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Targeting Interleukin-1 in Heart Failure and Inflammatory Heart Disease

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Abstract Heart failure (HF) is a clinical syndrome characterized by dyspnea, fatigue, and poor exercise capacity due to insufficient cardiac function. HF represents the leading cause of hospitalization among adult patients over 65 years of age. Neurohormonal blockade has improved clinical outcomes; however, HF incidence continues to rise, suggesting an urgent need to develop novel drugs that target a different pathophysiological paradigm. Inflammation plays a central role in many cardiovascular diseases. Interleukin-1 (IL-1), a prototypical proinflammatory cytokine, is upregulated in HF and associated with worse prognosis. Preclinical models suggest a beneficial effect of IL-1 blockade, and pilot clinical trials are currently underway to evaluate the role of IL-1 blockade to reduce inflammation, ameliorate ventricular remodeling, and improve exercise capacity in patients with HF.

Keywords Heart failure · Acute myocardial infarction · Inflammation · Interleukin-1 · Anakinra

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Introduction

Heart failure (HF) is a complex clinical syndrome characterized by fatigue, shortness of breath, and impaired exercise tolerance [1•]. HF may result from ischemic or nonischemic etiologies leading to impairment or loss of functional myocardium and represents a final common pathway for a variety of cardiac pathologies [1•]. As acute mortality for acute myocardial infarction (AMI) and sudden death due to ventricular arrhythmias have largely decreased, and life expectancy in the general population is increasing, the incidence of HF can only be expected to further increase [2]. Indeed, HF is now the leading cause of hospitalization in adult patients over 65 years of age [2].

Impaired cardiac function in HF is classically considered to be associated with reduced left ventricular ejection fraction (LVEF), HF with reduced EF (HFrEF). Nearly half of patients with HF have preserved EF (HFpEF), yet these patients have a similar degree of impaired cardiac function, mainly due to impaired cardiac filling and inability to maintain a cardiac output adequate to the needs [3•]. HFrEF is more often associated with ischemic injury or other means of loss of myocardium, whereas HFpEF is more often associated with chronic pressure overload or metabolic diseases (i.e., diabetes, morbid obesity) and associated with loss of function rather than loss of myocardium. The pathophysiology of HFpEF is less understood, and the progress in therapeutic efficacy has been less than in HFrEF [3•]. Over the past decades, indeed, successful HFrEF research has led to landmark advances in pharmacologic neurohormonal blockade, cardiac resynchronization therapy, implantable cardiodefibrillation, and ventricular assist devices, leading to significantly improved survival in HFrEF [1•]. The neurohormonal paradigm in HFrEF stipulates that a chronic state of low cardiac output and systemic congestion stimulates compensatory activation of the sympathetic nervous system and renin-angiotensin-aldosterone

system (RAAS), in which increased activity of norepinephrine, angiotensin II, and aldosterone predicts adverse clinical outcomes. Numerous phase III clinical trials have shown that pharmacologic inhibition of these pathways improves survival and life expectancy in HFrEF [1•].

Despite the improvements in cardiovascular outcomes with contemporary treatment approaches, HFrEF remains a progressive and incurable disease with poor quality of life and 5-year survival rates no better than many forms of cancer [2]. The increased awareness and likely also changes in cardiovascular risk profile in the population have led to an abrupt increase in the recognition and diagnosis of HFpEF, yet successful therapies for HFpEF are largely missing. These observations suggest the current treatment approaches to HFrEF or HFpEF fail to address one or more key pathophysiologic processes responsible for the development and progression of HF.

