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An Overview on Biomarkers of Inflammation and Disease Severity in Children with Congenital Cardiac Shunts

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Abstract:

Background: Congenital heart disease (CHD) comprises a heterogeneous group of structural and functional abnormalities of the heart and great vessels that arise from abnormal cardiac development during fetal life. Among these lesions, left-to-right cardiac shunts may produce pulmonary overcirculation, systemic venous congestion, and reduced effective systemic cardiac output, particularly when the shunt is hemodynamically significant. These hemodynamic disturbances may impair splanchnic perfusion and contribute to intestinal congestion, increased intestinal permeability, and disruption of the gut barrier, thereby promoting bacterial translocation and systemic inflammatory activation. Inflammatory cytokines appear to have an important role in this process. Interleukin-1β (IL-1β) is a major pro-inflammatory cytokine involved in innate immune activation, myocardial inflammation, and inflammatory signaling, whereas interleukin-10 (IL-10) acts as an anti-inflammatory cytokine that limits excessive immune responses and promotes restoration of immune homeostasis. In decompensated pediatric patients with left-to-right cardiac shunts, an imbalance between pro-inflammatory IL-1β activity and the counter-regulatory effects of IL-10 may reflect the severity of intestinal and systemic inflammation. Assessment of these cytokines, individually or as part of a pro-/anti-inflammatory profile, may therefore provide additional insight into the inflammatory burden associated with heart failure and gut-barrier dysfunction and may have potential diagnostic and prognostic value in affected children.

Keywords: Congenital heart disease; Left-to-right cardiac shunt; Interleukin-1β; Interleukin-10; Intestinal inflammation; Gut-heart axis; Pediatric heart failure; Cytokines.

Introduction:

Congenital heart disease (CHD) encompasses a broad range of structural and functional defects of the heart and great vessels, originating from abnormal cardiac morphogenesis in utero. These anomalies vary from simple defects, such as septal obstructions or valve lesions, which may close spontaneously, to complex life-threatening lesions (e.g., conotruncal and single ventricle anomalies) requiring early cardiac catheterization or open-heart surgery. Consequently, CHD represents the most extensive group of severe congenital malformations and stands as the leading cause of infant mortality **(1).** Ultimately, the specific hemodynamic alterations of each defect dictate the clinical priorities in patient management.

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I . Interleukin-1β (IL-1β)

Definition

Interleukin-1β (IL-1β) is a potent pro-inflammatory cytokine that plays a central role in innate immunity and inflammatory response. It is mainly produced by monocytes and macrophages in response to infection or tissue injury. IL-1β is synthesized as an inactive precursor (pro-IL-1β) and is subsequently processed into its biologically active form to mediate inflammation and host defense (**2)**

Structure

IL-1β is initially synthesized as an inactive 31-kDa precursor protein, known as pro-IL-1β, which lacks the signal peptide required for conventional secretion. Pro-IL-1β is subsequently cleaved, mainly by activated caspase-1, to generate the mature and biologically active 17-kDa form. Mature IL-1β possesses the characteristic β-trefoil structural fold of the IL-1 cytokine family, which facilitates its specific interaction with interleukin-1 receptors **(3).**

