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THE ROLE OF INTERLEUKIN-6 IN THE PATHOPHYSIOLOGY, PROGNOSIS, AND THERAPEUTIC TARGETING OF HEART FAILURE WITH REDUCED EJECTION FRACTION


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ИНТЕРЛЕЙКИН-6 НИНГ ОТИЛИШ ФРАКЦИЯСИ ПАСАЙГАН ЮРАК ЕТИШМОВЧИЛИГИДАГИ ПАТОФИЗИОЛОГИЯСИ, ПРОГНОЗИ ВА ТЕРАПЕВТИК НИШОН СИФАТИДАГИ РОЛИ

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РОЛЬ ИНТЕРЛЕЙКИНА-6 В ПАТОФИЗИОЛОГИИ, ПРОГНОЗЕ И ТЕРАПЕВТИЧЕСКОМ НАПРАВЛЕНИИ ПРИ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТИ С НИЗКОЙ ФРАКЦИЕЙ ВЫБРОСА

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Резюме. *Юрак етишмовчилиги отилиш фракцияси (HFrEF) пасайган шакли ҳанузгача дунё бўйича касалланиш ва ўлимнинг етакчи сабабларидан бири бўлиб қолмоқда, ва яллиғланиш (инфламмация) унинг ривожланишида асосий но-гемодинамик омил сифатида тобора кўпроқ эътироф этилмоқда. Яллиғланиш медиаторлари ичида интерлейкин-6 (IL-6) ўзининг марказий ўрни билан ажралиб туради у тизимли яллиғланиш, миокард ремоделлацияси ва нохуш клиник натижалар ўртасидаги боғлиқликни шакллантиради. Ушбу шарҳда IL-6 нинг юрак етишмовчилиги отилиш фракциясидаги патофизиологик ва прогностик аҳамияти ҳақидаги мавжуд далиллар таҳлил қилинади ва уни терапевтик нишон сифатида баҳолаш имкониятлари муҳокама қилинади. Кўтарилган IL-6 даражаси JAK/STAT3 ва MAPK сигнал йўлларини фаоллаштириб, миокард фиброзини, гипертрофияни ва апоптозни рағбатлантиради ҳамда эндотел дисфункцияси ва метаболик бузилишларга ҳисса қўшади. Популяцион тадқиқотлар, масалан MESA кохорти, IL-6 даражасининг ошиши юрак етишмовчилиги бошланишидан олдин юз беришини кўрсатган; Менделий рандомизация таҳлиллари эса IL-6R ген вариантлари билан кардиометаболик хавф ўртасидаги сабабий боғлиқликни тасдиқлайди. Клиник жиҳатдан ИЛ-6 касаллик оғирлиги ва шифохонага ётқизилиш частотаси билан кучли корреляция кўрсатади, ва у сурункали маркер сифатида TNF-α га қараганда яхшироқ прогностик кўрсаткич ҳисобланади. Сўнгги клиник синовлар, жумладан HERMES лойиҳаси, IL-6 ни зилтивекимаб ёрдамида ингибирлаш тизимли яллиғланиш ва юрак зўриқишини камайтириши мумкинлигини кўрсатмоқда, бироқ HFrEF учун якуний далиллар ҳали етарли эмас. Шунингдек, SGLT2-ингибиторлар ва ARNI препаратлари ҳам IL-6 даражасини иккиламчи тарзда пасайтирувчи таъсир кўрсатиши мумкин. Умуман олганда, IL-6 HFrEFда ҳам патоген медиатор, ҳам истиқболли терапевтик нишон сифатида намоён бўлади. Келгусидаги тадқиқотлар селектив IL-6 блокадаси тириклик давомийлигини яхшилаши ва юрак ремоделлациясини орқага қайтариш имконини бериш-бермаслигини аниқлаши зарур. Бу ёндашув кардиологияда аниқ йўналтирилган яллиғланишга қарши даврнинг бошланишини билдириши мумкин.*

Калит сўзлар: *Интерлейкин-6, юрак етишмовчилиги, яллиғланиш, фиброз, JAK/STAT3, зилтивекимаб, HFrEF.*