Evidence of an inflammatory response in heart disease has been accumulating for decades [4, 5••]. Inflammation is broadly described as the biological response to tissue injury or irritation [6••]. Inflammatory signaling is initiated at the site of local injury and is transmitted to the rest of the body by a series of chemical mediators known as cytokines. Interleukin-1β (IL-1β) is an apical pro-inflammatory cytokine that induces the synthesis and expression of several hundreds of secondary inflammatory mediators [6••]. While the inflammatory response is critical to stimulate the immune response to microbial infection, the role of inflammation becomes more difficult to characterize in noninfectious injury and may lead to further injury, and as such, inflammation is a *double-edged sword* [5••]. Early observational studies showed that increased concentration of inflammatory cytokines (such as IL-1β, IL-6, and tumor necrosis factor-α) were associated with the New York Heart Association (NYHA) functional class in HF patients [7–10]. Moreover, increased inflammation markers such as C-reactive protein (CRP)—a known surrogate for IL-1 activity—predicted a worse survival during acute coronary syndromes [11].

The aim of this review is to discuss the inflammatory role of IL-1 in HF, the molecular mechanisms of action, and the potential use of targeted IL-1 blockade to improve heart failure outcomes.

Interleukin-1 in Heart Failure: Cause or Effect?

The increase in IL-1 activity and/or surrogate inflammatory biomarkers in decompensated HF appears to be independent of whether the underlying cause of HF is acute or chronic ischemic cardiomyopathy, acute inflammatory cardiomyopathy, hypertensive heart disease, or idiopathic dilated cardiomyopathy [7–10]. This may reflect the fact that IL-1β production occurs in response to injury of variable nature and/or that the common pathophysiologic picture of advanced HF with tissue hypoperfusion and systemic congestion stimulates IL-1β production, independent of the initial injury (Fig. 1).

IL-1 in AMI and Postinfarction Remodeling

Ischemic cardiomyopathy remains the most common etiology of HF. Healing and remodeling of the cardiac tissue after ischemic injury is characterized by an intense inflammatory response [5••]. The cryopyrin inflammasome is a macromolecular structure responsible for the cellular amplification of the inflammatory response during tissue injury. The inflammasome is activated by danger and injury-related moieties and promotes IL-1β activation through cleavage of pro-IL-1β by caspase-1, the effector enzyme of the inflammasome [6••, 12, 13]. IL-1β induces chemotactic recruitment of leukocytes in the injured myocardium, promotes further production of cytokines and chemokines, and determines the systemic inflammatory response [6••].

In a mouse model of severe ischemic cardiomyopathy induced by experimental AMI, the formation and activation of the inflammasome—and subsequent release of IL-1β—promote cell death, adverse cardiac remodeling, and cardiac dysfunction; conversely, inhibition of the cryopyrin inflammasome [14] or IL-1 blockade (by genetic [15] or pharmacological means [16–20]) ameliorates cardiac remodeling and preserves, at least in part, cardiac function. These promising results in preclinical models led to two pilot clinical trials with anakinra in human patients with AMI. VCU-ART [21••] and VCU-ART2 [22••] enrolled a total of 40 patients with reperfused ST-segment elevated myocardial infarction (STEMI) with primary percutaneous coronary intervention (PCI) randomized to treatment with anakinra 100 mg daily or placebo for 14 days. Anakinra was safe with no major adverse clinical events and was associated with a blunted inflammatory response after AMI, a trend toward more favorable left ventricular remodeling on cardiac MRI, and a reduced incidence of HF at 3 months (30 vs 5 %, p=0.035), without any notable effects on the infarct size or on recurrence of AMI. These results formed the basis for additional studies of IL-1 blockade in higher-risk STEMI patients in the ongoing VCU-ART3 trial [23]. This trial will enroll 99 patients with STEMI, compare standard (100 mg daily) versus high-dose (100 mg twice daily) anakinra, and provide for a longer follow-up of up to 1 year.

