



# Heart Failure in Chronic Infectious and Inflammatory Conditions: Mechanistic Insights from Clinical Heterogeneity

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## Abstract

**Purpose of Review** The balance between inflammation and its resolution plays an important and increasingly appreciated role in heart failure (HF) pathogenesis. In humans, different chronic inflammatory conditions and immune-inflammatory responses to infection can lead to diverse HF manifestations. Reviewing the phenotypic and mechanistic diversity of these HF presentations offers useful clinical and scientific insights.

**Recent Findings** HF risk is increased in patients with chronic inflammatory and autoimmune disorders and relates to disease severity. Inflammatory condition-specific HF manifestations exist and underlying pathophysiologic causes may differ across conditions.

**Summary** Although inflammatory disease-specific presentations of HF differ, chronic excess in inflammation and auto-inflammation relative to resolution of this inflammation is a common underlying contributor to HF. Further studies are needed to phenotypically refine inflammatory condition-specific HF pathophysiologies and prognoses, as well as potential targets for intervention.

**Keywords** Heart failure pathogenesis · Chronic inflammatory and autoimmune disorders · Persistent inflammation · Trained immunity · Inflammation resolution

## Introduction

An increasing appreciation of heart failure (HF) phenotypic heterogeneity over the past decade has expanded mechanistic insights related to HF pathophysiology and progression [1, 2]. Augmenting traditional understandings of HF hemodynamics and neurohormonal modulation [3], an increasing

body of evidence highlights the role of inflammation in the pathogenesis and progression of various HF phenotypes [4, 5••]. In this context, reviewing diverse HF phenotypes in different chronic inflammatory and infectious conditions may offer insights into how distinct inflammatory pathways impact HF while also providing practical knowledge on inflammatory disease-associated HF for clinicians. We first review the state of the art regarding innate and adaptive immune responses in inflammation; we then discuss HF pathogenesis and presentation in various chronic inflammatory and infectious conditions; finally, we explore scientific gaps and potential therapeutic opportunities.

## Innate and Adaptive Immune Responses: Focused Overview for the Cardiologist

First, we will briefly provide an overview of innate and adaptive immune responses for the cardiologist; this overview informs the clinically focused discussion later in this article.

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## Innate Immunity

The human immune system is generally divided into two major components: innate and adaptive immunity [6]. Innate immunity generally acts as the first line of defense and is largely nonspecific, mediated by neutrophils, macrophages, dendritic cells, natural killer cells, monocytes, eosinophils, basophils, and mast cells [7, 8]. Pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) released from damaged cells are recognized by pattern recognition receptors (PPRs), which in turn can also detect endogenous host cellular damage [9]. This triggers downstream signaling cascades that activate nuclear factor- $\kappa$ B, as well as interferon regulatory factor transcription factors, and activator protein 1, leading to transcription of pro-inflammatory cytokines [9]. Innate immune cells enacting these cellular programs demonstrate functional plasticity depending on local conditions and antigenic exposures. Indeed, whereas exposure to certain antigens and adverse metabolic conditions can lead to persistent inflammatory hyperactivation, in non-disease conditions, cells such as macrophages can actively resolve inflammation [10–14].

## Trained Immunity: Innate Immune Memory

Recent evidence suggests that innate immune cells have the capacity to build memory [15], an emerging concept termed “trained immunity” or “innate immune memory” [16]. While likely intended to protect against re-infection or other secondary foreign agents, this memory can become maladaptive and harm the host. Indeed, exposure to certain stimuli, such as oxidized cholesterol particles, can lead to epigenetic reprogramming of innate immune cells [16, 17] and drive prolonged inflammatory hyperactivation [16, 18•, 19]. These changes are increasingly implicated in cardiovascular inflammation and, in concert with adaptive immune changes, may serve as important links between antigenic exposures (infectious and noninfectious) and atherosclerosis [18•].

