Biomarkers in Heart Failure

Inflammatory Markers in Heart Failure

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Overview

- Evidence of cytokine hypothesis
- Characteristics of inflammatory markers in heart failure
- Immune modulation in heart failure

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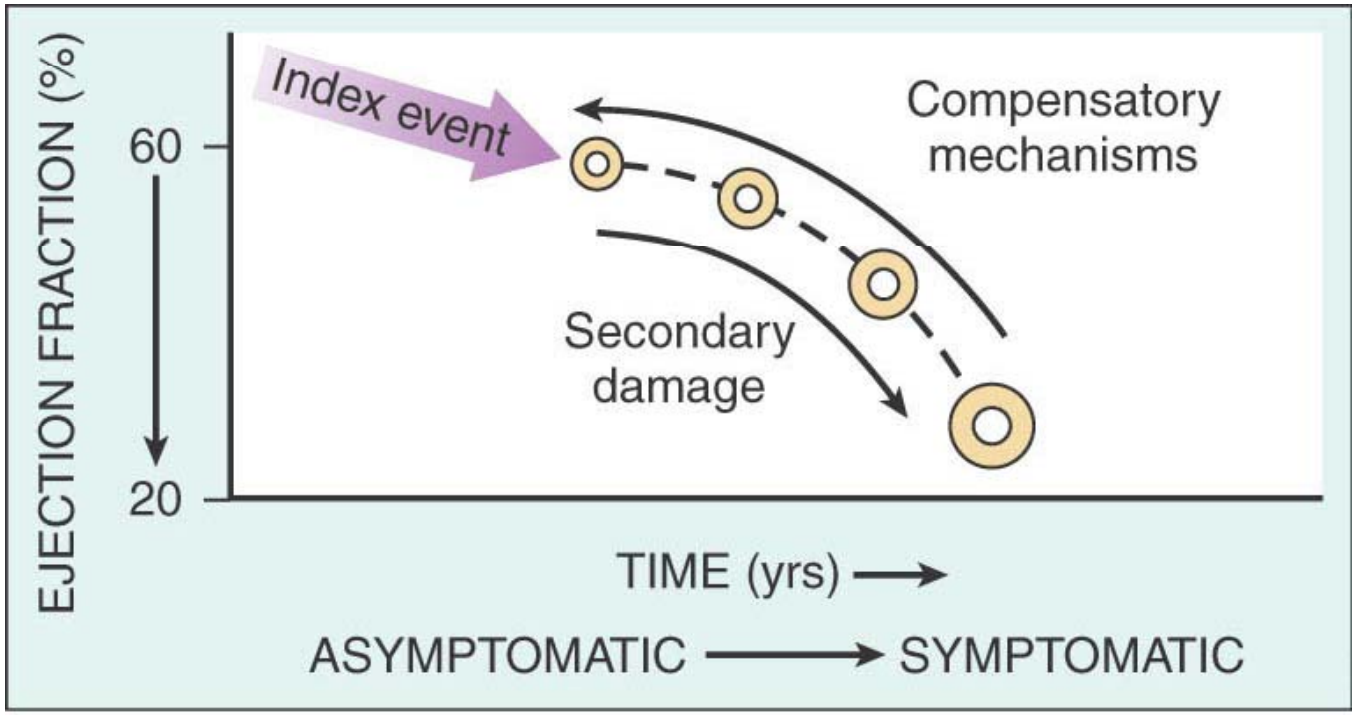
- **Evidence of cytokine hypothesis**
- **Characteristics of inflammatory markers in heart failure**
- **Immune modulation in heart failure**

Pathogenesis of Heart Failure



Hemodynamic

↓

Neurohormonal

+

Cytokine system

Mechanisms and models in HF: A combinatorial approach. Circulation 100:99, 1999

Inflammatory cytokines in Heart Failure

- Inflammatory cytokines in patients with heart failure were first described in 1990
- Tumor Necrosis Factor (TNF) levels were measured in 33 patients with chronic heart failure, 33 age-matched healthy controls
- Results: Circulating levels of TNF are increased in patients with chronic heart failure and this elevation is associated with the marked activation of the renin-angiotensin system seen in patients with end-stage cardiac disease

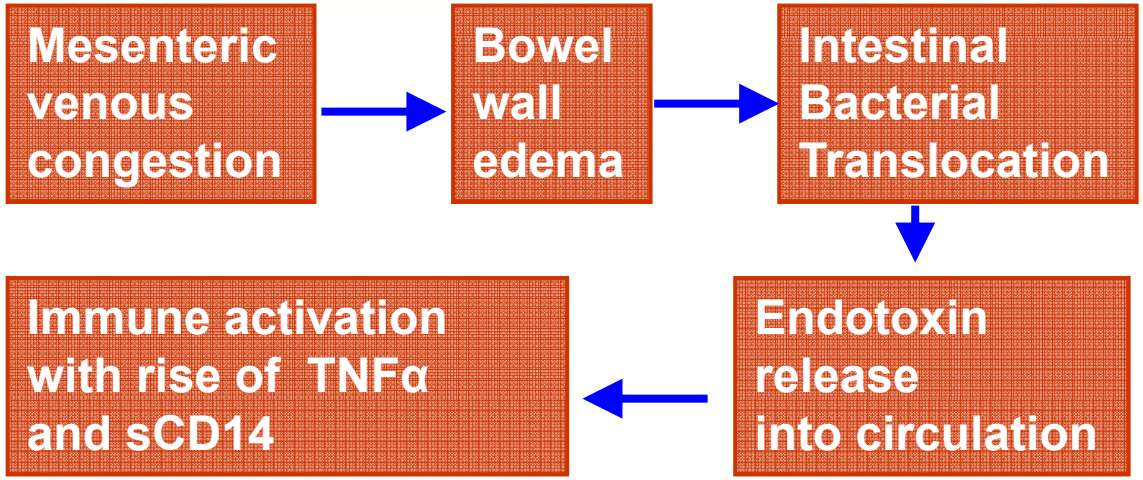
Levine B, KalmanJ et al.N EnglJ Med. 1990;323(4):236-41