The MRC-ILA Heart Study [24••] is a recently published randomized trial to analyze the effect of anakinra on markers of inflammation in smaller, non-ST elevation AMI (NSTEMI). This double-blinded, placebo-controlled study recruited 182 patients with NSTEMI presenting less than 48 h from onset of chest pain and treated 1:1 to one daily dose of anakinra (100 mg) subcutaneous or placebo for 14 days. Anakinra reduced the area under the curve for CRP over the

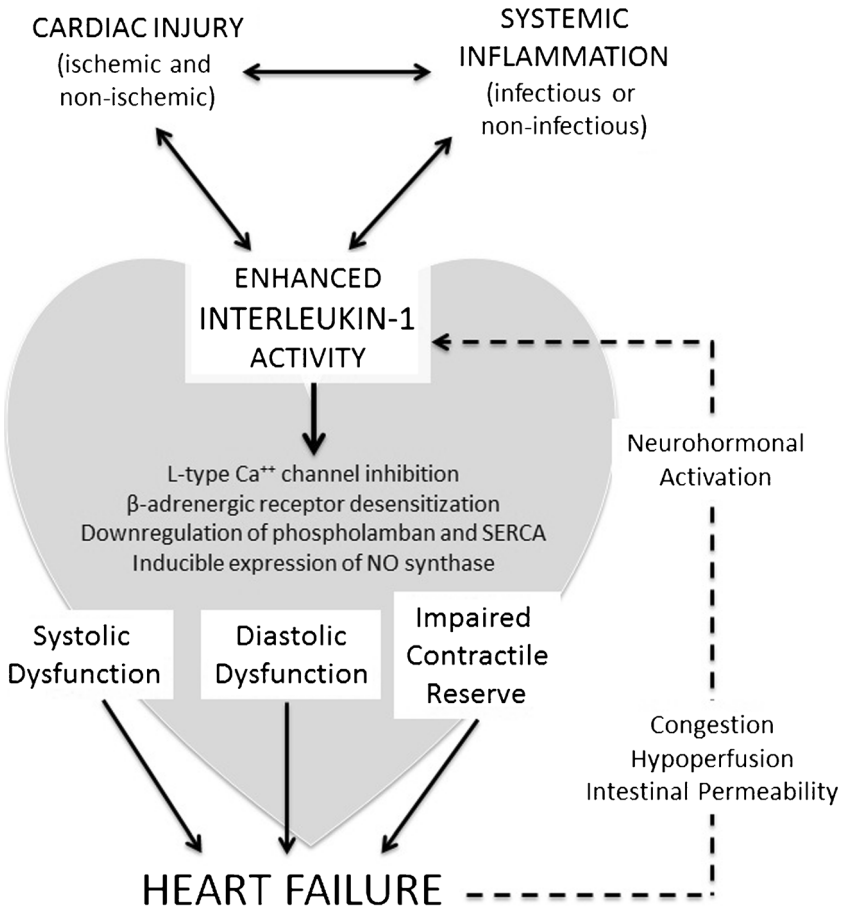

Fig. 1 Schematic representation of the effects of interleukin-1 on heart function. Ca^{++} calcium, *NO* nitric oxide, *SERCA* sarco-endoplasmic reticulum calcium ATPase

first 7 days (primary end point) by 49 % (geometric mean ratio = 0.51, 95 % confidence interval (CI) 0.32–0.79; p=0.0028), thus confirming the central role of IL-1 as a key mediator in the systemic inflammatory response in AMI. Anakinra also had no effect on infarct size, however an unexpected higher incidence of major adverse cardiac events at 12 months (defined as death of any cause, recurrent AMI, stroke) was observed in the anakinra- vs placebo-treated patients [24••]. Unfortunately, details regarding the cardiac and noncardiac death rates, the characteristics of the recurrent AMI and stroke, and the incidence of heart failure are not provided. Whether this secondary finding is biologically plausible and clinically relevant still remains unknown and requires further studies [25].

IL-1 in Inflammatory Cardiomyopathy

Acute inflammatory injury to the heart occurs also during acute inflammatory cardiomyopathy (myocarditis). Activation of the cryopyrin inflammasome in the heart has been described in an animal model of inflammatory cardiomyopathy [26], as well as in biopsy specimens of patients with acute myocarditis [27]. Blocking IL-1 in this setting may represent a viable therapeutic strategy to prevent progression to HF [13, 28–30].