## Adaptive Immunity

Adaptive immune responses are relatively specific and mediated largely by B and T cells, which can act independently, in concert with innate immune cells [20], and occasionally with one another [21] to clear pathogens. T cells mature in the thymus, differentiate into memory or effector cells, and are essential to immune memory and homeostasis; T cell receptors (TCRs) recognize a diverse set of environmental and infectious antigens, presented by antigen-presenting cells such as dendritic cells, and can subsequently enact a

number of inflammatory and/or inflammation-resolving programs [22–24]. This balance between inflammation and its resolution depends on antigen- and milieu-specific triggers, which drive T cell differentiation (e.g., with distinct helper or cytotoxic functions) and related signature cytokine production [22, 25, 26]. B cells, meanwhile, are derived from the bone marrow and, upon encountering antigen epitopes, mature into immunoglobulin-secreting plasma cells or memory B cells [27, 28]. Although B cell memory is central to lasting immune protection against pathogens [29], failure of self-tolerance immune checkpoints can result in autoantibody production with related auto-immune conditions such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) [27].

## Balance Between Inflammatory Hyperactivation and Resolution: Implications for Myocardial Disease and HF

Relevant to myocardial disease pathogenesis, unresolving inflammation can yield adverse ventricular remodeling, dysfunction, and ultimately HF [5••, 9, 30]. The time course of these varies depending on the underlying pathophysiology. A particularly acute and overt manifestation of immune-mediated HF is myocarditis, in which profound T cell activation plays a central role; in experimental infectious and inflammatory myocarditis, blunting T cell responses [31], particularly  $CD4^+$  T cells and their receptors (but perhaps not  $CD8^+$  T cells), ameliorates cardiac inflammation, damage, and dysfunction [32, 33]. Apart from acute infectious and inflammatory myocarditis, subtle differences in inflammation persistence vs. resolution impact cardiac function following local injury as occurs in myocardial infarction (MI). For instance, tyrosine kinase receptors expressed on macrophages (such as AXL and MerTK) increase pro-inflammatory responses and result in adverse ventricular remodeling and progression to HF, whereas their blockade ameliorates ischemia–reperfusion MI-induced HF [34]. Post-MI responses from the adaptive immune compartment are likewise essential to dictating the net-reparative vs. harmful impact on myocardial function and HF. T regulatory cells may provide a net-resolving effect related to wound healing after MI (perhaps via modulating inflammatory macrophage responses [35]), although the overall effect of T cells on post-MI inflammation vs. resolution remains under debate [36–38]. Meanwhile, B cells appear to be implicated in post-MI adverse remodeling and HF [39], but further study is needed on myocardial-specific effects of B cells as well as the pathophysiologic significance of myocardial autoantibodies [37, 40–43]. These experimental models, though largely focused on acute/subacute injury, have provided essential mechanistic insights into immune-mediated mechanisms of cardiac injury and dysfunction. Further mechanisms and related models of innate

and adaptive immune responses implicated in HF pathogenesis have been discussed in detail elsewhere and are beyond the scope of this review [5•, 44]. With our brief foregoing review of immune response elements as a foundation, the remainder of this review focuses on clinically relevant presentations and underlying pathophysiologies of HF in distinct chronic infectious and inflammatory conditions; an overview of these diverse immunopathogenic mechanisms in the context of other common causes of cardiac injury is provided in Fig. 1.

## Heart Failure in Chronic Inflammatory Conditions: Clinical Presentations and Mechanistic Correlates

Chronic inflammatory and autoimmune disorders are associated with a range of cardiovascular comorbidities including ASCVD, conduction abnormalities, valvular disease, and HF [45]. The increased risks for CVDs vary depending on the condition and stem from complex interactions between immunity-specific factors, accelerated atherosclerosis, persistent inflammation, microvascular disease, higher prevalence of CVD traditional risk factors, and off-target therapeutic effects [46–48]. Given diverse chronic inflammatory disease pathophysiologies, HF manifestations in these conditions are likewise non-uniform. Here, we present the current state of the art—based on admittedly limited existing data—on specific chronic inflammatory disease-associated HF risks and presentations.