Cytokine Hypothesis

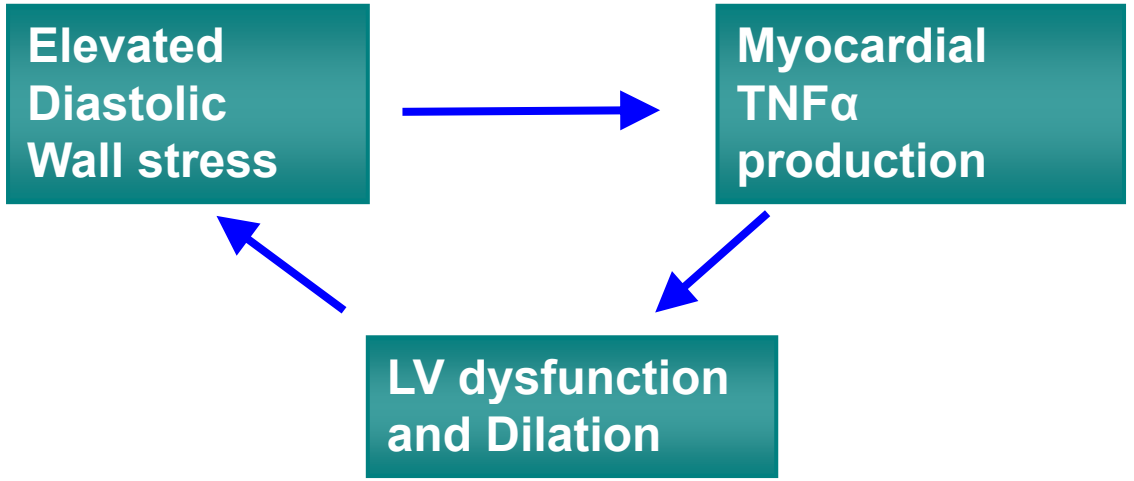
- Heart failure progresses, at least in part, as a result of the toxic effects exerted by endogenous cytokine cascades on the heart and the peripheral circulation

How are cytokines activated in heart failure?

