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ROLE OF INTERLEUKINS IN HEART FAILURE

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ABSTRACT

Heart failure (HF) is a multifaceted medical condition marked by the inability of the heart to effectively pump blood to fulfil the body's requirements. Interleukins, including IL-6, IL-8, IL-10, IL-17, IL-18, IL-33, IL-5, IL-7, IL-9 and IL-13 have been implicated in various aspects of HF pathophysiology, such as angiogenesis, inflammation, fibrosis, oxidative stress and cardiac remodelling. Numerous studies have indicated altered interleukin levels in HF patients compared to healthy controls, suggesting their potential as prognostic indicators and markers of disease severity. Moreover, interleukins influence critical cellular processes associated with HF pathogenesis, such as immune cell activation, cardiomyocyte apoptosis, neurohormonal regulation and endothelial dysfunction. A comprehensive understanding of interleukin's roles in HF may lead to the development of innovative therapeutic strategies targeting inflammation and immune dysregulation. This review highlights the increasing importance of interleukins as key contributors to HF pathophysiology and underscores the potential for targeting interleukin pathways as novel therapeutic approaches for managing and treating HF.

Keywords: Heart failure, Interleukin, Cytokines, Myocardial infarction, Ventricular hypertrophy

INTRODUCTION

Heart failure (HF) occurs when the heart can't pump enough blood to meet the body's needs, often due to conditions like heart disease or a previous heart attack. Heart failure (HF) stands as a significant contributor to illness and death in developed nations, persisting as the foremost reason for mortality among the elderly on a global scale [1]. Benjamin et al., noted that common indicators of heart failure include breathlessness, tiredness, and reduced capacity for physical activity. Despite numerous improvements in managing heart failure, it continues to be an incurable and progressive condition. The 5-year mortality rate for heart failure among the American population has been approximated to vary between 50% and 70% [2].

Deswal and colleagues provided an in-depth understanding that the advancement of heart failure involves intricate mechanisms, with numerous factors involved in its pathophysiology [3]. Studies by Rauchhaus et al., proposed that heart failure transcends mere cardiac pumping dysfunction; it manifests as a systemic disorder [4]. Levine et al., disclosed that prolonged activation of various compensatory systems, such as the renin-angiotensin and β-adrenergic systems, is acknowledged as a notable contributor to heart failure [5]. Torre-Amione et al., explained that the effectiveness of inhibitory agents targeting these systems in reducing morbidity and mortality has been unsatisfactory, indicating that important pathways may still be unidentified [6]. Several trials proposed by Gullestad et al., and Nevers et al., indicated that inflammation may play a pivotal role in initiating and exacerbating heart failure [7,8].

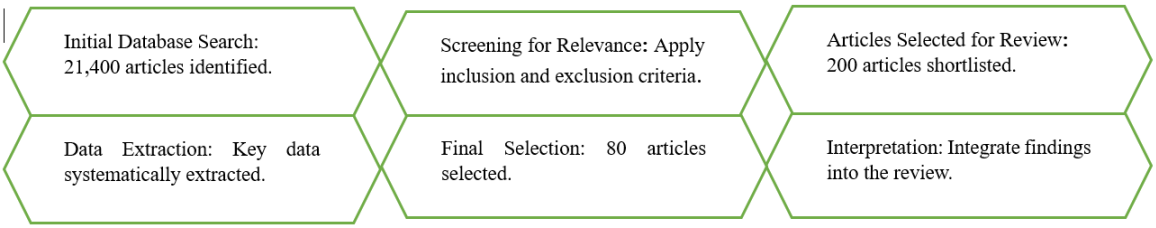
Ammirati et al., reviewed that inflammation is the biological reaction to tissue injury or irritation. As in the case of viral myocarditis, immune activation might result from extrinsic antigens directly, or indirectly from cardiac damage and subsequent encounter with self-antigens, potentially instigating an immune reaction against the heart [9]. Miliopoulos et al., noted that continual activation of the immune system is associated with the emergence of the progression of left ventricular hypertrophy into heart failure. As molecular messengers, cytokines transport inflammatory signals from the site of localized injury to different parts of the body [10].