### Rheumatoid Arthritis

Patients with rheumatoid arthritis (RA) are at elevated risk for CVDs in general [49, 50•] and HF in specific, even after adjustment for cardiovascular risk factors and underlying ischemic heart disease [49, 50•, 51•]. Regarding HF phenotypes in RA, RA patients with HF were more likely to have preserved ejection fraction compared to non-RA patients [52, 53]. RA-associated HF risk may be particularly apparent among women; women with RA are 3- to fourfold more likely to have diastolic dysfunction compared with women without RA with similar demographic and clinical profiles [54]. Perhaps not surprisingly, worse disease control and related heightened autoimmune inflammation in RA associate with adverse cardiac remodeling [55] marked by excess fibrosis [56], impaired diastolic function, and HF [51•]. A single-center electronic records–based study suggested that chronic methotrexate treatment is associated with lower risk for HF among RA patients; however, further clarification is needed regarding effects of specific disease-modifying antirheumatic drugs (DMARDs) on HF pathogenesis and progression in RA [51•].

### Systemic Lupus Erythematosus

Patients with systemic lupus erythematosus (SLE) are at heightened risk for a variety of CVDs, in particular atherosclerosis and thrombosis; they are likewise at heightened risk for pericarditis, endocarditis, valvular disease, and HF [57]. Prevalence of HF in patients with SLE is estimated to be between 1 and 10% [58] and HF incidence is 3–5 times higher in SLE patients compared to controls [59]. Limited data exist regarding HF phenotype in SLE; in a single-center study evaluating left ventricular ejection fraction (LVEF) trajectory over time in patients with chronic inflammatory diseases, SLE was more commonly associated with heart failure with preserved or midrange ejection fraction (HFpEF, HFmrEF) rather than with reduced ejection fraction (HFrEF) [60•]. A diversity of mechanisms are implicated in SLE-associated HF. These include premature athero-thrombosis and MI (with related myocardial damage), chronic myocardial inflammation (in absence of acute ischemic injury), and microvascular dysfunction/ischemia [58]. Further studies are needed to clarify specific mechanisms underlying SLE-associated HF [58, 59].

### Systemic Sclerosis

Systemic sclerosis (SSc) is associated with significantly elevated risk for CVDs including pulmonary hypertension, valvular diseases, arrhythmias, and heart failure [61]. In a single-center study of patients with various chronic inflammatory diseases, patients with SSc had the highest incidence of HF of all chronic inflammatory diseases—and as much as 7- to eightfold higher than controls—even after adjustment for demographic and clinical covariates of relevance [62•]. The phenotypic presentation of HF associated with SSc also appears to be distinct from that of other chronic inflammatory diseases. Isolated right-sided heart failure is quite common in SSc [63], which is perhaps not surprising given the high prevalence of pulmonary arterial hypertension in SSc [64]. Even in SSc patients without overt HF, abnormal cardiac tissue structure and mechanics are common: approximately 1/3<sup>rd</sup> of SSc patients have late gadolinium enhancement on cardiac magnetic resonance imaging [65] and diastolic dysfunction is highly prevalent [66]. The pathophysiology of SSc-associated myocardial dysfunction and HF involves a deleterious combination of fibrosis and ischemia, with existing fibrosis exacerbating ischemia due to mechanical limitation of blood flow, resulting in further ischemia/injury and fibrosis; epicardial vasospastic phenomena (referred to as “myocardial Raynaud’s phenomenon”) are also implicated [62•, 67–69]. Prognosis of SSc-associated HF is poor, and approximately 25% of deaths in patients with SSc are due to cardiac causes, mainly heart failure and arrhythmias [70].

