Inflammatory Cytokines In Heart Failure: Role in Etiology and Utility As Biomarkers

By

Ebtihag Hamdi
Definition of cytokines

Soluble small protein molecules, secreted by one cell, that can alter behaviour or properties of the cell itself or another cell.
Families of cytokines

- INFs
- Chemokines
- Members of TNF family
- Hemopoietins (ILs)
- EGF family (EGF, TGF\(\alpha\))
- FGF1
- Cysteine knots (TGF\(\beta\) including activin A, VEGF, PDGF)
- CSFs
Cytokine hypothesis

HF progresses, at least in part, as a result of toxic effects exerted by endogenous cytokine cascade, on myocardium and peripheral circulation.

Expression occurs once LV dysfunction is triggered (not initiating).
Cytokine hypothesis

Increased levels (especially sTNFRs) appear to be strong predictors of mortality than traditional prognostic factors (LVEF, NYHA class, \(O_2\) consumption, wasting).

Persistent activation is independent of etiology.

Biomarkers or contributors??
Cytokines: nature and properties

- Regulate immune responses and host response to infection.
- Are communication molecules between immune cells and ECs.
- Are either proinflammatory or anti-inflammatory.
- Cascade initiated by IL-1 by stimulating release of IL-2, IL-6, TNFα.
- Interaction with their receptors is mandatory.
- Role of inhibitors?
Stimuli for production

- Autoimmunity
- Infection / endotoxin
- Mechanical overload, shear stress
- Ischemia, hypoxia
- Ox-LDL, ROS, AII

Inflammatory cytokines in HF
- TNF$\alpha$
- IL-1$\beta$
- IL-6
- Chemokines (MCP-1, IL-8)

Cellular and cardiac events
Cytokines

$\uparrow$ TNF$\alpha$

Molecular and cellular changes
- Reexpression of fetal gene program
- Expression of inflammatory cytokines
- Alterations in MMP/TIMP-balance
- Decreased $\beta$-adrenergic responsiveness
- Altered $\text{Ca}^{2+}$-homeostasis

Structural changes
- Myocyte hypertrophy
- Ventricular dilatation
- Fibrosis
- Leukocyte infiltration

Heart failure
IL-13
TGF-β
Leptin

MCP-1
IL-1β
TNFα
IL-8

IL-4
IL-1Ra
IL-10
sTNF-Rs

IL-13
TGF-β
Leptin
What causes ↑ inflammation in HF?

- Autoimmunity and variable microbes, promoting persistence of inflammation (IDCM).
- Chlamydia pneumoniae, cytomegalovirus – antigens cause myocardial damage (ischemic CM).
- GI tract endotoxins – trigger immune activation during edema episodes.

Antimicrobials and role in HF??
A pathogenic role?

- Effects on contractility, hypertrophy, ↑ apoptosis enhancing remodeling.
- ↑ cytokine myocardial expression of adhesion molecules, TNFα and IL-6, cytokine and chemokine receptors suggesting a role.
- ↑ cytokine expression in circulating leucocytes at protein and mRNA levels especially in coronary circulation (myocardial stretch, esp. IL-6).
CV actions of cytokines

- **IL-6**: ↑ SNS activation, ↑ BP.
- **TNFα**: involved in AII-mediated responses as salt appetite, LVH, HTN.
- **IL-10**: ↓ TNFα, Cox-2 in brain, sympathoexcitation in HF (rat model).

Neurogenic HTN relates to vascular inflammation.

↑ cytokines damages blood-brain barrier.

Inhibition of inflammatory cytokines improves cardiac function.
TNF-\(\alpha\)

- Promotes cardiomyocyte apoptosis, \(\downarrow\) ECM, \(\uparrow\) ROS.
- \(\downarrow\) contractility, possibly mediated by NO, is adaptive during ischemia-reperfusion, but maladaptive later – role in stunning.

Alters intracellular Ca homeostasis, hence \(\rightarrow \downarrow\) contractility.