- Endotoxin-induced cytokine production



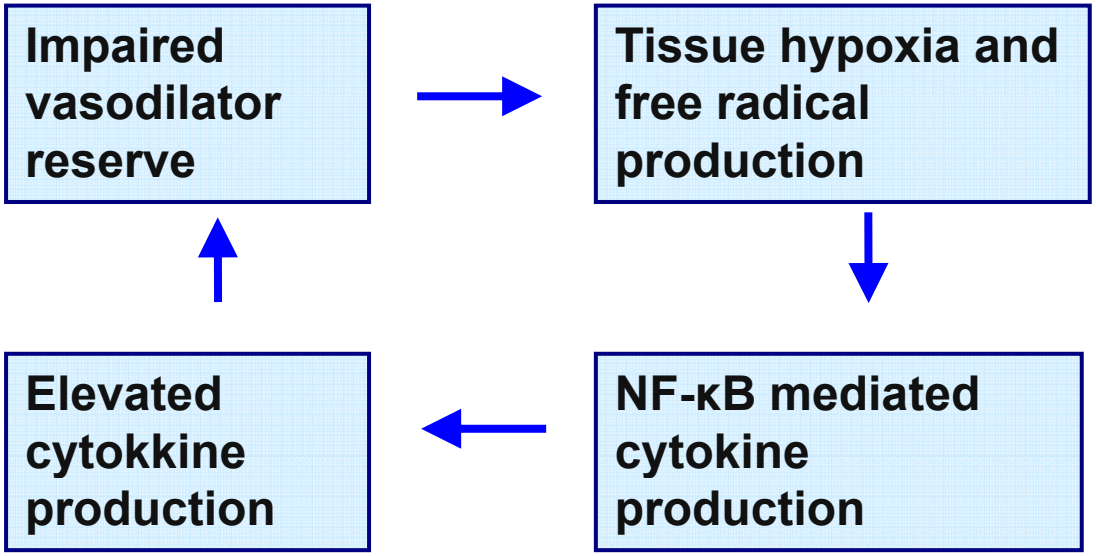
- Myocardial cytokine production



European Journal of Heart Failure 1 1999 309-312

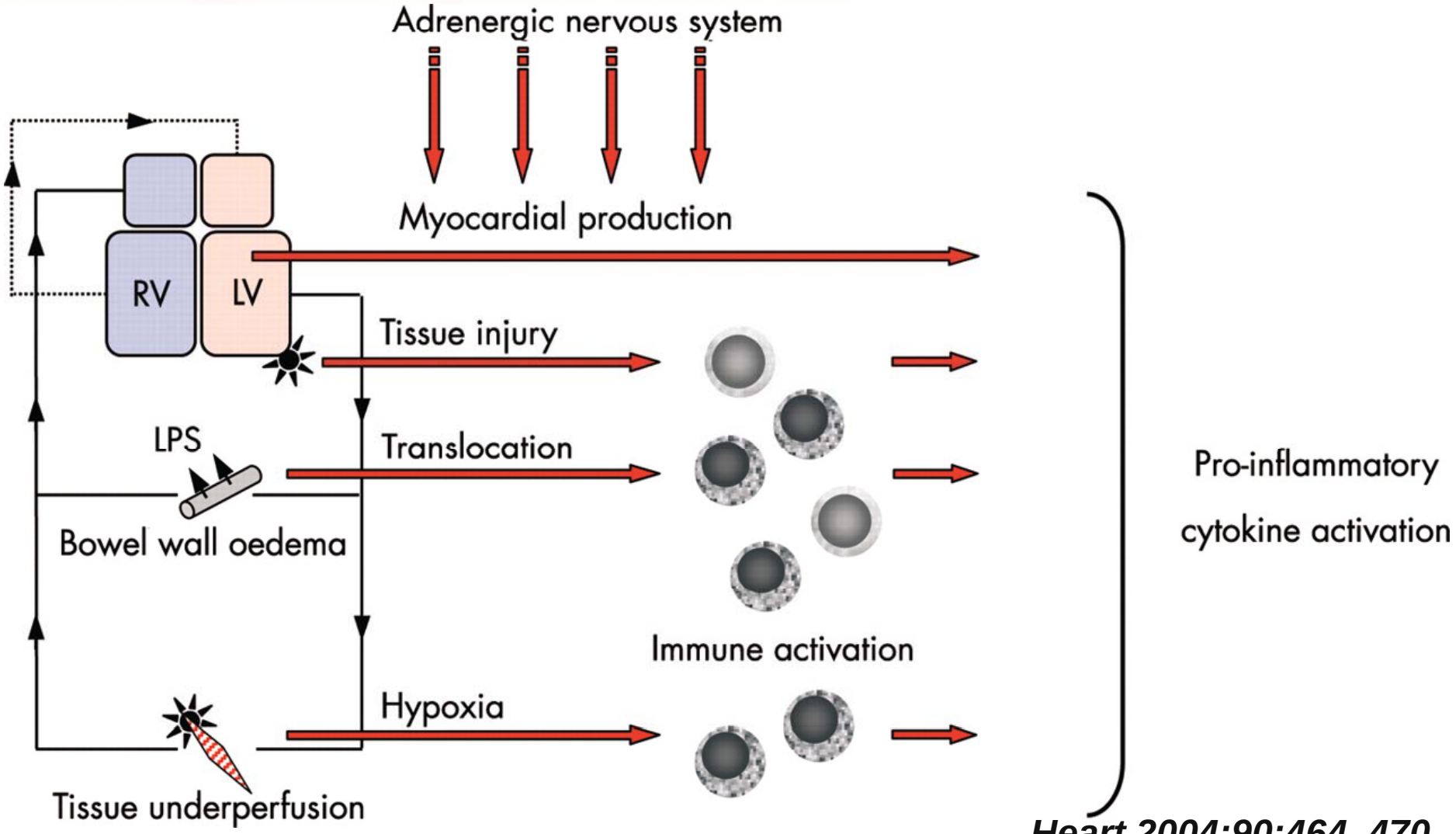
How are cytokines activated in heart failure?