### Diversity in Immune-Mediated Pathogenic Mechanisms of Heart Failure

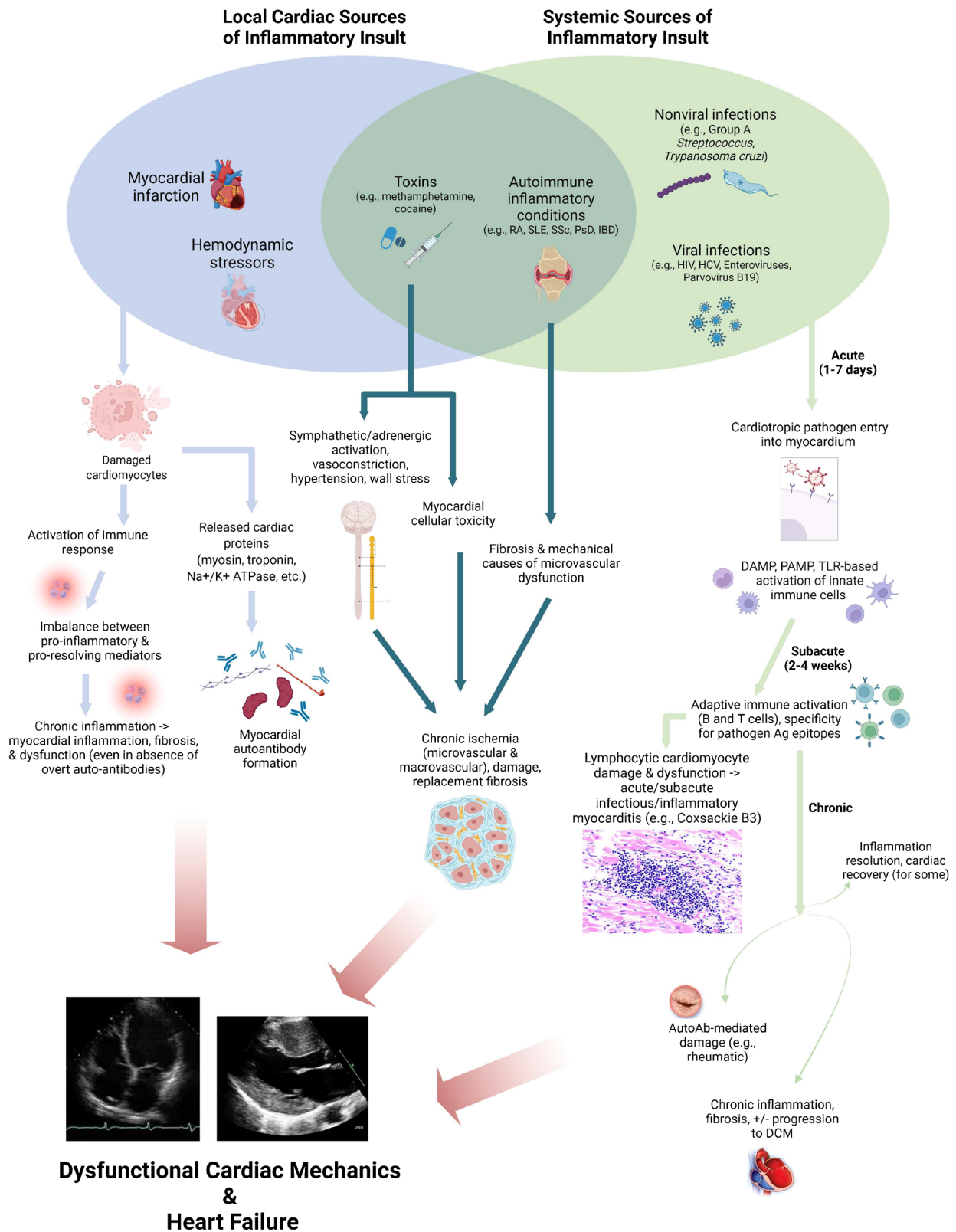


Fig. 1 Diversity of heart failure immunopathogenesis: infection, auto-inflammation, and impaired injury responses



## Psoriatic Disease

Psoriatic disease (PsD), which includes psoriasis and psoriatic arthritis, is also associated with increased risk of CVDs, with a considerable literature demonstrating PsD-associated vascular inflammation implicated in atherosclerotic CVDs [71–73]. Furthermore, HF incidence appears to be higher among PsD patients than controls [74, 75], although findings have been non-uniform across cohorts [76] and may depend on PsD severity [77], with worse PsD severity conferring higher HF risk.

