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REVIEW

From Bench to Bedside: New Approaches to Therapeutic Discovery for Heart Failure

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Heart failure is a significant global health problem, which is becoming worse as the population ages, and remains one of the biggest burdens on our economy. Despite significant advances in cardiovascular medicine, management and surgery, mortality rates remain high, with almost half of patients with heart failure dying within five years of diagnosis. As a multifactorial clinical syndrome, heart failure still represents an epidemic threat, highlighting the need for deeper insights into disease mechanisms and the development of innovative therapeutic strategies for both treatment and prevention. In this review, we discuss conventional heart failure therapies and highlight new pharmacological agents targeting pathophysiological features of the failing heart, for example, non-coding RNAs, angiotensin receptor-neprilysin inhibitors, cardiac myosin activators, BGP-15 and molecules targeting GRK2 including M119, gallein and paroxetine. Finally, we address the disparity between phase II and phase III clinical trials that prevent the translation of emerging HF therapies into new and approved therapies.

Keywords Heart Failure • Therapeutics • miRNA • Fibrosis

Introduction

Heart failure (HF) is a debilitating disease in which abnormal function of the heart leads to inadequate supply of blood to tissues and organs to meet their metabolic demands. Various factors can contribute to HF pathogenesis, such as myocardial infarction, ischaemia, hypertension or genetic cardiomyopathies. Heart failure is a significant global health problem which is becoming worse as the population ages [1,2]. Despite significant advances in cardiovascular medicine and management, mortality rates remain high, with almost 50% of HF patients dying within five years of diagnosis [3]. Further, conventional pharmacological treatments largely delay disease progression and death due to HF, but they do not cure HF [4]. As a multifactorial clinical syndrome, HF still represents an epidemic threat, highlighting the need for deeper insights into disease mechanisms and the development of innovative therapeutic strategies. In this review, we will highlight current and new pharmacologic agents for the treatment of heart failure and discuss new therapeutic approaches (e.g., RNA-based therapies, small molecules) with potential to enter clinical trials.

Pathological Cardiac Hypertrophy

A hallmark of HF development is pathological cardiac hypertrophy, characterised by an increase in cardiomyocyte size and thickening of ventricular walls. It is initially thought to be a compensatory response of the heart to increased workload to maintain heart function. However, with a sustained haemodynamic load, pathological cardiac hypertrophy will proceed, and structural and functional cardiac anomalies develop (reviewed in [5–8]). This is associated with dilation of the ventricle, progressive fibrosis, loss of cardiac myocytes and cardiac dysfunction. At the molecular level, pathological

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hypertrophy is commonly associated with alterations in cardiac contractile proteins (α-myosin heavy chain and β-myosin heavy chain), increased expression of foetal genes (e.g. atrial natriuretic peptide [ANP], B-type natriuretic peptide [BNP], α-skeletal actin) and down regulation of calcium handling proteins (e.g. sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase 2a [SERCA2a]). Other biochemical changes include excessive autophagy, inadequate angiogenesis and chronic inflammation. At the metabolic level, there is a switch from fatty acid to glucose utilisation, although glucose metabolism decreases with the progression to heart failure, thus the heart is unable to produce sufficient energy to meet the body's metabolic demands. Together, these events lead to impaired contractile performance and contribute to the progression of heart failure (reviewed in [5–8]) (Figure 1).

The signalling pathways of pathological cardiac hypertrophy are incredibly complex and are reviewed in detail elsewhere [6–8]. In addition, cross-talk between cardiomyocytes and other cardiac cell types (e.g. cardiac fibroblast) occurs that influences cardiac function and pathophysiology [9,10]. In response to a pathological insult, factors including angiotensin II (Ang II), endothelin 1 (ET-1) and noradrenaline (NE) are released and bind to G_q protein-coupled receptors (GPCR) which in turn activate multiple downstream effectors to stimulate hypertrophy. These downstream signalling effectors of Gq include calcineurin, calcium/calmodulin-dependent protein kinase (CaMK), mitogen activated protein kinases (MAPKs), phospholipase C (PLC), protein kinases (PKC) and histone deacetylases (HDACs) [6–8]. Phosphoinositide 3 kinase (PI3K)[p110γ] is also activated by GPCR pathways and negatively regulates cardiomyocyte contractility by modulating the activity of phosphodiesterases (PDEs) and cAMP [11]. Recent studies have uncovered new findings related to the role of calcineurin and CaMKII in the heart [12], as well as the complexities surrounding activation of extracellular signal-regulated kinases (ERK1/2) at two distinct phosphorylation sites via G protein subunits [13]. Further, some of the molecules implicated in these pathways have been the targets of pharmaceutical development which will be discussed in this review.

Pathological hypertrophy – the diseased heart
▪ Increased heart size
▪ Decreased heart function
▪ Fibrosis and apoptosis
▪ Increased foetal gene expression
▪ Decreased calcium handling proteins
▪ Inflammation
▪ Irreversible
▪ Increased mortality

Figure 1 Key morphological and functional characteristics of pathological hypertrophy.

Conventional Pharmacological Therapies

The goals for therapy of HF are ultimately to minimise risk factors, reduce symptoms, slow progression of the disease and improve survival. Multiple interventions are available to the clinician, ranging from lifestyle modifications (e.g. exercise) to surgical and device interventions. A host of clinical trials have demonstrated that careful pharmacologic management can achieve these goals in a majority of patients. Conventional pharmacological therapies include beta blockers or diuretics, and a number of agents that inhibit the deleterious effects of the Renin–Angiotensin–Aldosterone–System (RAAS).

Inhibition of the RAAS System

Vasoconstriction, sodium and water retention, aldosterone release, ventricular remodelling, and myocardial hypertrophy are well-known detrimental consequences of excessive circulating angiotensin II. A number of current medications target different points of the RAAS to attenuate these effects, including angiotensin converting enzyme inhibitors (ACE inhibitors), angiotensin II receptor antagonists (ARBs), and mineralocorticoid receptor antagonists (MRAs) (reviewed extensively elsewhere [7,14–18]). In brief, ACE inhibitors are generally used as first-line therapy for the treatment of a number of cardiovascular and renal diseases. The beneficial effects of ACE inhibitors have been studied in thousands of patients with varying aetiologies and stages of HF (see review [18]). Angiotensin converting enzyme inhibition has repeatedly been shown to attenuate cardiac remodelling and improve heart function in patients with HF and after myocardial infarction. Angiotensin II receptor antagonists are an appealing option in patients who are intolerant to ACE inhibitors. Angiotensin II receptor antagonist therapy is considered an alternative to first line ACE inhibitor therapy due to fewer randomised, controlled trials in patients with HF as well as possible inferiority to ACE inhibitors. Several clinical trials have illustrated a reduction in morbidity and mortality in patients with left ventricular dysfunction (see [14,18,19]). Mineralocorticoid receptor antagonists are prescribed in addition to ACE inhibitors, ARBs and β-blockers. The first MRA developed was spironolactone and was shown to reduce hospitalisation and total mortality in patients with severe HF [20]. Further benefit for HF patients was observed with the next generation MRA, eplerenone (Bert Pitt, 2003 NEJM). However, in patients with chronic HF and preserved ejection fraction, spironolactone failed to provide any significant benefit [21].

Beta Blockers

Beta blockers are administered to control HF symptoms (such as shortness of breath, high blood pressure or weakness), which occur due to the release of excess catecholamines. Beta blockers have produced almost uniformly beneficial effects in patients with HF from various causes