Direct Effects of IL-1 on Cardiac Function

In addition to regulating healing in the injured heart and cardiac remodeling after injury, IL-1 may also exert a direct effect on cardiac function. Animal models describe a reversible systolic dysfunction and reduced LV contractility reserve following a single or multiple injections of IL-1β in otherwise healthy mice [31, 32••]. In these studies, a single injection of IL-1β (3 mcg/kg) induced a significant transient reduction in the global systolic function that occurred within 4 h and resolved within 24 h of injection. Moreover, these mice also exhibited impaired contractile reserve as measured by a reduced responsiveness to isoproterenol (β agonist) at 4 h after IL-1β injection, which is a hallmark of HF. After 15 days of daily IL-1β injection, mice exhibited a similar reduction in resting LVFS and impaired response to isoproterenol [31]. However, resting function and isoproterenol responsiveness returned to baseline values on day 20 (5 days after completing IL-1β injections), suggesting that the effects of IL-1β on cardiac function are reversible and may be a viable target for pharmacologic intervention in HF patients [31]. In a model of

severe ischemic cardiomyopathy in the mouse, immediate and delayed treatment with an IL-1β blocker prevented the progressive impairment in contractile reserve, and this was seen even if the IL-1β blocker was initiated 1 week after AMI, when the injury is already established, as well as very late in the course at 10 weeks, when the left ventricle is markedly dilated and the systolic dysfunction is severely depressed, thus showing that IL-1 activity modulates cardiac function even when the injury and the adverse remodeling is established [19, 20].

Recent studies have focused on the role of IL-1 in myocardial injury and cardiac dysfunction related to cancer treatment, such as doxorubicin chemotherapy and chest irradiation [33–36].

IL-1 Is a Cardiodepressant Factor in Heart Failure

To evaluate the clinical relevance of circulating IL-1 activity, mice were injected with plasma obtained from patients with acute decompensated systolic HF during hospital admission or from patients with stable systolic HF or from subjects without any apparent cardiovascular disease [32••, 37]. Similar to the exogenous IL-1β administration, the plasma from advanced HF patients (but not from healthy control patients) induced a significant systolic and diastolic dysfunction and reduced contractile reserve following a single injection, suggesting the presence of circulating cardiodepressant factor in the plasma of acute decompensated HF patients [32••, 37]. Notably, however, these effects were not seen in mice pretreated with anakinra or an IL-1β antibody, showing that the cardiodepressant factor operated through an IL-1-dependent mechanism [20, 37]. This is consistent with the role of IL-1 as a cardiodepressant factor in severe sepsis [38].

Plasma from patients with stable systolic HF induced an intermediated phenotype in the mouse: mice injected with plasma derived from compensated patients with elevated plasma levels of CRP, a surrogate of IL-1 activity, displayed normal resting systolic function but significantly impaired contractile reserve [32••].

Mechanisms of Action of IL-1 in Heart Failure

The effects of IL-1 on cardiac function are through multiple concomitant molecular mechanisms (Fig. 1). IL-1β is the main circulating form of IL-1, responsible for systemic effects [6••]. IL-1α is an intracellular transcription factor released during cell injury and death. All known IL-1 effects are mediated by the binding to the $IL\text{-}1R_1$ and dependent on the recruitment of an accessory protein (IL-1RAcP). The IL-1R1/IL-1RAcP recruits multiple adaptor proteins: among these the myeloid differentiation, factor 88 (MyD88) has been well characterized, leading to activation of IL-1R-associated kinases (IRAKs) and tumor necrosis factor receptor-associated factor 6 (TRAF-6) that leads to activation of transcriptional factors such as p38 mitogen-activated protein kinase (p38 MAPK) and nuclear translocation of the nuclear factor-κB (NF-κB) [6••]. Many of the effects of IL-1 are indeed secondary to new transcription of synthesis of secondary mediators. There are several hundreds target genes [6••]. Among the mechanisms linking IL-1 to impaired systolic function, the inhibition of L-type calcium channels and the uncoupling of the β-adrenergic receptor (β-AR) from the adenylyl cyclase (AC) are the most commonly characterized [13, 39–43]. Furthermore, transcriptional and posttranslational changes in phospholamban and sarcoplasmic/endoplasmic reticulum calcium ATPase (SERCA) have been reported [44]. IL-1 also increases nitric oxide synthase (NOS) expression leading to increased nitric oxide (NO) activity, which is thought to mediate additional disruption of calcium and β-AR signaling, and dysfunction of the mitochondria [45–47].