Abstract. *Heart failure with reduced ejection fraction (HFrEF) remains one of the leading causes of morbidity and mortality worldwide, and inflammation has emerged as a major non-hemodynamic driver of its progression. Among inflammatory mediators, interleukin-6 (IL-6) plays a particularly central role in linking systemic inflammation, myocardial remodeling, and adverse outcomes. This review discusses current evidence on the pathophysiological and prognostic significance of IL-6 in HFrEF and explores its potential as a therapeutic target. Elevated IL-6 activates the JAK/STAT3 and MAPK signaling pathways, promoting myocardial fibrosis, hypertrophy, and apoptosis, and contributes to endothelial dysfunction and metabolic disturbance. Population-based studies, such as the MESA cohort, demonstrate that increased IL-6 levels precede heart failure onset, while Mendelian randomization analyses confirm a causal relationship between IL6R variants and cardiometabolic risk. Clinically, IL-6 correlates with disease severity and hospitalization, outperforming other cytokines such as TNF-α as a chronic biomarker. Recent trials, including HERMES, suggest that IL-6 inhibition with ziltivekimab can reduce systemic inflammation and cardiac stress, although definitive evidence in HFrEF is still lacking. Standard therapies like SGLT2 inhibitors and ARNIs may also exert secondary IL-6–lowering effects. Taken together,*

IL-6 represents both a pathogenic mediator and a promising target in HFrEF. Future research must clarify whether selective IL-6 blockade can translate into improved survival and reverse remodeling, marking a transition toward an era of precision anti-inflammatory cardiology.
Keywords: *Interleukin-6, heart failure, inflammation, fibrosis, JAK/STAT3, ziltivekimab, HFrEF.*

Introduction. Despite all our progress in the treatment of heart failure with reduced ejection fraction (HFrEF), it still remains one of the most challenging syndromes in cardiology. Even when patients receive beta-blockers, ACE inhibitors, ARNI, or SGLT2 inhibitors, the inflammatory burden continues to play a critical role in worsening the disease. Among the inflammatory mediators, interleukin-6 (IL-6) has received major attention in recent years as both a biomarker and a potential therapeutic target [1–3]. IL-6 is not a single-pathway cytokine; it influences cardiomyocyte metabolism, endothelial activation, and even neurohormonal signaling. It is produced by macrophages, fibroblasts, and cardiomyocytes under stress conditions, acting through the JAK/STAT3 and MAPK pathways [4,5]. Chronic IL-6 activation can therefore link systemic inflammation with local myocardial injury. In this review, I will summarize what we currently know about IL-6 in the context of HFrEF from molecular mechanisms to its clinical and prognostic implications with emphasis on emerging therapeutic possibilities.

Pathophysiological Role of IL-6 in HFrEF. The "cytokine hypothesis" of heart failure has been around for decades, but now we have stronger molecular evidence to support it. IL-6, together with TNF-α and IL-1β, forms a vicious cycle of inflammation and remodeling in the failing heart [6,7]. The cytokine activates the gp130 receptor complex, triggering downstream STAT3 phosphorylation, fibroblast proliferation, and myocyte apoptosis. Over time, this contributes to progressive ventricular dilation and reduced systolic performance. IL-6 also stimulates local oxidative stress and endothelial dysfunction, which in turn worsen myocardial perfusion. Ahmed and colleagues [6] demonstrated that IL-6 levels rise in proportion to disease severity and are closely linked to TNF-α and IL-1β, but unlike them, IL-6 tends to persist chronically even when the acute phase has passed. This persistence is one reason why IL-6 might be a more stable target for therapy. The MESA study provided valuable insight into this relationship. Ahmad et al. [1] reported that individuals with higher IL-6 concentrations had greater coronary artery calcium burden and a higher risk of developing heart failure over time. This observation nicely connects IL-6 with the ischemic substrate that frequently leads to HFrEF.

Further, genetic data have strengthened causality. Using Mendelian randomization, Cupido et al. [8] showed that variants in IL6R associated with lower receptor signaling also correlated with reduced cardiovascular risk. This supports the concept that IL-6 is not merely an epiphenomenon but a causal contributor in the cardiometabolic pathway. One of the most damaging effects of IL-6 is on myocardial fibrosis. By inducing TGF-β and connective tissue growth factor (CTGF), IL-6 promotes extracellular matrix deposition, which stiffens the ventricle and impairs contraction [9]. Wang et al. [19] observed that in HFrEF patients, lowering IL-6 with dapagliflozin therapy corresponded with improved fibrosis biomarkers. This may not be a direct IL-6 blockade, but it certainly hints that modulation of inflammation is part of the drug's benefit.