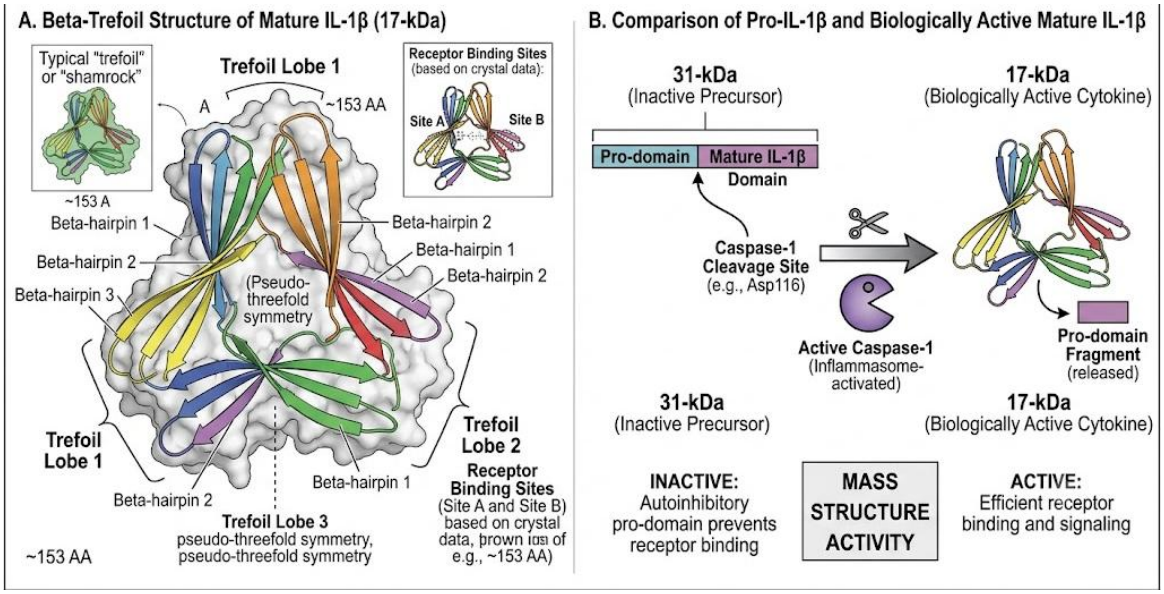


Figure .1 Structure of Interleukin-1β showing its mature form and caspase-1–mediated activation. **Source: Created by the researcher based on Abbate et al. (3).**

Biosynthesis and Secretion

The production and release of IL-1β generally involve two coordinated signals. The first signal is initiated by the recognition of pathogen-associated molecular patterns or damage-associated molecular patterns, resulting in the transcription and synthesis of pro-IL-1β and inflammasome components. The second signal promotes inflammasome assembly and caspase-1 activation, leading to the cleavage of pro-IL-1β into its mature form. Because IL-1β lacks a conventional signal peptide, it is released through non-classical secretory mechanisms, including gasdermin D-mediated membrane pore formation and pyroptotic cell death **(4).**

Mechanism of Action

Mature IL-1β exerts its biological effects by binding to interleukin-1 receptor type I (IL-1R1) on responsive cells, including cardiomyocytes, endothelial cells, and cardiac fibroblasts. Ligand binding promotes the recruitment of the IL-1 receptor accessory protein and the formation of an active receptor complex. This complex subsequently recruits the adaptor protein MyD88 and activates downstream NF-κB and mitogen-activated protein kinase pathways, resulting in the transcription of several pro-inflammatory genes **(3).**

Biological Functions

Beyond its classic role in innate immunity against infections, IL-1β mediates several systemic and localized effects that contribute to cardiovascular pathology:

Fever Induction: Acts as a central pyrogen to initiate fever.

Leukocyte Recruitment: Stimulates hepatic acute-phase protein synthesis and promotes endothelial activation to recruit leukocytes to injury sites.

Cardiomyocyte Dysfunction: Directly alters the contractile properties and survival of cardiomyocytes. **Developmental Importance**: Disruption of the IL-1 family signaling has been linked to premature birth, reflecting its fundamental role in physiological homeostasis **(4)**

Regulatory mechanism

Where it has been detailed previously, the IL-1β/IL-1R1/MyD88/NF-κB signaling pathway becomes subject to various adjunct mechanisms of endogenous regulation. One of these mechanisms is the IL-1 receptor antagonist (IL-1Ra), which binds competitively to IL-1R1 and blocks signaling, along with decoy receptor IL-1R2, soluble forms of which capture IL-1β and prevent it from coupling with the receptor. Such regulatory mechanisms invoke a pharmacological rationale for therapeutic IL-1 blockade, including recombinant IL-1Ra (anakinra). Overall, such mechanisms have been shown to alleviate the severity of systemic inflammation with decompensated heart failure by interrupting the pathway at the receptor **(5).**