- Extramyocardial cytokine production



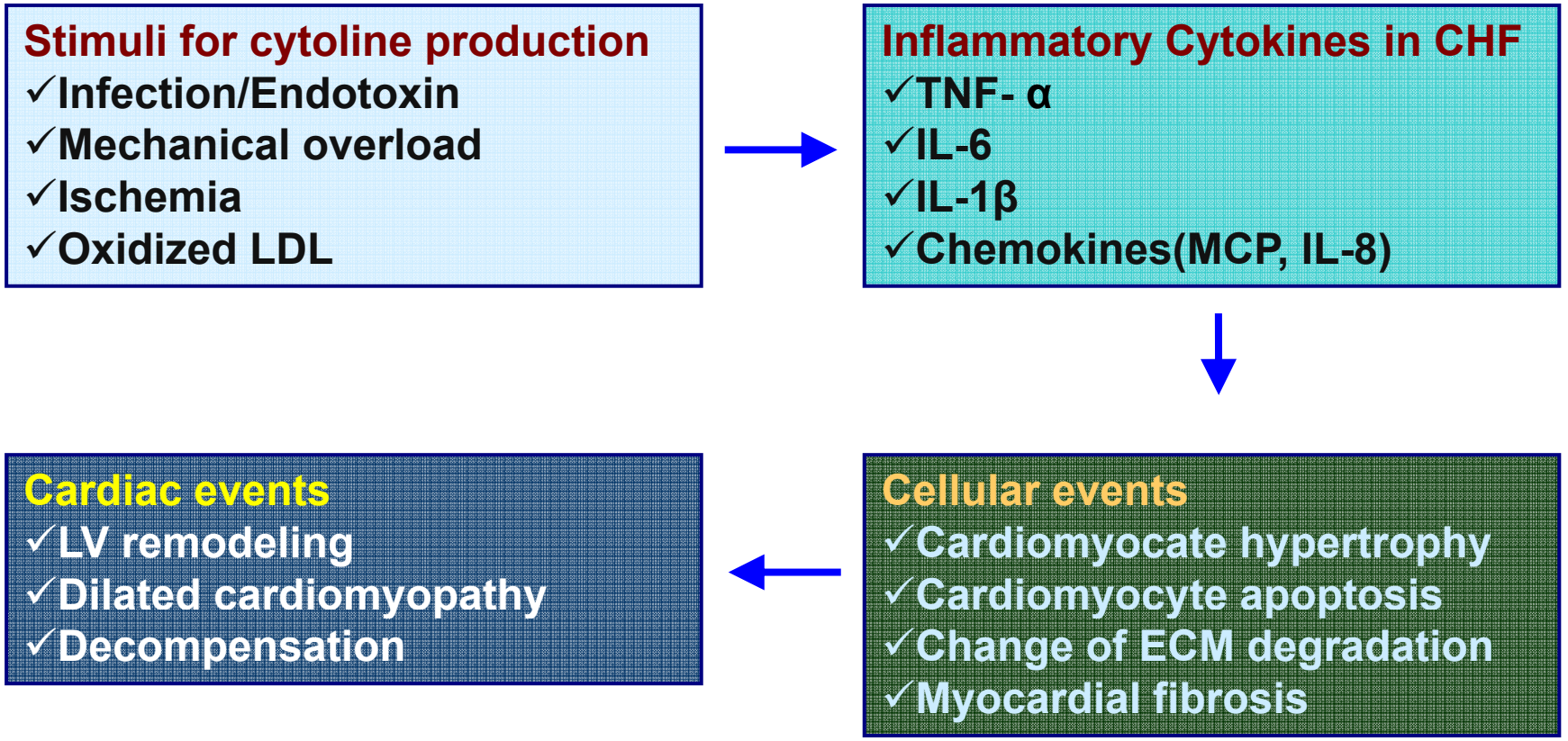
European Journal of Heart Failure 1 1999 309-312

How are cytokines activated in heart failure?



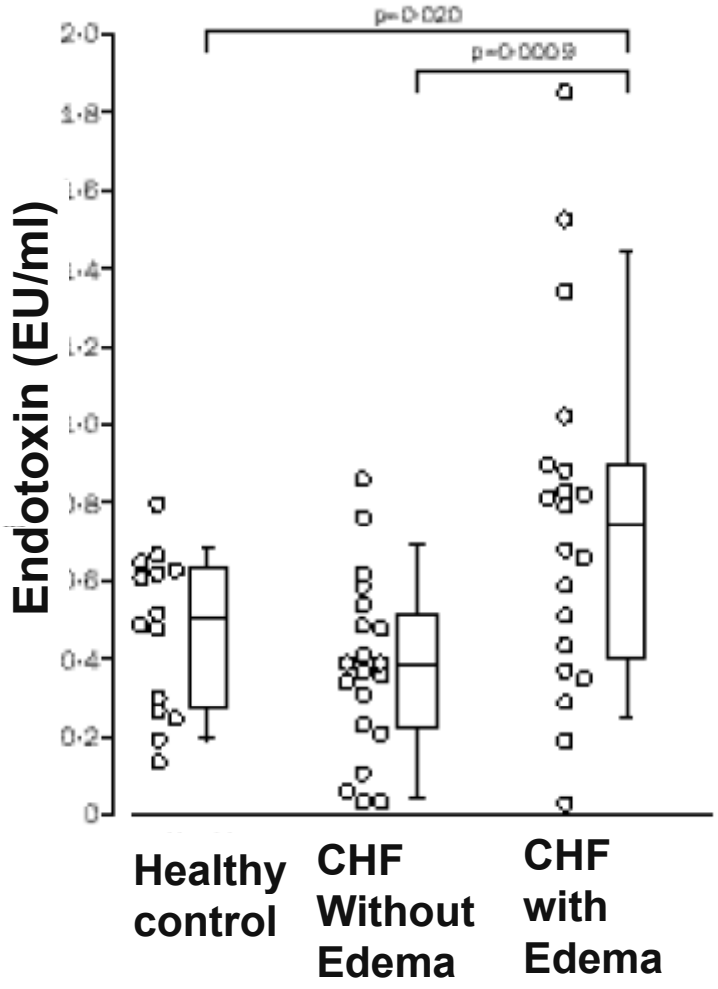
Heart 2004;90:464–470.