In my own clinical experience, patients with chronically elevated inflammatory markers often have a more fibrotic phenotype on imaging higher ECV on cardiac MRI which fits with the mechanistic data.

Biomarker and Prognostic Implications. Many studies have tried to position IL-6 as a reliable biomarker in chronic heart failure. Povar-Echeverría et al. [14] found that in elderly outpatients, IL-6 levels predicted adverse outcomes independently of NT-proBNP. This is clinically meaningful: in elderly patients where renal dysfunction makes natriuretic peptides less specific, IL-6 could add prognostic value. Meta-analyses support this view. Gui and Rabkin [9] found that IL-6 is significantly higher in HFrEF compared to HFpEF, suggesting that IL-6 is particularly linked with the systolic dysfunction phenotype. Similarly, Albar et al. [3] noted that IL-6 and CRP were the best inflammatory markers distinguishing reduced from preserved ejection fraction heart failure. Acute heart failure exacerbations are often accompanied by infection or ischemic triggers, and IL-6 levels surge during these events. Vasques-Nóvoa et al. [18], in the EDIFICA registry, reported that IL-6 was markedly elevated in acute decompensation and independently predicted short-term mortality. Takagi et al. [17] described similar findings, showing that high IL-6 levels correlated with corticosteroid responsiveness and poor hemodynamic status. In everyday clinical practice, I often see IL-6 rise along with CRP during hospital admissions, but the resolution after diuresis is variable implying that inflammation is not only a bystander but a key mechanism of decompensation.

The interplay between IL-6, IL-1β, and TNF-α deserves emphasis. Ahmed et al. [6] demonstrated that while TNF-α spikes early in decompensation, IL-6 remains persistently elevated throughout chronic heart failure, correlating with cachexia, anemia, and endothelial dysfunction. This makes IL-6 a better integrative biomarker of chronic systemic involvement than TNF-α alone.

IL-6 as a Therapeutic Target. Targeting IL-6 is an appealing idea. It represents a node connecting inflammation, fibrosis, and metabolism. As Ridker and Rane [16] explained, IL-6 signaling occurs through classic and trans-signaling pathways; the latter drives most of the deleterious cardiovascular effects. Therefore, selective blockade of IL-6 trans-signaling could provide benefit without fully suppressing host immune defense. Ridker [15] first proposed the concept of IL-6 inhibition for cardiovascular event reduction after observing that lowering IL-6 predicted benefit in the CANTOS and RESCUE programs. More recently, the HERMES trial tested ziltivekimab — an IL-6 ligand blocker — in patients with systemic inflammation and HF with mildly reduced or preserved EF [13]. Although not exclusively HFrEF, the trial found significant reductions in CRP and NT-proBNP, suggesting modulation of systemic inflammation and myocardial stress. It is tempting to extrapolate these findings to HFrEF populations, particularly those with elevated CRP or obesity-related inflammation. However, we still need dedicated trials in true reduced-EF cohorts to confirm whether IL-6 inhibition can translate into better survival or reverse remodeling.

Interestingly, several drugs we already use in HFrEF exert secondary anti-IL-6 effects. SGLT2 inhibitors like dapagliflozin [19,20] reduce circulating IL-6 and TNF-α, possibly through improved mitochondrial metabolism and less oxidative stress. Boulet et al. [5] noted similar anti-inflammatory actions with ARNI and mineralocorticoid antagonists. So even if we don't yet have IL-6 blockers in daily cardiology practice, we may already be modulating this pathway indirectly.

Translational and Clinical Perspectives. It would be quite useful to combine IL-6 with traditional markers for risk stratification. Pandhi et al. [12] included IL-6 among a panel of biomarkers linked with congestion and systemic inflammation, showing incremental prognostic value beyond NT-proBNP. A multiparametric score incorporating IL-6 could help tailor anti-inflammatory or metabolic therapy intensity.From a practical standpoint, IL-6 testing is not yet routine in cardiology clinics, but as assays become more standardized, I believe we will increasingly rely on such markers for precision management.