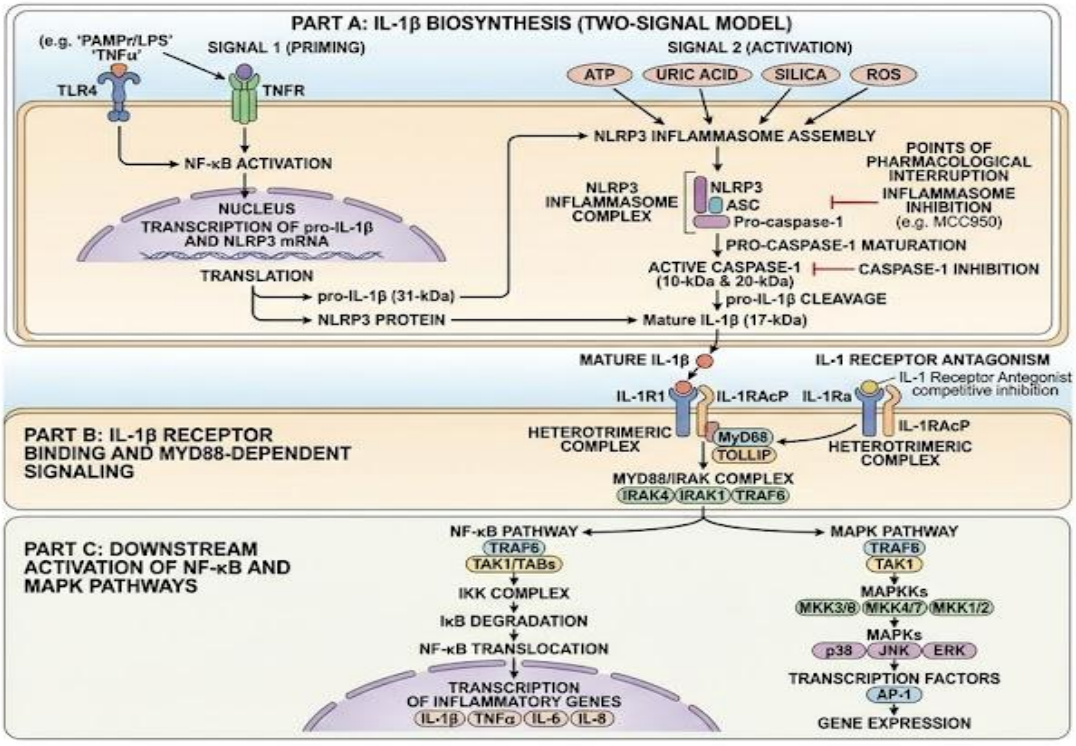


Figure 2. IL-1β signaling pathway showing inflammasome activation, downstream signaling, and therapeutic targets. **Source: Developed by the researcher based on Abbate et al. (3).**

Clinical Significance

L-1β has emerged as a clinically important inflammatory cytokine in cardiovascular diseases. Recent evidence demonstrated that IL-1β promotes myocardial inflammation and contributes to disease progression in arrhythmogenic cardiomyopathy by enhancing inflammatory responses and adverse cardiac remodeling. These

changes impair myocardial stability and accelerate disease progression, highlighting IL-1β as a promising therapeutic target and a potential biomarker for disease activity **(6).**

Role of IL-1β in Heart Failure

In the case of heart failure, one of the functions of IL-1β is to bridge hemodynamic and neurohormonal disturbances with inflammation-related cellular and molecular pathways**. Groza et al. (7)** suggest the many early signs of inflammation worsening may lead to overt heart failure from compensated cardiac disease. Additionally, new studies have emerged supporting the idea that the inflammatory IL-1β pathway plays a major role in the progression of heart failure, and heart failure patients may benefit from the inflammatory blockade of IL-1. For example, **Van Tassell et al. (5)** describe decompensated heart failure inflammation as the most clinically significant form of inflammation, and blockade of IL-1 is one of the most effective ways to address this. Furthermore**, Szabo et al. (8)** discuss the growing body of evidence supporting the potential heart failure benefits from the blockade of inflammatory mediators. This study suggests that inflammation diminishing interventions may be able to strengthen existing therapeutic interventions that address the neurohormonal imbalances associated with heart failure.