The migration of T-cells to the left ventricle has been recognized as pivotal in the progression of heart failure [8]. Chung et al., investigated that the precise mechanisms involved remain poorly understood. Studies on animals have shown that increased levels of TNF-α can induce the onset of dilated cardiomyopathy [11], indicating that cytokines alone might trigger and exacerbate heart failure.

Mann et al., described that autoantibodies production, inflammatory responses activation, pro-inflammatory cytokines production and release, complement system activation and Class II major histocompatibility complex molecules overexpression collectively contribute to heart failure (HF) development [12]. Deftereos et al., suggested that despite attempts to inhibit immune pathways, no improvement in HF outcomes has been observed, using TNF-α inhibitors such as infliximab and in some cases, mortality rates have increased [13]. While colchicine trials have demonstrated decreases in inflammatory factor concentrations, these changes have not translated into clinical improvements for HF patients. Although nonspecific immunomodulation therapy has

shown by Torre-Amione et al., stated that benefits for specific patient groups, traditional therapy for acute HF decompensation has not resulted in decreased inflammatory cytokine levels, despite improvements in clinical parameters [14]. Milani et al., proposed that the use of amiodarone has been associated with increased serum TNF-α levels [15, 16].

METHODS



Interleukin-1β

Intracellular pro-inflammatory cytokine interleukin-1β (IL-1β) binds to its receptor and attracts adaptor proteins such as MyD88, this in turn triggers signaling pathways downstream that are essential for the immunological response [17]. This leads to the activation of TRAF-6, IRAKs, and subsequent transcription factor activation. IL-1β induces increased expression of nitric oxide synthase (NOS) and affects sarcoplasmic/endoplasmic reticulum calcium ATPase (SERCA). Following myocardial injury, the inflammasome formation leads to IL-1β activation, promoting leukocyte migration and cytokine synthesis. Studies in mice show a correlation between ischemia duration and IL-1β concentration. IL-1β contributes to changes in ventricular function and post-ischemic heart remodelling.

It was discovered that the quantity of IL-1β was connected to the NYHA functional class regardless of the underlying cause of heart failure [18]. Studies suggest that a larger proportion of patients exhibit elevated levels relative to IL-1 itself of IL-1 soluble receptor or receptor antagonists [18]. Elevated IL-1 levels in sepsis [19] and viral myocarditis [20] have been associated with increased cardiac structural alterations. Van Tassell et al., revealed that additionally, inhibiting this cytokine has been demonstrated to slow the progression to heart failure [21, 22].

Interleukin-6 a

Kishimoto et al., highlighted interleukin-6's (IL-6) diverse roles in immune activation, while cautioning about its potential to induce tissue fibrosis with prolonged inflammation [23]. IL-6 operates through its receptor (IL-6R) and can trigger both pro-inflammatory and anti-inflammatory responses. Fischer et al., emphasized the significance of the heart failure involving the JAK/STAT1/3 pathway in addition to additional pathways that the gp130 receptor subunit activates [24]. Boengler et al. described Janus kinases (JAKs) as pivotal in cytokine signaling, facilitating the activation of STAT proteins [25]. STAT3 triggers the Survivor Activating Factor Enhancement (SAFE) pathway, an innate protective signaling mechanism that limits cell death caused by cardiac

stress and promotes ischemic postconditioning to prevent reperfusion injury. Many downstream targets are involved in the JAK/STAT3 pathway, including Bcl-xL, cyclin D1, E1, p21, Mcl-1, Fas, Bcl-2 and vascular endothelial growth factor (VEGF). Lecour et al., stated that this pathway can also be activated by a number of substances, including erythropoietin, insulin, bradykinin, leptin, adrenoreceptors, opioids, cannabinoid agonists, resveratrol, and biogenic amines found in red wine, such as ethanolamine and melatonin [26].