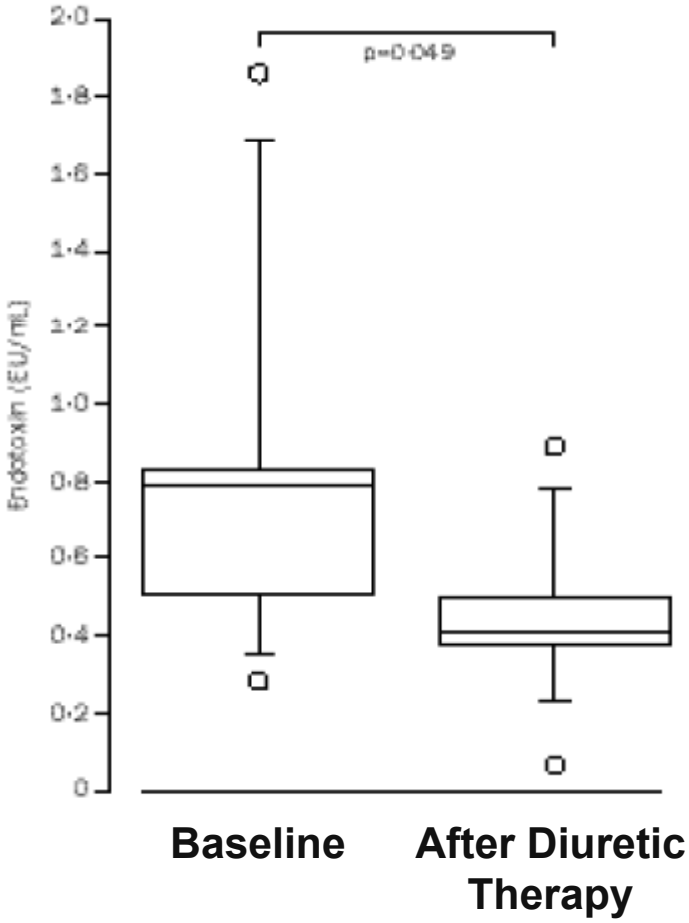
Cytokines as pathogenic mediators of chronic heart failure



DamåsJK et al Curr Control Trials Cardiovasc Med.2001;2 (6): 271–277

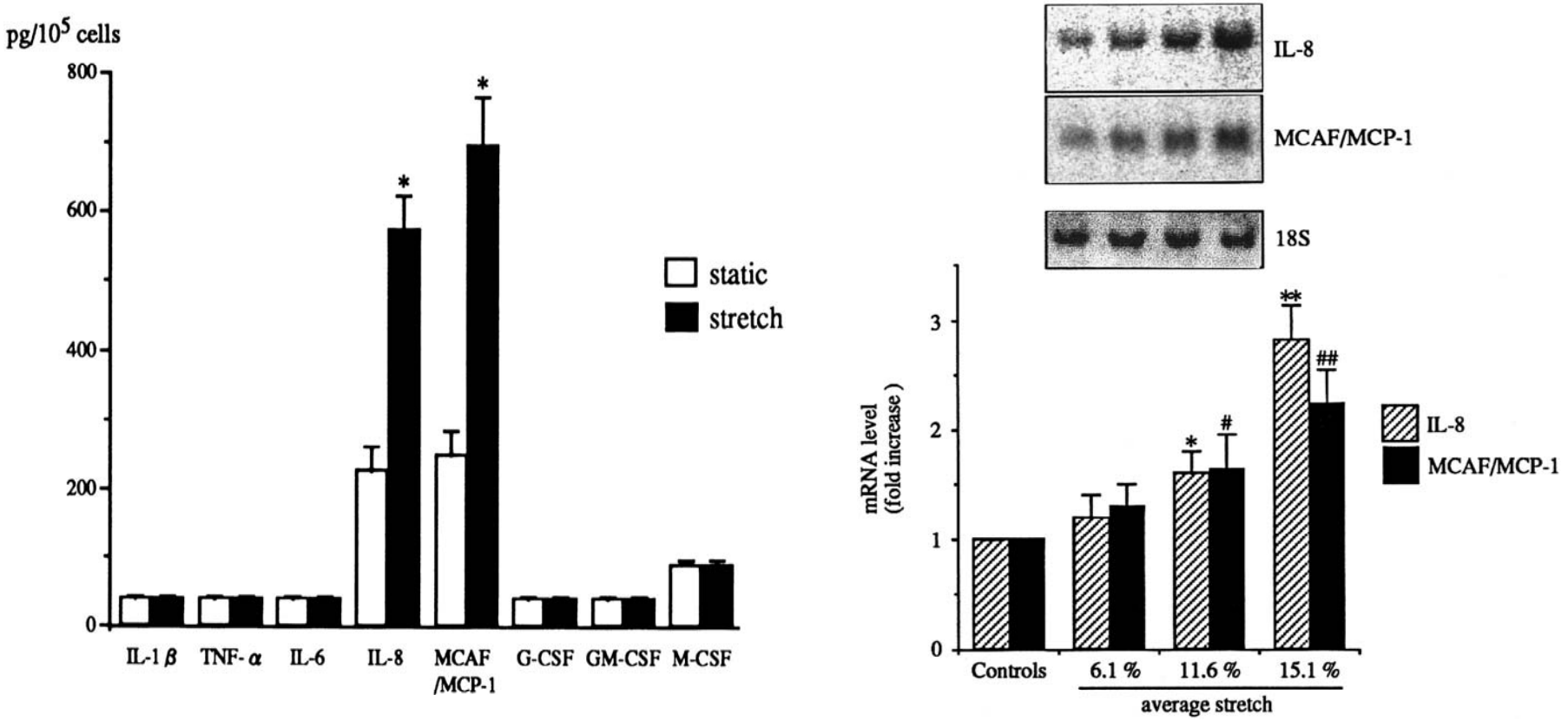
Endotoxin induced cytokine production in chronic heart failure