Role of IL-1β in Intestinal Inflammation

IL-1β is highly involved in intestinal inflammatory cascades. Disruption of the intestinal mucosal barrier—often secondary to poor blood perfusion and congestion in heart failure—leads to the translocation of bacterial products and endotoxins into the systemic circulation. This systemic endotoxemia triggers the activation of the NLRP3-IL-1β axis, serving as a critical convergence point linking gut barrier dysfunction directly to cardiac pathology **(3)**

Role of IL-1β as an Inflammatory Biomarker

Due to its integral role in the early stages of the inflammatory cascade, IL-1β and its associated markers have been assessed to ascertain inflammatory activity in cardiac diseases. Identifying these markers helps distinguish patient populations that may benefit most from targeted anti-inflammatory treatments. Recent reviews of heart failure biomarkers suggest that incorporating IL-1β into a multi-marker strategy—alongside traditional natriuretic peptides—offers a promising approach to tackle the complex hemodynamic and inflammatory components of heart failure severity **(9).**

II Interleukin-10 (IL-10)

Definition

Interleukin-10 (IL-10) is an anti-inflammatory cytokine produced mainly by monocytes and macrophages. It inhibits the production of pro-inflammatory cytokines and regulates immune responses to maintain tissue homeostasis **(10).**

Structure

Interleukin-10 is a small, non-covalently associated homodimeric protein belonging to the class II cytokine family. Each monomer is predominantly composed of alpha-helical structures, and the biologically active cytokine interacts with a receptor complex containing IL-10R1 and IL-10R2 subunits. This alpha-helical architecture is structurally distinct from the beta-trefoil configuration characteristic of IL-1 family cytokines **(11).**

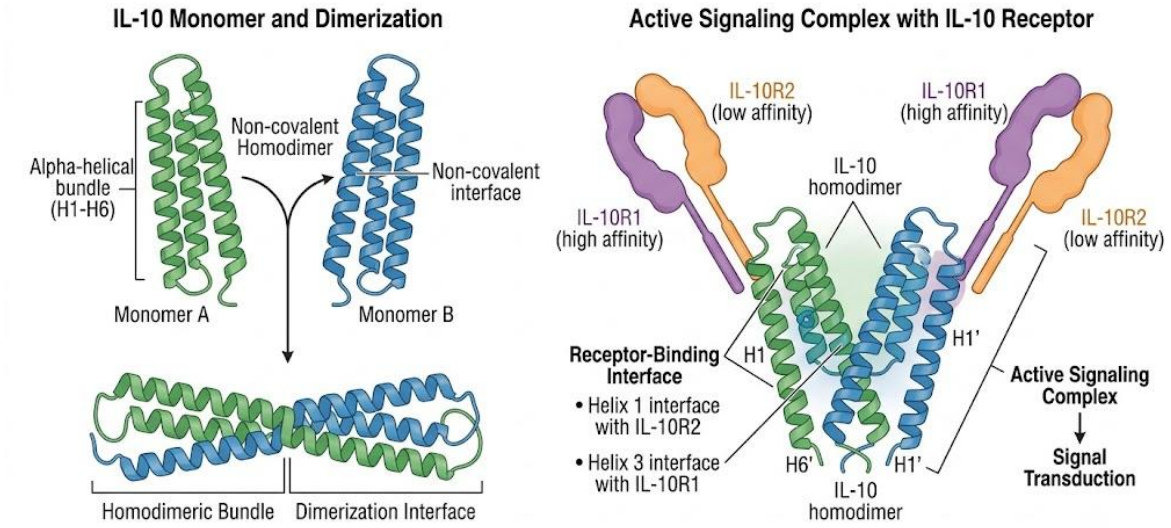


Figure 3. Schematic representation of interleukin-10 homodimerization and its interaction with the IL-10 receptor complex. **Source: Developed by the researcher based on Li and Yao (12).**

Biosynthesis and Secretion

IL-10 is produced as part of a counter-regulatory response following immune activation. Important cellular sources include regulatory T cells, alternatively activated macrophages, monocytes, B lymphocytes, and selected T-helper cell populations. Unlike IL-1β, which requires inflammasome-dependent processing before release, IL-10 is synthesized and released through the conventional secretory pathway. Its production helps restrict the duration and intensity of inflammatory responses and promotes the restoration of immune homeostasis **(8).**