Initial Clinical Experience

Among HF patients, there is a significant correlation between declining functional class and increasing levels of cytokines including IL-1β and surrogate markers [7–10, 48]. The proposed mechanisms of IL-1-induced systolic dysfunction and β-AR desensitization contributing to impaired exercise capacity in HF have been the basis for pilot proof-of-concept studies.

The first clinical study to evaluate the effects of IL-1 blockade on cardiac function reported that a single injection of anakinra (150 mg) in patients with rheumatoid arthritis without HF significantly improved parameters of myocardial contractility and relaxation, coronary flow reserve (measured by echocardiography), and endothelial function (measured by brachial artery flow-mediated dilatation) [49]. These effects were observed within 3 h of the dose and were sustained after 1 month of repeated dosing. Notably, however, a parallel group of patients treated with triamcinolone experienced no measureable benefits [49–51]. Similar beneficial effects were seen in a group of patients with rheumatoid arthritis and coronary artery disease [52]. A subsequent case report showed reduced severity of dyspnea (improved NYHA functional class) and an improvement in peak aerobic capacity (measured by cardiopulmonary testing) in a patient with rheumatoid arthritis and HF 16 weeks after replacing etanercept (50 mg weekly) with anakinra (100 mg daily) [53•].

The first clinical trial to prospectively test IL-1 blockade in patients with HF was an open-label, single-arm study in seven ambulatory patients with symptomatic systolic HFrEF (LVEF <40 %) and high levels of CRP (>2 mg/L) [32••]. Patients underwent baseline cardiopulmonary exercise testing (CPX), followed by a 14-day treatment with anakinra (100 mg daily)