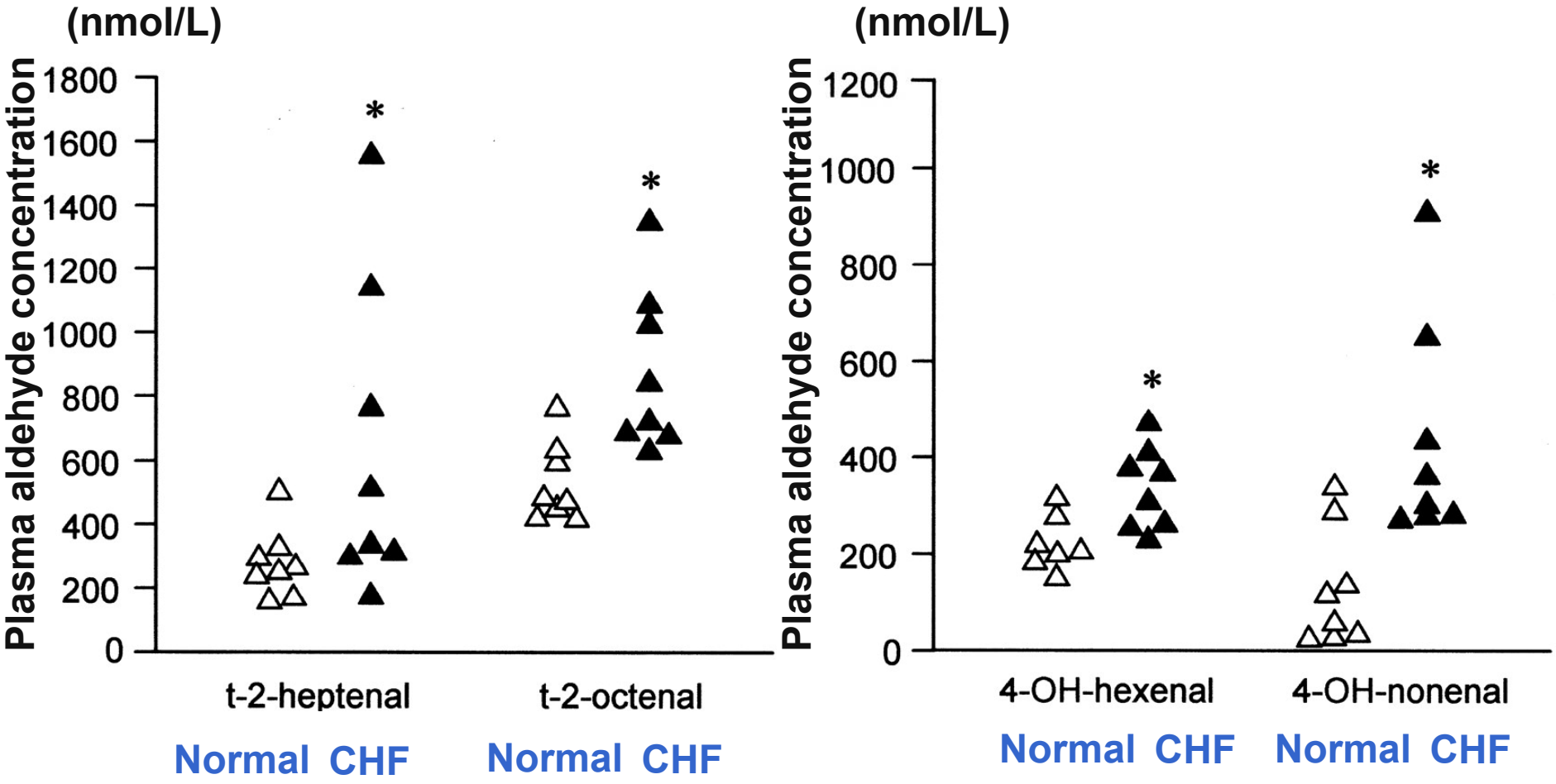
Lancet 1999; 353 : 1838 – 42

Cellular stretch stimuli induce upregulation of cytokine production



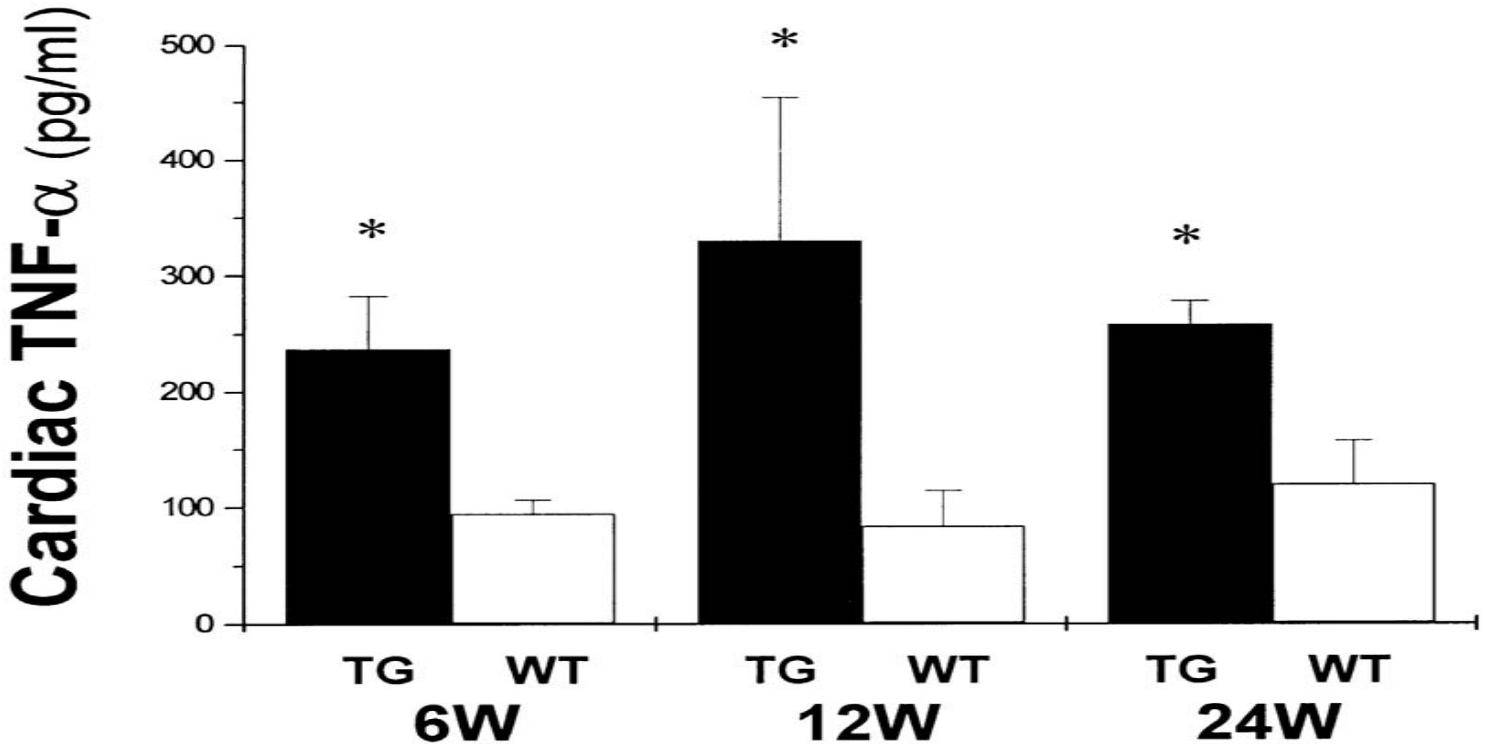