- At low concentration, it adaptive (short-term), \(\uparrow\) concentration is maladaptive (long-term).
- TNFR_{II} correlates with poor short-term prognosis.
- Correlates with baseline PCP.
TNF-α

- Down regulates cNOS → endothelial dysfunction.
- Stimulates other cytokines (IL-1, IL-6, TNFα itself, IL-8)
- ↓ IGF-1, ↓ mitochondrial energy transfer in skeletal muscles.
- TNFα receptor-1 – abundant, produces ill effects
- TNFα receptor 2 – more protective.
- Action is reversible.
Other effects of TNF-α

- Anorexia
- Cachexia
- Insulin resistance
- Activation of iNOS
  - ↓ skeletal muscle blood flow
- Fibrotic factor
  - ↑ O₂ consumption
- Regulation of MMP, TIMP, impact on remodeling.
How does plaque instability occur?

- Role in triggering SMCs apoptosis.
- ECM synthesis inhibited.
- IL-8 $\rightarrow$ migration and proliferation of SMC.
- Possible calcification (TGF-β).
- Angiogenesis.
Adverse biological effects of inflammatory cytokine cascade in chronic heart failure

I. Heart

- Promotion of left ventricular remodeling, dilatation.
- Depression of cardiac contractility.
- Abnormalities of intracellular calcium handling, $\beta$ adrenergic signalling.
- Cardiomyocyte hypertrophy.
- Cardiomyocyte apoptosis.
- Cardiac fibrosis, collagen production.
Adverse biological effects of inflammatory cytokine cascade in chronic heart failure

II. Vasculature

- Progression of atherosclerosis.
- Oxidative stress
- NO impairment.
- Vasoconstriction.
- Endothelial cell apoptosis.
- Adverse vascular remodeling.
Adverse biological effects of inflammatory cytokine cascade in chronic heart failure

III. Skeletal muscle

- Decreased skeletal muscle blood flow.
- Anabolic/catabolic imbalance.
- Inhibition of protein synthesis.
- Skeletal muscle cell apoptosis.
- Cachexia.
Side-effects of INF\(\alpha\), IL-2, TNF\(\alpha\)

*When given as treatment may produce:*

- Flu-like symptoms, ↑ sleep, ↓ appetite, malaise, depression.
- Memory and cognitive impairment, possible confusion or aggressive behaviour.
CV drugs: effects on inflammatory cytokines

- **ACEI** (↓ IL-6)
- **Big dose of enalapril**, (↓↓↓ IL-6 and septal thickness)
- **Candesartan** (↓ TNFα, ↓ IL-6)
- **β-blockers** (↑ IL10, ↓ TNFα)
- **Carvedilol** (downregulates IL-6)
- **Amlodipine** (↓ IL-6, no change in TNFα)

**But:**
- Effects are minimal
- Immunomodulation is needed.
Results with anti-TNF$\alpha$ are not encouraging.

1. Etanercept (sTNF receptors).
2. Infliximab (antibody).
3. IL-2 receptor monoclonal antibody (DacllIximab).

RECOVER, RENAISSANCE, RENEWAL, ATTACH
Immunomodulatory therapy: A possible therapy?

**Pentoxifylline:**
- platelet antiaggregant, ↓ TNFα production – some benefit in IDCM.

**IV immunoglobulins**
- ↓ apoptosis, TNFα, IL-1β, chemokines
- ↑ IL-10

**Immunoadsorption**
Lowering cholesterol – welcomed or not?

Benefit in ischemic HF, since atherogenic lipid profile correlates with inflammatory cytokines.

Statins control iNOS, eNOS expression and proapoptotic effect of cytokines on SMC.

Inhibit MCP-1, $\downarrow$ ox-LDL, $\downarrow$ sVCAM-1 – $\downarrow$ chemotaxis and neutrophil endothelial interactions.

$\downarrow$ TNF$\alpha$, IL-1, IL-6 from macrophages.
Other influences on TNFα

- Vesnarinone, pimobendan, amrinone.
- Aspirin
- Adenosine
- Amiodarone
- Digitalis
- Cortisol
- n-3 polyunsaturated FA.
- TIMP (Batimastat)
- Vitamin D (↑ IL-10)
- Physical exercise
- VAD
Prognostic implications

↑ inflammatory cytokines and chemokines relate directly to deterioration of NYHA class and cardiac function.

Better prognosis if TNF$\alpha < 6.5$ pg/ml.

TNF$\alpha$, IL-6, TNFRs 1,2 are independent predictors of mortality in advanced HF (VEST).

TNFR-1 strongest prognosticator independent of HF severity.
Prognostic implications

So, ↑ cytokines is not only an epiphenomenon, but may reflect or cause important pathologic changes in chronic advanced HF.

Is it practical to measure?

In whom?

what therapy?