Table 1 Completed clinical trials of anakinra

Study, year	Population (*n*)	Regimen (duration)	Primary end point (follow-up)	Results	Notes
Ikonomidis et al., 2008 [49–51]	Rheumatoid arthritis (23)	Anakinra (100 mg single injection)	Multiple end points (3 h) Flow-mediated forearm dilatation (FMD) Coronary flow reserve (CFR) E/E′ ratio Follow-up at 30 days available for an open-label phase of the study comparing with triamcinolone	FMD Baseline, 5.3 % Placebo, 4.8 % Anakinra, 9.7 % ($p<0.001$ vs baseline) CFR Baseline, 2.39 Anakinra, 2.41 Placebo, 2.85 ($p<0.001$ vs baseline) E/E′ Baseline, 10.2 Placebo, 9.8 Anakinra, 8.9 ($p=0.018$ vs baseline)	Similar benefits were observed in a series of patients who received 30 days treatment with anakinra versus prednisolone
VCU-ART, 2010 [21••]	STEMI (10)	Anakinra (100 mg daily for 14 days)	ΔLVESVi on cardiac MRI (3 months)	Anakinra, −3.2 mL/m^2 Placebo, +2.0 mL/m^2 ($p=0.033$)	ΔCRP correlated with remodeling ($r=+0.71$, $p=0.02$); more events in the placebo group
VCU-ART2, 2013 [22••]	STEMI (30)	Anakinra (100 mg daily for 14 days)	ΔLVESVi on cardiac MRI (3 months)	Anakinra, +1.4 mL/m^2 Placebo, +1.0 mL/m^2 (p=NS)	VCU-ART and VCU-ART2 combined showed reduction in incidence of new HF with anakinra (30 vs 5 %, $p=0.035$)
AIR-HF, 2012 [32••]	HFrEF (7)	Anakinra (100 mg daily for 14 days)	Change in aerobic capacity (peak VO_2) and ventilatory efficiency (VE/VCO_2) between baseline and 14 days	VO_2 Baseline, 12.3 mL/kg/min 14 days, 15.1 mL/kg/min ($p=0.016$) VE/VCO_2 Baseline, 28.1 14 days, 24.9 ($p=0.031$)	Open-label, single arm, nonrandomized design
D-HART, 2014 [58••]	HFpEF (12)	Anakinra (100 mg daily for 14 days)	Placebo-corrected difference in the interval change in peak VO_2 from baseline to posttreatment follow-up point (total follow-up=28 days)	Anakinra vs placebo, +1.2 mL/kg/min, $p=0.009$	Reduction in CRP correlated with improvement in VO_2 ($R=-0.60$, $p=0.002$)
Ikonomidis et al., 2014 [52]	Rheumatoid arthritis+ coronary artery disease (60)		Multiple end points (3 h) Flow-mediated forearm dilatation (FMD) Coronary flow reserve (CFR) E/E′ ratio	FMD Baseline, 4.2 % Placebo, 4.3 % Anakinra, 9.7 % ($p<0.05$ vs baseline) CFR Baseline, 2.1 Placebo, 2.1 Anakinra, 2.8 ($p<0.05$ vs baseline) E/E′ Baseline, 14.1 Placebo, 14.0 Anakinra, 10.7 ($p<0.05$ vs baseline)	A cohort of 20 patients without CAD served as an additional control group
MRC-ILA Heart, 2014 [24••]	NSTEMI (182)	Anakinra (100 mg daily for 14 days)	7-day area under the curve of CRP (total follow-up=1 year)	Anakinra vs placebo, 49 % reduction (95 % CI 0.32–0.79; $p=0.02$)	Higher incidence of MACE at 12 months with anakinra

Δ*CRP* change in C-reactive protein level, *HF* heart failure, *HFrEF* HF with reduced ejection fraction, *HFpEF* HF with preserved ejection fraction, *hsCRP* high-sensitivity C-reactive protein, Δ*LVESVI* change in left ventricular end-systolic volume index, *MI* myocardial infarction, *MRI* magnetic resonance imaging, *VE/VCO₂* ventilatory efficiency, *VO₂* peak oxygen consumption

and a final CPX. Besides reducing CRP and IL-6 levels by 84 and 90 %, respectively, IL-1 blockade with anakinra significantly improved CPX performance measured by peak oxygen consumption (VO_2, +2.9 mL/kg/min), ventilatory efficiency (VE/VCO_2, −3.2), and total exercise time (+2.9 min) [32••]. Although limited by the lack of a placebo group, aerobic exercise capacity quantification by VO_2 or VE/VCO_2 represents strong independent, placebo-insensitive predictor of mortality and hospitalization in HF [54]. Another intriguing finding was the reduction of IL-1β plasma concentration after blockade treatment. In most physiological systems, receptor inhibition stimulates upregulation of the receptor agonist due to interruption of the negative feedback loop. The reduction of IL-1β concentration following IL-1 receptor blockade suggests that IL-1β follows a positive feedback loop in heart failure and implies an autoinflammatory pathophysiology [55].