Studies by Narazaki et al., have uncovered a decoy receptor known as sgp130, which acts as a natural inhibitor of IL-6 trans-signalling [27]. Villegas et al., discovered in cell culture that IL-6 inhibits the transcriptional activity responsible for the expression of beta- and alpha-myosin heavy chain, cardiac-alpha-actin, and sarcoplasmic reticulum Ca2+ ATPase (SERCA2) [28]. Yan et al., observed that in heart failure (HF) patients, both soluble IL-6-type receptors and IL-6 are present, and their levels correlate with the NYHA functional class (6, 18) as well as left or right ventricular function [29, 30].

A greater proportion of patients exhibit heightened IL-6 levels compared to sIL-6R levels. Eiken et al., observed an increase in gene expression of IL-6 and its receptors in both ischemic and nonischemic end-stage heart failure [31, 32]. Tsutamoto et al., associated IL-6 with adverse outcomes and the stimulation of the sympathetic nervous system [33].

Jug et al., identified IL-6 as a more reliable independent prognostic predictor than hsCRP in chronic stable heart failure [34]. In contrast, Rogers et al., reported in the Corona Trial that there was no proven association between IL-6 levels and myocardial infarction, stroke, or cardiovascular death in chronic symptomatic systolic heart failure [35]. However, sgp130 was correlated with mortality from all causes. Dolenc et al., demonstrated that IL-6 independently predicts systolic pulmonary artery pressure in severe heart failure [36]. Vasan et al., associated elevated IL-6 levels with an increased risk of heart failure in individuals without preexisting cardiovascular diseases [37].

Interleukin-8

The CXCL8 gene controls the expression of interleukin-8 (IL-8), which is a crucial mediator of inflammation. Harada et al., found that IL-8 serves multiple functions, including promoting angiogenesis, directing neutrophil and granulocyte movement, and stimulating phagocytosis. Its activation is triggered by various factors like hypoxia, shear stress, ischemia, and other stimuli that activate the NF-κB pathway [38]. Damas et al., suggested that cells possessing toll-like receptors, such as macrophages, epithelial cells, smooth muscle cells, and endothelial cells, are responsible for producing IL-8. Specifically, within the human heart, IL-8 is predominantly localized within cardiomyocytes [39].

In the studies of Damas et al., and Cappuzzello et al., proved that IL-8 levels were higher in heart failure (HF) patients in contrast to controls in good health, suggesting a possible connection to poorer clinical outcomes in HF [40, 41]. When compared to healthy donors, Nymo et al. discovered lower amounts of IL-8 mRNA in explanted hearts from end-stage HF patients [42]. De Gennaro et al., discovered that elevated IL-8 concentration predicted

HF development post-myocardial infarction (MI) [43]. During the initial 6 weeks following ST-segment elevation myocardial infarction (STEMI), there was less improvement in left ventricular function associated with greater levels of IL-8.

Interlekin-10

IL-10, an anti-inflammatory cytokine, is produced by mast cells, activated T cells, B cells, and macrophages. It plays a vital role in inhibiting matrix metalloproteinase and pro-inflammatory cytokine production, as well as controlling immune cell development, differentiation, and activity [44]. Furthermore, IL-10 functions as a strong suppressor of pro-inflammatory cytokines and prevents the migration of macrophages and monocytes to damage sites. Silvestre et al., discovered that individuals with heart failure (HF) had higher levels of IL-10, which positively correlated with NYHA class [45].

However, another study by Dixon et al., found no alteration in IL-10 concentration among HF patients. Studies conducted on mice demonstrated the cardioprotective effects of IL-10 [46]. Recombinant IL-10 administered to IL-10 knockout mice demonstrated improvements in systolic function, reversal of cardiac remodelling, reduced caspase-3 activation, decreased expression of hypertrophic and inflammatory genes, and increased levels of the anti-apoptotic protein Bcl2. Verma et al., demonstrated that IL-10 operates via STAT3, suppressing nuclear factor-κB activation and counteracting STAT3 inhibition. Persistent activation of STAT3 yielded outcomes akin to IL-10 administration, resulting in decreased expression of ANP, BNP, and TNF-α genes [47].