Arteriosclerosis, Thrombosis, and Vascular Biology. **1998;18:894-901**

The Oxidative Stress Hypothesis of Congestive Heart Failure



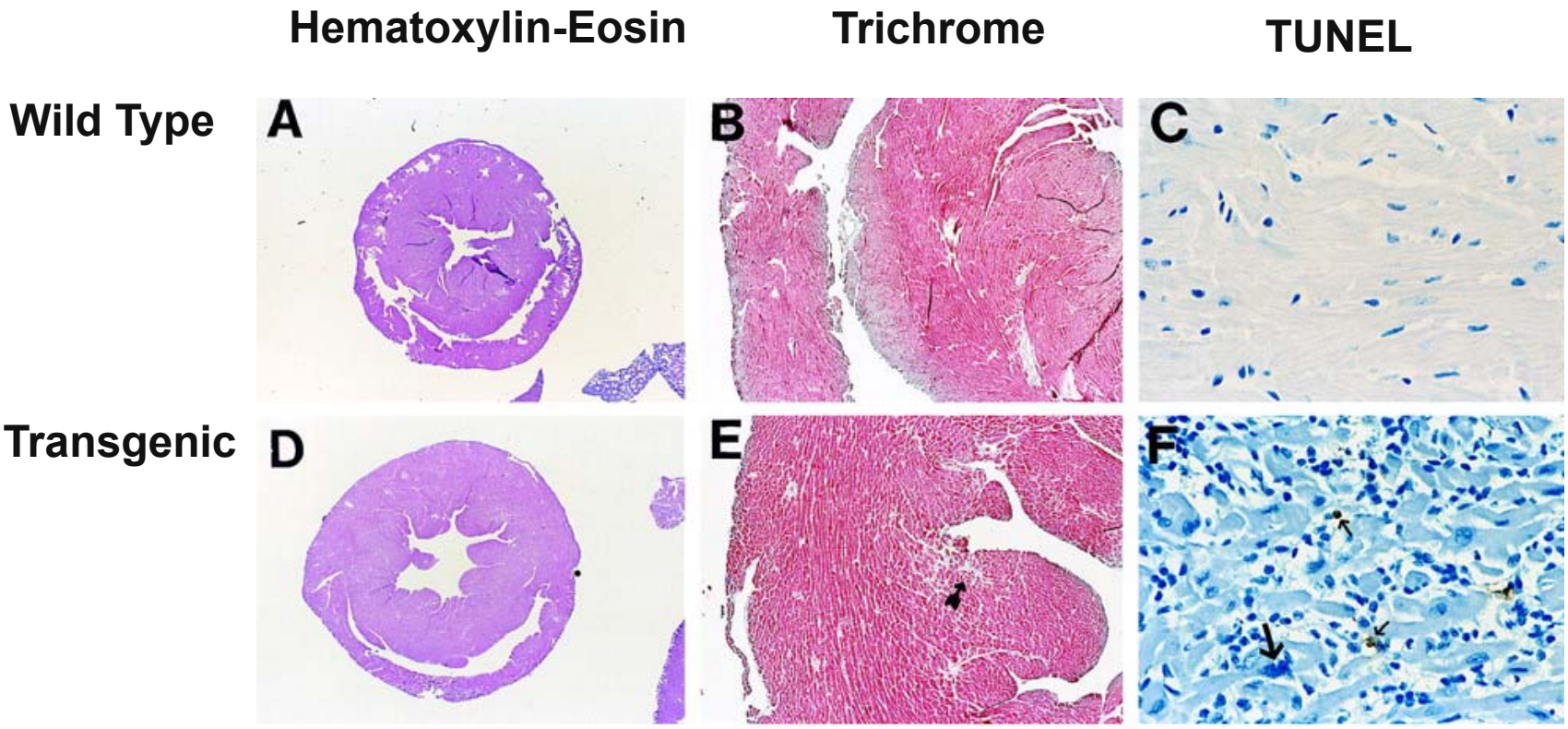
Chest. 2001;120:2035-2046.)