Mechanism of Action

IL-10 initiates its biological effects by binding to a receptor complex composed of IL-10R1 and IL-10R2 subunits. Receptor activation stimulates the JAK/STAT3 signaling pathway, resulting in STAT3 phosphorylation and translocation into the nucleus. Activated STAT3 promotes the expression of anti-inflammatory and regulatory genes while suppressing NF-κB-mediated pro-inflammatory signaling. Through this mechanism, IL-10 counterbalances the inflammatory effects of pathways involving IL-1β and other pro-inflammatory cytokines **(11).**

Biological Functions

IL-10 limits inflammatory responses by reducing the production of pro-inflammatory cytokines and restricting the activation of monocytes and macrophages. It also decreases excessive antigen-presenting activity and supports regulatory immune-cell functions. These effects promote the resolution of inflammation, protect tissues against prolonged inflammatory injury, and contribute to the restoration of physiological homeostasis. Such anti-inflammatory regulation is particularly relevant in heart failure, where persistent inflammation is associated with myocardial dysfunction and disease progression **(8).**

Regulator mechanism.

The regulatory activity of IL-10 depends primarily on activation of the IL-10R/JAK/STAT3 pathway. Following receptor activation, STAT3 enters the nucleus and induces transcriptional programs that restrict inflammatory cytokine production and reduce NF-κB-mediated signaling. The balance between this anti-inflammatory pathway and opposing pro-inflammatory pathways influences the severity and persistence of immune-mediated myocardial injury in pediatric heart failure **(12).**

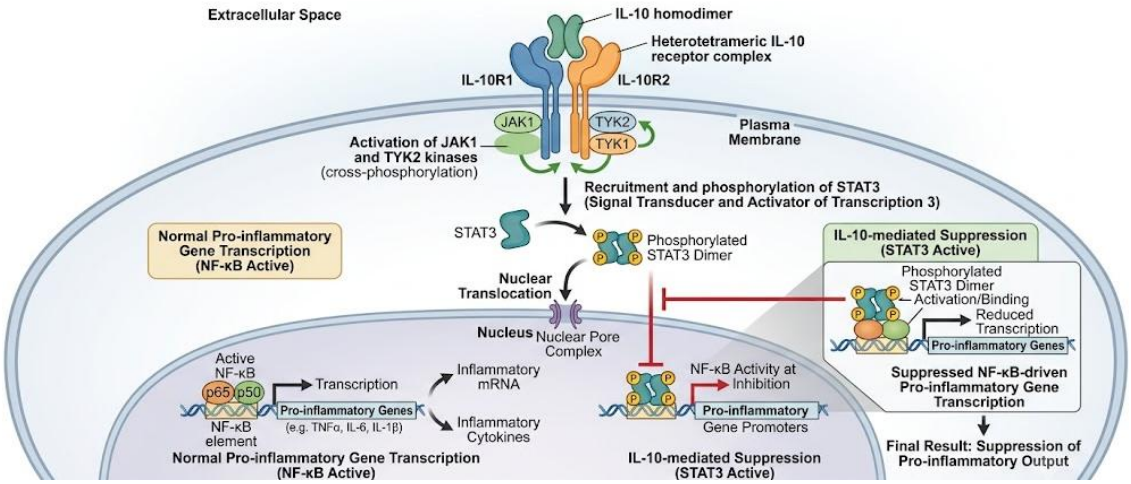


Figure 4. Schematic representation of the IL-10 signaling pathway showing JAK/STAT3 activation and suppression of pro-inflammatory signaling. **Source: Developed by the researcher based on Khider et al. (11).**

Clinical Significance

Clinically, IL-10 reflects the counter-regulatory immune response that limits excessive and prolonged inflammation. Its circulating level, particularly when interpreted alongside pro-inflammatory cytokines such as IL-1β, may provide a more comprehensive indication of the balance between inflammatory activation and immune regulation. Disruption of this balance may contribute to persistent myocardial inflammation, adverse cardiac remodeling, and the progression of heart failure. Therefore, assessment of IL-10 together with pro-inflammatory mediators may have potential diagnostic and prognostic value in inflammatory phenotypes of pediatric heart failure **(12).**

