalized therapeutic strategies for each phenotype rather than waiting for the perfect panacea for all. Medical progress in discovering new AHF drugs has substantially stalled in the past 20 years; nevertheless, advances in data technology,[192] along with developments in clinical trials design and research focused on individual phenotypes,[191] could help to bring a new generation of therapies into clinical use.

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