Despite limited mechanistic data related to PsD-specific HF pathogenesis, there are several potential mechanisms that may be implicated in PsD-associated HF. Persistent uncontrolled inflammation appears to be central: tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), profoundly elevated and HF associated with worse prognosis [78], is a key pro-inflammatory mediator in PsD [79]. Moreover, psoriasis is associated with endothelial dysfunction and arterial stiffness, consequently leading to HF by decreasing coronary flow reserve [80, 81]. Patients with PsD have been observed to have coronary microvascular dysfunction (CMVD) due to the systemic inflammation, with one study reporting the prevalence of CMVD to be 61.3% in patients with PsD compared to 38.4% in matched controls [82]. Another study linked PsD to cases of dilated cardiomyopathy (DCM) [83], and hypothesized that an autoimmune process may play a role in development of DCM, as well as cytokine-induced collagen impairment leading to myocardial fibrosis and dysfunction [84].

## Inflammatory Bowel Diseases

Findings related to inflammatory bowel disease (IBD) and HF have been inconsistent. One retrospective longitudinal cohort study found that patients with inflammatory bowel disease (IBD) have a two-fold increase in incidence of HF (with ulcerative colitis patients being at higher risk than patients with Crohn's disease) [85], and another observed an approximately 1.4-fold IBD-associated relative increase in HF hospitalization risk [86]. However, a separate study observed no significant IBD-associated HF risk [77]. Among patients with IBD, disease severity appears to associate with HF risk [86] and women with IBD may have an especially elevated relative risk for HF [85]. Altered collagen metabolism is thought to play a role in pathophysiology of HF in patients with IBD [87]; patients also may develop myocardial fibrosis due to vitamin deficiencies, microvascular endothelial dysfunction, and altered nitric oxide-mediated vasodilation [88, 89].

## Infectious Causes of Heart Failure: Role of Inflammation

Innate and adaptive immune responses to foreign pathogens, while essential for pathogen clearance and acute infection resolution, can lead to self-tissue damage in the setting of excess and mistargeted inflammation. In this context, we will discuss distinct infectious triggers of deleterious cardiac inflammation resulting in HF, which highlight both the diversity of infectious causes of HF and the central role of immune responses in each of these conditions.

### Acute Infectious-Inflammatory Myocarditis

The clinical manifestation of myocarditis is broad, ranging from mild and virtually asymptomatic to severe, fulminant heart failure resulting in cardiogenic shock. An estimated 1–5% of patients with acute viral infections may develop a form of myocarditis, ranging from asymptomatic myocardial inflammation to overt HF; young men have the highest risk [90, 91]. The most common pathogens implicated in acute myocarditis are viruses, including enteroviruses such as coxsackieviruses, parvovirus B19, Epstein-Barr virus, and human herpesvirus-6 [92], and more recently, SARS-CoV-2 [93–95]. Myocarditis can also be caused by non-viral infectious agents including bacteria, *Chlamydia*, *Rickettsia*, fungi, and protozoa [96].

Although pathogens may be inciting factors in myocarditis, experimental models suggest that host immune responses to these pathogens—rather than the pathogens themselves—are perhaps the most important determinant of myocarditis pathophysiology and presentation. For instance, in a model of coxsackievirus-induced myocarditis [97, 98•], virus-infected cardiomyocytes die, resulting in damage-associated molecular patterns and related innate immune activation, and after being phagocytosed, have their antigen epitopes presented to T cells and B cells, which perform key effector functions in cardiac injury and development of myocarditis [98•]. This robust immune activation may drive antigenic self-targeting; for instance, studies of cytomegalovirus (CMV) [99] and coxsackievirus [100] models of myocarditis have demonstrated shared epitopes between viral particles and cardiac myosin, resulting in persistent myocardial auto-inflammation and myocarditis. These considerations highlight the overlap between infectious-inflammatory and autoimmune myocarditis, as infections have the potential to generate autoimmune responses. This is perhaps best highlighted by rheumatic heart disease, discussed next.