Role of IL-10 in Heart Failure

In heart failure, the extent of the mediated counter-regulation of IL-10 is thought to affect the extent of pro-inflammatory response caused by hemodynamic stress, neurohormonal activation, and gut-derived bacterial translocation . Isolated loss of IL-10 signaling in the context of stimulation is likely to cause unrestrained inflammatory injury and disease progression. This also supports the generalized assumption that the excess of mediators that causes inflammation and injury is not the only cause of the inflammation. **(11).**

Role of IL-10 in Intestinal Inflammation

Interleukin 10 (IL-10) has a prominent homeostatic function in the intestinal mucosa, suppressing the immune response to the large commensal microbial population present in the gut under normal conditions. With respect to heart failure-induced intestinal hypoperfusion and congestion with the increased permeability, while IL-10-mediated counter-regulation would be expected to limit the extent of the inflammatory response to bacterial translocation, insufficient IL-10 function would allow unconstrained cytokine response, worsening the systemic inflammatory response, and ultimately aggravate cardiac function (**13).**

Role of IL-10 as an Anti-inflammatory Biomarker

IL-10 can be utilized as a biomarker in conjunction with pro-inflammatory markers such as IL-1β. As an anti-inflammatory cytokine, IL-10 is a directly measurable circulating marker of counter-regulatory immune activity. The ratio of pro- and anti-inflammatory cytokines can provide more discriminative value and greater prognostic value than either marker used in isolation. **(11).**

III Relationship Between IL-1β, IL-10 and Left-to-Right Cardiac Shunts

Gut-Heart Axis

The integrated understanding of the gut-heart axis presented in Chapter II provides the clearest understanding of the interaction of IL-1β and IL-10 with left-to-right cardiac shunt lesions. Children with troublesome left-to-right shunts develop chronic pulmonary congestion with increasing congestion of the systemic veins. There is also a reduction in effective cardiac output, which impairs blood flow to the splanchnic circulation. These factors contribute to the development of gut inflammation and the resultant inflammatory signaling **(13).**

Mechanism of Intestinal Inflammation in CHD

In children with lesions causing left-to-right shunts, factors such as pulmonary overcirculation and decreased output of the systemic circulation contribute to the effects associated with heart failure, plus the barrier dysfunction caused by the surgery of cardiopulmonary bypass, and overcirculation dysbiosis. In already existing cardiac diseases in children, barrier dysfunction of the intestinal system, and dysbiosis, are increased by cardiopulmonary bypass surgery, which helps to understand the structural problems of the heart and leads to the inflammation of the intestines **(14).** Studies of the dysbiosis of the intestinal microflora in children with heart problems shows shifts in the intestinal microflora occur early, and suggests that the cardiac shunts are the initial cause of the dysbiosis in the gut (**15).**

Cytokine Imbalance in Decompensated Heart Failure

In tension-dependent decompensation of left-to-right shunt-related heart failure, the balance of the pro-inflammatory activity, dominated by the signaling pathway of IL-1β, is shifted toward a predominance of pro-inflammatory activity. This shift occurs in opposition to the counter-regulatory activity of IL-10. With heart failure from congenital heart disease (CHD), the Gut-Brain Axis of the Gut Microbiome presents the evidence of the disturbed shunt circulation of the gut-brain (blocked by cytokine inflammation) and the connection between the shunt-related metabolic dysfunction and systemic inflammation. This evidence was derived from metabolomic studies of CHD that show shunt-related disorders (**16).**

Role of IL1β, IL10 in Gut-Heart Axis.