Frangogiannis et al., conducted certain animal experiments showed that following myocardial ischemia and reperfusion injury, there is an elevation in IL-10 levels, reaching a peak at 96–120 hours post-reperfusion [48]. Stumpf's review indicates that IL-10 has demonstrated the ability to inhibit the heart's inflammatory cell infiltration and decrease the expression of pro-inflammatory cytokines [49]. In models of acute myocardial infarction, IL-10 enhanced myocardial function and offered protection against adverse cardiac remodelling. Krishnamurthy et al., observed that IL-10 knockout mice have impaired left ventricular function, heightened fibrosis, and increased cardiomyocyte apoptosis [50].

Interleukin-17

Onishi et al., find out that many immune cell types, such as lymphoid tissue inducer cells, natural killer T cells, macrophages, NK cells, dendritic cells, T helper cells, and γδ-T cells are among the cell types that generate the pro-inflammatory cytokine interleukin-17 (IL-17). IL-17 induces the production of multiple cytokines, leading to the recruitment of neutrophils and monocytes to sites of inflammation [51]. Wuyts et al., reported that IL-17's activity involves several pathways, including NF-κB-DNA, MAPK, JNK, and ERK [81]. Eid et al. revealed that IL-17 collaborates with IFN-γ to activate inflammatory responses and enhance the synthesis of various cytokines [52]. Li et al., observed increased IL-17 levels in HF patients compared to healthy controls, associated with the

NYHA class [53, 54]. Sandip et al., found that rs8193037 in IL-17 represents a separate risk factor for both ischemic and nonischemic heart failure while rs4819554 within IL17RA predicted cardiovascular mortality in congestive HF individuals [55].

Pro-inflammatory role of interleukin-18

Interleukin-18 (IL-18), a pro-inflammatory cytokine in the IL-1 superfamily, is produced by various cells like macrophages, monocytes, and keratinocytes. It collaborates with IL-12 to activate cell-mediated immunity, stimulating the production of cytokines such as IFN-γ by NK cells and T cells [56]. By JNK and PI3-kinase pathways, IL-18 is linked to the migration and proliferation of smooth muscle and fibroblast cells [57]. IL-18 activation induces GATA4, enhancing ANP expression in cardiomyocytes [58], and activates NF-κB, p38 MAPK, and ERK [59]. Additionally, IL-18 promotes apoptosis through both extrinsic and intrinsic pathways, augmenting TNF-α effects and increasing caspase-3 activation [60].

Interleukin-33

Roussel et al. found that Interleukin-33 (IL-33), belonging to the IL-1 superfamily, is frequently localized within the nuclei of diverse cell types present in blood vessels, such as epithelial cells, smooth muscle cells, fibroblasts, keratinocytes, and endothelial cells [61]. According to Seki et al., there are two different types of the IL-33 receptor: the soluble variant (sST2) and the membrane-bound ST2L form, which is seen in cardiomyocytes and fibroblasts. The soluble sST2 acts as a decoy receptor induced by mechanical stress in cardiomyocytes, thus hindering IL-33's anti-hypertrophic effects [62]. One earlier study by Segiet et al., demonstrated a decline in IL-33 levels among HF patients compared to healthy controls [63].

Other interleukins

Sanderson described that interleukin-5 (IL-5) is a cytokine that is essential for the development and maturation of B cells and eosinophils. It also contributes to the generation of immunoglobulins and eosinophil activation [64]. Timmers et al. noted that IL-5, produced by Type 2 T helper cells and mast cells, decreases in individuals with HF, correlating with disease duration in severe cases with ischemic cardiomyopathy. In mice post-myocardial infarction, cardiac IL-5 expression also declines [65]. ElKassar and Gress described IL-7 as a hematopoietic growth factor produced by various cells, crucial for B, T, and NK cell development and survival. In HF patients, IL-7 levels decrease, impacting CD8+ T cell persistence in the heart, linked to myocardial damage in chronic Chagas' disease cardiomyopathy [66, 67]. Goswami and Kaplan state that interleukin-9 (IL-9) stimulates the growth and activity of mast cells, Th2 cytokine production, and the differentiation, proliferation, and survival of hematopoietic cells [68]. Marra et al. discovered that the STAT pathway is responsible for the activation of IL-9 secretion, which is induced by many stimuli such as TGF-β, IL-2, IL-4, IL-25, and IL-33. Elevated IL-9 levels in HF patients had an inverse relationship with left ventricular ejection fraction [69]. Knoops and Renauld associated increased IL-9 in the bloodstream with higher risks of adverse outcomes and reduced