Approximately half of HF patients, however, have preserved systolic function (HFpEF) [3•]. While these patients may present with symptoms of dyspnea and fatigue that are similar to patients with HFrEF, there is striking divergence in the response to pharmacotherapy. Similar to HFrEF, however, systemic inflammation markers are also associated with poor prognosis in HFpEF [56, 57]. The D-HART [58••] pilot study was the first study to evaluate the effects of IL-1 blockade on aerobic exercise capacity in patients with HFpEF, diagnosed using the criteria set forth by the European Society of Cardiology [59], and systemic inflammation (CRP >2 mg/L). This double-blind, placebo-controlled, randomized crossover trial included 12 patients treated for 14 days with anakinra or placebo followed by crossover to the alternative treatment for 14 additional days. CPX was performed at baseline and at completion of 14 and 28 days of treatment. Patients experienced a significant improvement in exercise capacity after treatment with anakinra (VO_2, +1.2 mL/kg/min, $p=0.009$) compared to after receiving placebo. The reduction of CRP levels, a surrogate marker of IL-1β activity, also correlated with improvement in peak VO_2. These pilot clinical studies in HFrEF and HFpEF provide preliminary proof-of-concept evidence to link enhanced IL-1 activity to exercise intolerance in patients with HF (Table 1).

Future Research Avenues

Additional phase II clinical studies are ongoing to evaluate anakinra in HFrEF and HFpEF (Table 2).

The Anakinra in Decompensated Heart Failure (ADHF) trial will determine whether increased IL-1 activity in patients with acute decompensated HF is a modifiable factor [60]. The study will enroll 30 hospitalized patients with HF, LVEF <50 %, and elevated CRP (>5 mg/L) and randomize them to 14 days treatment with anakinra 100 mg or placebo. The primary end point will evaluate the inflammatory burden using CRP levels.

The Recently Decompensated Heart Failure Anakinra Response Trial (RED-HART) will evaluate the safety and efficacy of anakinra in adult patients with recently decompensated heart failure and systolic dysfunction (LVEF <50 %), in the attempt to improve postdischarge clinical conditions and prevent hospital readmissions [61]. This randomized, double-

Table 2 Ongoing clinical trials of anakinra

Study, year	Population (*n*)	Regimen (duration)	Primary end-point (follow-up)	Notes
CANTOS, 2012 [63]	Prior MI (18,200)	Canakinumab (50, 150, or 300 mg SQ every 3 months)	Composite: nonfatal MI, nonfatal stroke, cardiovascular death (event-driven follow-up)	Sub-study will evaluate changes in aerobic exercise capacity during the first year of treatment in 30 patients with HFrEF
ADHF, 2014 [60]	HFrEF (30)	Anakinra (100 mg daily for 14 days)	Area under the curve of hsCRP on day 3 (follow-up=14 days)	Treatment initiated within 24 h of admission for acute decompensated HF Patients receive anakinra 100 mg twice daily for the first 3 days
RED-HART, 2014 [61]	HFrEF (60)	Anakinra (100 mg daily for 2 or 12 weeks)	Aerobic exercise capacity (peak VO_2) at 2 weeks (follow-up=24 weeks)	Patients enrolled within 14 days of recent hospitalization for acute decompensated HF
VCU-ART3, 2014 [23]	STEMI (99)	Anakinra (100 mg daily or twice a day for 14 days)	Area under the curve of hsCRP on day 14 (follow-up=1 year)	Secondary analysis will evaluate incidence of new HF
D-HART2, 2014 [62]	HFpEF (60)	Anakinra (100 mg daily for 12 weeks)	Aerobic exercise capacity (peak VO_2) and ventilatory efficacy (VE/VCO_2 slope) at 4 weeks (follow-up=24 weeks)	Patients with a prior admission for HF Prespecified criteria for diastolic dysfunction at baseline

Δ*CRP* change in C-reactive protein level, *HF* heart failure, *HFrEF* HF with reduced ejection fraction, *HFpEF* HF with preserved ejection fraction, *hsCRP* high-sensitivity C-reactive protein, Δ*LVESVI* change in left ventricular end-systolic volume index, *MI* myocardial infarction, *MRI* magnetic resonance imaging, *VE/VCO_2* ventilatory efficiency, *VO_2* peak oxygen consumption

blinded, placebo-controlled trial will enroll 60 patients who will be treated within 2 weeks after discharge with anakinra 100 mg daily for 2 weeks, anakinra 100 daily for 12 weeks, or placebo daily for 12 weeks with a follow-up of 24 months. The primary end point will evaluate aerobic exercise performance by CPX.