### Rheumatic Heart Disease

Rheumatic heart disease (RHD) is a relatively common (0.55 to 11 per thousand individuals worldwide [101])

pan-carditis with prominent valvular involvement, resulting in heart failure in approximately one-third of affected individuals and worse outcomes in women [102, 103]. Molecular mimicry and autoantibodies are hallmarks of rheumatic carditis. Heart-reactive antibodies have been isolated from the serum of patients with RHD for decades, and RHD was recognized as an autoimmune sequelae of group A streptococcal infection [104]. Initially, molecular mimicry was defined as shared identical amino acid sequences between host tissue and the bacterium [105]. However, studies using monoclonal antibodies have helped identify other types of molecular mimicry, such as antibody recognition of alpha-helical coiled-coil molecules, a protein structure shared among different host proteins (cardiac myosin, tropomyosin, vimentin, keratin, and laminin) and streptococcal M protein. A third type of molecular mimicry is cross reactivity between diverse molecules such as DNA, proteins, and carbohydrates [105]. In RHD, molecular mimicry between group A streptococcal protein and cardiac proteins leads to both humoral and cellular autoimmune reactions. Antibodies recognize internal biomarkers which cross-react with the streptococcal antigen. These autoantibodies can then cause inflammation of the endothelium (in particular valvular endothelium), driving vulnerability to autoreactive T cell infiltration. Resulting inflammation causes scarring and damage of the valve, which can worsen with recurrent infection and make penicillin prophylaxis important to prevent worsening [101].

### Chronic Chagas Cardiomyopathy

Chagas disease is a sequelae of infection with the intracellular parasite *Trypanosoma cruzi* [106] that affects 6 to 8 million people worldwide [107] and wide range of presentations. Approximately one-quarter of infected patients progress to chronic Chagas cardiomyopathy (CCC), with one-quarter of these presenting with reduced left ventricular ejection fraction (LVEF) [108]. Parasitic persistence appears to be required for CCC development; a combination of direct parasitic damage and inflammatory T cell responses have been implicated, although the extent to which either is the primary driver of disease remains up for debate [109].

### Human Immunodeficiency Virus

The epidemiology, pathogenesis, and presentation of human immunodeficiency virus (HIV)-associated heart failure have evolved considerably over the past two decades. Our group and others have discussed the evolving nature and immunopathogenesis of HIV-associated HF previously [110–114]; an in-depth discussion is beyond the scope of this article. In the modern antiretroviral therapy (ART) era, proportionate CVD mortality [115] and the global CVD burden [116] among

people with HIV have increased considerably. People with HIV have significantly higher risks for heart failure, including HFpEF and HFrEF, than HIV-uninfected controls even after adjustment for demographic and clinical confounders [117•, 118•, 119]. Poor viral control and immune progression (marked by circulating viremia and lower CD4 + T cell counts) are associated with particularly elevated HF risk for people with HIV, but individuals on ART without significant immune progression (e.g., CD4 decline) continue to have elevated HF risks [117•, 118•, 119]. In the modern ART era, the putative pathophysiologies of HIV-associated HF are diverse and somewhat less overt/direct than other viral infections; these include impaired myocardial responses to ischemia [120], metabolic dysregulation related to both chronic infection/inflammation and certain antiretrovirals, autonomic dysregulation, and convergence of other factors such as drug toxicity (in particular, methamphetamines and cocaine) and smoking [121]. In reality, multiple co-existing pathophysiologic “hits” are likely involved in HIV-associated HF [122], with underlying immune dysregulation and pro-inflammatory bias [123•] driving maladaptive, tissue-damaging responses to subsequent challenges ranging from hypertension to co-infection. Importantly, HIV-associated HF risks are especially pronounced in women, who have higher rates of HF hospitalizations and CVD mortality [124–126].