cardiopulmonary functional capacity in HF patients. IL-9 triggers the Gp130/JAK/STAT pathway, providing protection against the advancement of heart failure [70]. Wynn noted that different types of immune cells, including CD4 cells, eosinophils, basophils, mast cells, NK cells, NK T cells, and others, produce interleukin-13 (IL-13) in gastrointestinal lymphoid tissue.

IL-13 facilitates the switch of immunoglobulin E (IgE) classes, enhances IgE production in B cells, upregulates CD23 and MHC Class II expression, and regulates resistance against intracellular parasites [71]. According to Nishimura's analysis, it helps B cells mature and differentiate and reduces macrophage activity, which stops pro-inflammatory cytokines from being produced. Compared to healthy persons, IL-13 levels are higher in HF patients. These values exhibit an inverse relationship with left ventricular ejection fraction and a positive link with brain natriuretic peptide, CRP, and the NYHA functional class [72].

Table:1- IL effects in heart failure

Interleukin	Effect in heart failure	References
IL -1β	Inflammation, myocardial remodeling, endothelial dysfunction, neurohormonal activation, and systemic complications.	[73]
IL- 5	Dysregulated immune responses can exacerbate inflammation and contribute to disease progression.	[74]
IL- 6	Synthesis and release of extracellular matrix proteins, such as collagen, and mediates the activation of matrix metalloproteinases (MMPs), which degrade the extracellular matrix, contributing to fibrosis and remodeling in HF.	[75]
IL – 7	Dysregulation of immune responses is a prominent feature, characterized by chronic inflammation and immune cell activation.	[76]
IL- 8		

	IL-8 plays a role in angiogenesis, the process of new blood vessel formation. In HF, angiogenesis is impaired, leading to inadequate blood supply to the myocardium and worsening cardiac function.	[77]
IL- 9	IL-9 may influence the production of pro-inflammatory cytokines and chemokines by immune cells, exacerbating inflammation in the myocardium and contributing to myocardial damage.	[78]
IL -10	It can reduce myocardial apoptosis, fibrosis, and hypertrophy, and improve cardiac function.	[79]
IL- 13	Affect cardiomyocyte contractility, calcium handling, and apoptosis.	[80]
IL-17	Ampaired angiogenesis contributes to inadequate blood supply to the myocardium and worsening cardiac function.	[81]
IL- 18	Dysregulated immune responses are a hallmark of HF, and IL-18 may contribute to immune-mediated cardiac injury and inflammation.	[82]

CONCLUSION

The examination of interleukin's role in heart failure (HF) underscores their significant impact on disease progression. Interleukins such as IL-6, IL-17, IL-8, IL-18, IL-33, IL-5, IL-10, IL-7, IL-9, and IL-13 influence various aspects of HF, including inflammation, angiogenesis, oxidative stress, fibrosis, and cardiac remodeling. Multiple studies have noted changes in interleukin levels in HF patients compared to healthy individuals, suggesting their potential as prognostic markers and indicators of disease severity. Additionally, interleukins play a crucial role in regulating fundamental cellular processes implicated in HF pathogenesis, such as cardiomyocyte apoptosis, immune cell activation, endothelial dysfunction, and neurohormonal regulation. Understanding the

intricate roles of interleukins in HF offers valuable insights into potential therapeutic targets for managing and treating the condition. Targeting interleukin pathways holds promise for developing novel therapeutic strategies aimed at mitigating inflammation and immune dysregulation in HF. This review highlights the increasing significance of interleukins as pivotal mediators in HF pathophysiology and emphasizes the potential for leveraging interleukin pathways to improve HF management and patient outcomes. Further research is needed to elucidate the specific mechanisms underlying interleukin-mediated effects in HF and to develop targeted interventions effectively addressing these pathways.

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CONFLICT OF INTEREST

The authors declare that there are no conflict of interests.

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