The D-HART2 clinical trial will enroll 60 patients with HFpEF, evidence of diastolic dysfunction, and elevated CRP and randomize them 2:1 to either anakinra 100 mg daily for 12 weeks or placebo [62]. Exercise capacity will be assessed by CPX at baseline and 4, 12, and 24 weeks. Secondary end points will measure changes in cardiac structure and function by transthoracic echocardiography (baseline, week 4, week 12, and week 24) accompanied by stress echocardiography to assess contractile reserve at baseline and at week 12.

Canakinumab is a monoclonal antibody that targets human IL-1β and is currently approved for treatment of cryopyrin-associated periodic syndromes (CAPS)—a disease state driven by persistent overexpression of IL-1β. The Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) is a phase III, randomized, placebo-controlled, dose-ranging study to evaluate the use of canakinumab to prevent cardiovascular death, MI, or stroke in patients with elevated CRP and a history of AMI [63]. This multinational trial aims to enroll 10,000 patients worldwide and represents the largest anti-cytokine trial ever conducted. Enrolled patients will receive subcutaneous injections of canakinumab every 3 months for the duration of the trial. Secondary end points will include all-cause mortality, diabetes, atrial fibrillation, heart failure, venous thromboembolism, and macular degeneration. It is expected that at least 10 % of enrolled patients will have some degree of HF, which will represent a relatively large subgroup of patients. Results from phase II clinical trials on the effects of canakinumab on biomarkers show that canakinumab induces dose-dependent reductions in CRP and IL-6; nonsignificant trends toward reductions in HbA1c, glucose, and insulin levels; and a dose-dependent increase in serum triglycerides [64]. A sub-study of the CANTOS clinical trial of canakinumab or placebo in 30 patients with prior AMI and symptomatic HFrEF is ongoing [65].

Conclusions

Heart failure is a cardiovascular condition that represents a final common pathway for ischemic and nonischemic cardiomyopathy. Despite the clear benefits of contemporary treatment strategies, the disease continues to advance, representing the leading cause for hospitalization among patients older than 65 years of age in the USA. There is an urgent need to explore novel pathophysiologic mechanisms to identify new opportunities to improve quality of life, slow disease progression, and improve survival.

Inflammation appears to play a key role in cardiovascular disease and could raise a new pathophysiological paradigm in heart failure. IL-1β, the prototypical proinflammatory cytokine, may play a key role in infarct healing and ventricular remodeling and in the suppression of myocardial contractility and relaxation in HF.

Several preclinical studies have shown the role of IL-1β activity in models of cardiovascular disease. First, IL-1β administration induces contractile dysfunction in isolated cardiomyocytes and a reversible cardiomyopathy in the mouse. Second, IL-1β was shown to increase within hours in ischemic models of HF and is associated with progressive nature of cardiac dysfunction. Third, IL-1β signaling blockade in mice using pharmacological inhibitors or genetic deletion limited postinfarction ventricular remodeling, a known risk factor of HF, and also improved ventricular systolic and diastolic function, remodeling and contractility reserve, as well as survival. Pilot phase II clinical studies support the hypothesis that IL-1 blockade is a safe and effective strategy to reduce inflammation in patients with HF. It remains unknown, however, whether this strategy will ultimately translate to reducing morbidity and mortality.

Compliance with Ethics Guidelines

Conflict of Interest Benjamin W. Van Tassell has received research support through grants from the National Institutes of Health (NIH) and the American Heart Association (AHA) and has a patent for novel cryopyrin inhibitors pending.

Juan M. Valle Raleigh declares that he has no conflict of interest.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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