Determining how IL-1β, IL-10, and the gut-heart axis interact with left-to-right cardiac shunts is clinically relevant to closing the shunt, . Research on IL-1β and IL-10 proves that early closure of the shunt can prevent the establishment of a self-sustaining cycle of hemodynamic compromise, intestinal barrier breakdown, and cytokine imbalance. This may also limit the inflammatory burden that the child experiences, as well as the potential negative impacts on the child's growth and neurodevelopment caused by the inflammation (**17).**

Measuring IL-1β and IL-10 either separately or as a composite pro-/anti-inflammatory ratio is important for gauging potential diagnostic value. This may assist routine echocardiographic assessment and biomarkers of heart failure severity in children with left-to-right shunts. This measurement also assesses inflammatory disease severity that may help complement imaging of heart and shunt structure, and hemodynamics. This measurement also aligns with several studies that are promoting multi-marker biomarker paradigms for cardiorespiratory and heart failure in children (**9).**

Beyond diagnosis, the degree of cytokine imbalance may have prognostic importance, as it could reveal children who are more at risk of developing decompensated heart failure, pulmonary vascular disease, and Eisenmenger physiology, the left to right shunt complications. This may also help in the future to classify which children would benefit the most from early surgery or from anti-inflammatory techniques which are being considered in the other heart failure patients. (**5).**

Strong mechanistic evidence connects IL-1β with cardiovascular and intestinal inflammation and excessive inflammation is restrained by IL-10's immunoregulatory function. Most literature on congenital heart disease (CHD) in children focuses on IL-1. Therefore, there is still much to discover on the role of IL-10. Children with left-to-right shunt lesions and heart failure have been neglected in research on the IL-1/IL-10 axis. This is a significant area for further exploration and justifies the necessity for a thorough future study on the IL-1β/IL-10

axis balance. Such an evaluation may serve as both a diagnostic and prognostic instrument to children with left-to-right cardiac shunts. This research addresses current evidence gaps **(12).**

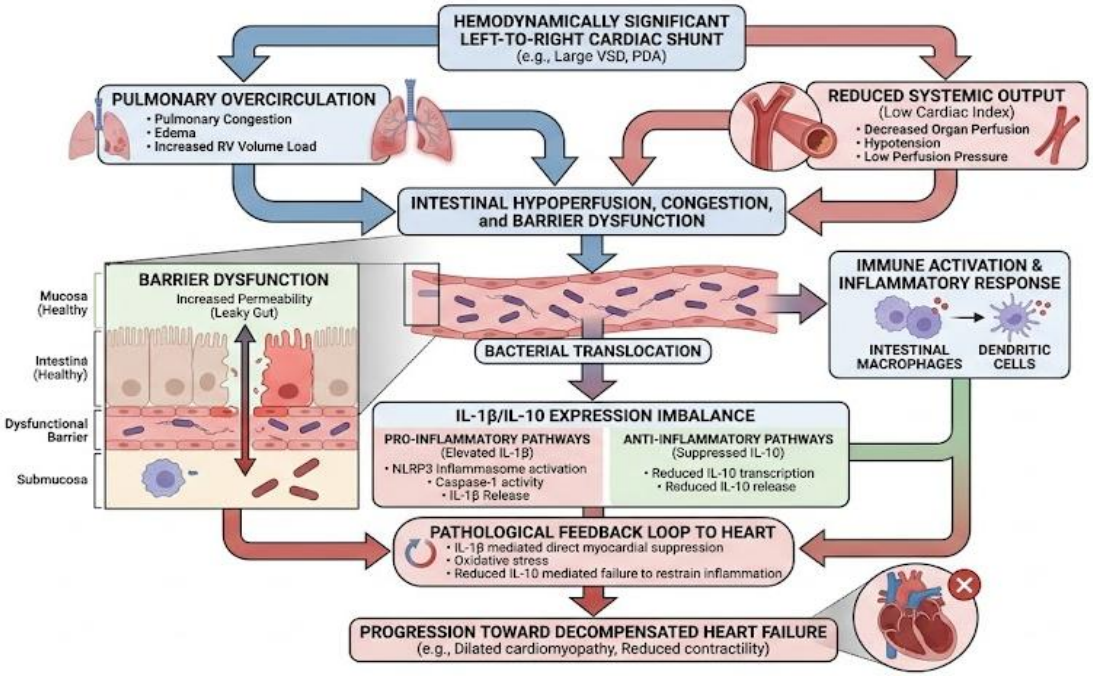


Figure 5. Proposed mechanism linking left-to-right cardiac shunts, intestinal barrier dysfunction, IL-1β/IL-10 imbalance, and the progression of heart failure**. Source: Developed by the researcher based on Li and Yao (12).**

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