### Hepatitis C Virus

Several studies have described associations between chronic hepatitis C virus (HCV) infection and HF [127, 128], yet limited pathophysiologic knowledge exists regarding this association. Perhaps the most likely mechanism by which HCV contributes to CVD and HF relates to chronic inflammation and immune dysregulation, similar to chronic HIV infection [129]. Patients with HCV have been observed to have higher levels of pro-inflammatory cytokines, including TNF- $\alpha$  and IL-6 [130–133]. HCV infection is also associated with intestinal bacterial overgrowth, which can lead to bacterial translocation into the bloodstream, increasing LPS levels, triggering toll-like receptor (TLR) activation, and resulting in systemic inflammation [134, 135]. Importantly, effective treatment of HCV appears to decrease CVD risks [129, 136–138].

### Leveraging Insights from Chronic Inflammatory and Infectious Conditions: Immune Targeting in Heart Failure

Fortunately, for most chronic inflammatory and infectious causes of myocardial dysfunction and HF, treatment of the underlying inflammatory/infectious condition decreases associated HF risks to some extent. Yet, HF risks remain elevated in many of these conditions despite effective

therapy; accordingly, exploring existing and potential therapies offers the potential to yield disease-specific and broader insights into immune-targeted HF therapy.

In chronic inflammatory conditions, effects of immunomodulatory medications on HF risk appear to depend on the medication, its target(s), and the underlying population in which medications are used. Although corticosteroids reduce systemic inflammation, they can induce dyslipidemia, insulin resistance, and obesity, known CVD risk factors, and increase risk of CVDs including HF [139]. Immunosuppressants, such as mycophenolate mofetil, cyclophosphamide, and azathioprine, have shown inconsistent associations with ASCVD risk, without as clearly defined effects on HF [129, 140–143]. Perhaps the clearest demonstration of the barriers between inflammatory disease-specific efficacy and broader application is with TNF- $\alpha$  antagonists: whereas observational studies of RA patients suggested a benefit of TNF- $\alpha$  antagonists in reducing rates of HF hospitalization [144], this HF-reducing benefit was not replicated when TNF- $\alpha$  antagonists were tested in the general HF population without RA [145, 146]. Perhaps more promising are the results of a sub-analysis of the Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS), in which treatment of post-MI patients with canakinumab, an IL-1 $\beta$  antagonist, led to a dose-dependent reduction in HF hospitalization and a composite of HF hospitalization and mortality [147••]. A separate, smaller trial of IL-1 receptor antagonist anakinra in post-MI patients likewise yielded a reduction in incident HF [148]. Effects of colchicine on HF are less clear, as randomized trials have focused largely on post-MI recurrence of athero-thrombotic CVD rather than HF and variably suggested benefit [149] or neutrality/possible harm [150]. The reason behind the heterogeneous response to immunomodulatory agents in different HF populations is likely related to the unique mechanism underlying HF development in various diseases. Once we better define the pathophysiology of HF in these diseases, we will be able to find better targets for intervention specific to each population.

Several novel targets for immunomodulation in HF treatment are under exploration. One such proof-of-concept example is the use of transient antifibrotic chimeric antigen receptor (CAR) T cells to reduce myocardial fibrosis in mouse models of HF [151••]. Other novel approaches include engineered biomaterials used to induce macrophage-mediated inflammation resolution in cardiac injury models [152, 153], as well as engineered cardioprotective T regulatory cell administration or induction [154, 155]. While these immune-targeted therapies remain largely in the proof-of-concept stage, considerable interest in further development of immunomodulatory therapies

for HF exists with the goal of fundamentally altering problematic myocardial tissue substrates in HF.

## Conclusion

Several chronic inflammatory and infectious conditions confer increased risks for HF. The pathophysiologies and clinical presentations of these condition-specific HF etiologies differ; however, an imbalance between persistent inflammation and resolution thereof is centrally implicated in myocardial tissue damage, dysfunction, and resultant HF. Given limited clinical and mechanistic data, further studies are needed to define condition-specific HF pathophysiologies. These studies offer the dual potential of impacting the immediate, real-world care of patients with HF-associated inflammatory and infectious conditions, as well as informing novel developmental immune-targeted therapies in HF.

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## Declarations

**Conflict of Interest** The authors declare no competing interests.

**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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- Of importance
- Of major importance

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