While IL-6 plays a role in both HFpEF and HFrEF, evidence suggests it becomes more prominent as systolic dysfunction develops. Alogna et al. [4] and Chia et al. [7] found IL-6 predicts incident HFpEF in community populations, but in established HFrEF, IL-6 levels are much higher and directly linked to worse survival. That may indicate IL-6 is not only a trigger but also a marker of disease transition from early diastolic dysfunction toward irreversible systolic failure.

Going forward, we need large HFrEF-specific IL-6 inhibition trials to confirm causality. Combining genetic insights [8], observational cohorts [1], and imaging data may help define the subgroup most likely to benefit for instance, patients with high CRP, metabolic syndrome, or ischemic etiology. Integration with multi-omics could also identify downstream metabolites reflecting IL-6 activity.At the translational level, understanding how IL-6 interacts with cardiac fibroblast senescence and mitochondrial function (topics highlighted by Alogna and colleagues [4]) could open new precision medicine avenues.

Conclusion. In summary, IL-6 is a pivotal mediator in HFrEF, driving myocardial inflammation, fibrosis, and metabolic remodeling. Elevated IL-6 levels predict progression and adverse outcomes across chronic and acute stages of the disease. Mechanistic, genetic, and therapeutic evidence collectively suggest that IL-6 is not just a biomarker but an actionable target. Still, clinical cardiology is not quite ready to routinely use IL-6 inhibitors; we need more robust data on efficacy and long-term safety. Nevertheless, modulating IL-6 directly or indirectly may become part of the next generation of anti-inflammatory cardiology, complementing neurohormonal and metabolic therapies. As clinicians, we often see patients whose heart failure remains "hot" even after optimal therapy persistent fatigue, cachexia, elevated CRP. These are the patients where IL-6 oriented interventions might one day make the difference.

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РОЛЬ ИНТЕРЛЕЙКИНА-6 В ПАТОФИЗИОЛОГИИ, ПРОГНОЗЕ И ТЕРАПЕВТИЧЕСКОМ НАПРАВЛЕНИИ ПРИ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТИ С НИЗКОЙ ФРАКЦИЕЙ ВЫБРОСА

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Резюме. *Сердечная недостаточность с низкой фракцией выброса (СНнФВ) остаётся одной из ведущих причин заболеваемости и смертности во всём мире. За последние годы стало ясно, что воспаление это не просто сопутствующий феномен, а важный не-гемодинамический фактор, ускоряющий прогрессирование заболевания. Среди множества провоспалительных медиаторов особое место занимает интерлейкин-6 (IL-6), который связывает системное воспаление с ремоделированием миокарда и неблагоприятными исходами. В этом обзоре рассматриваются современные данные о патофизиологическом и прогностическом значении IL-6 при СНнФВ, а также обсуждается его потенциал в качестве терапевтической мишени. Повышенный уровень IL-6 активирует сигнальные пути JAK/STAT3 и MAPK, что способствует развитию фиброза, гипертрофии и апоптоза кардиомиоцитов, а также нарушению функции эндотелия и обмена веществ. Крупные популяционные исследования, такие как когорта MESA, показали, что рост концентрации IL-6 предшествует развитию сердечной недостаточности. Кроме того, анализы менделевской рандомизации подтвердили причинно-следственную связь между вариантами гена IL6R и кардиометаболическим риском. В клинической практике уровень IL-6 хорошо коррелирует с тяжестью заболевания и частотой госпитализаций, зачастую превосходя по информативности другие цитокины, включая TNF-α. Недавние клинические испытания, например HERMES, показали, что ингибирование IL-6 препаратом зилтивекимабом может снижать системное воспаление и уровень сердечного стресса, хотя убедительных доказательств его пользы именно при СНнФВ пока нет. Интересно, что стандартные препараты такие как ингибиторы SGLT2 и ARNI также, по-видимому, оказывают вторичный эффект по снижению уровня IL-6. Мы рассматривает IL-6 не только как патогенетический медиатор, но и как перспективная терапевтическая цель при СНнФВ. Будущие исследования должны ответить на вопрос, сможет ли селективная блокада IL-6 улучшить выживаемость пациентов и обратить патологическое ремоделирование, открывая путь к новой эре прецизионной противовоспалительной кардиологии.*

Ключевые слова: *сердечная недостаточность, интерлейкин-6, зилтивекимаб, СНнФВ, воспаление, фиброз, JAK/STAT3.*