TNF- α levels in TNF-α transgenic mice (TG) and wild-type control mice (WT)



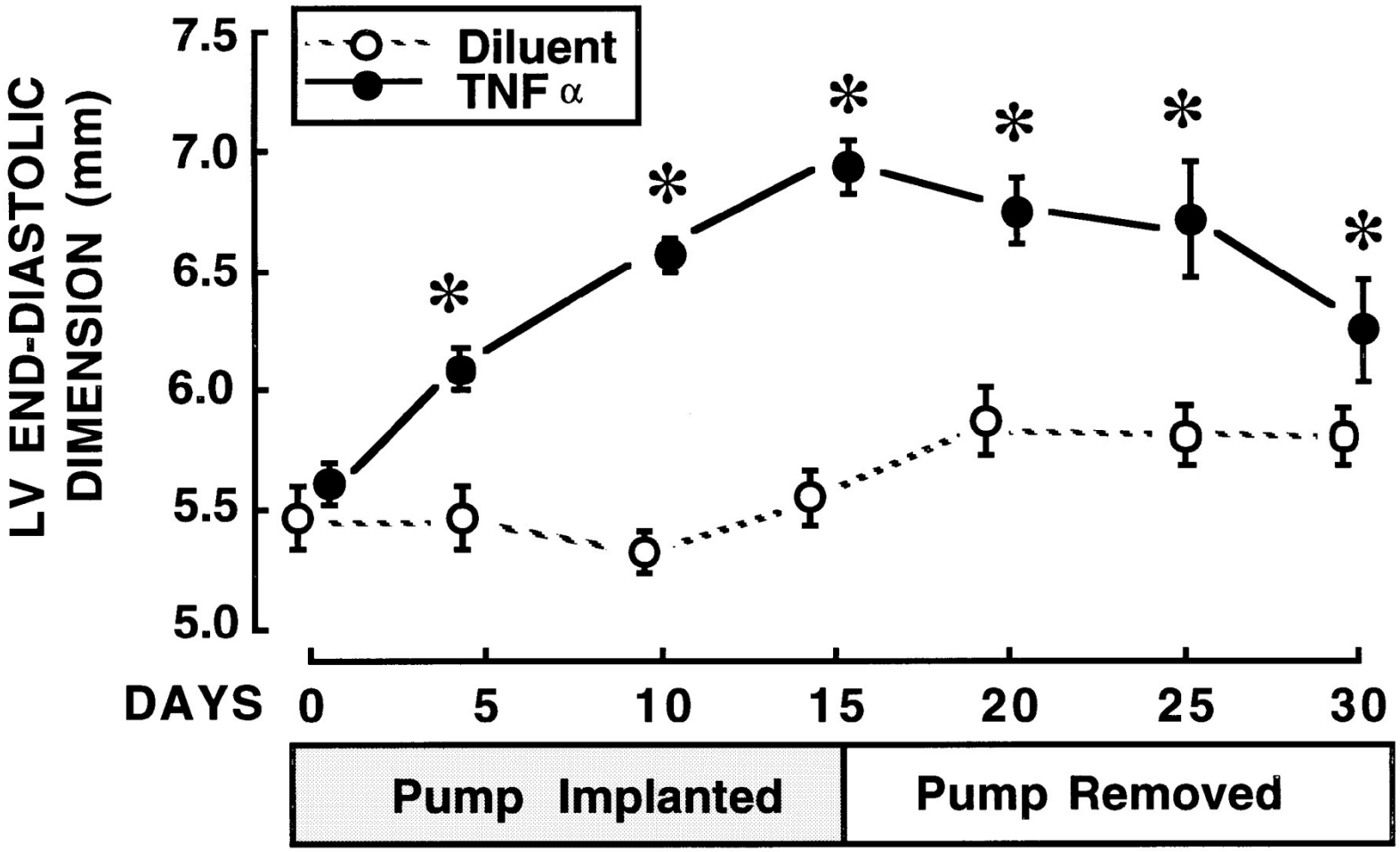
Circ Res. 1997;81:627–635

Histopathologic change in TNF-α transgenic mice



Circ Res. 1997;81:627–635

Effects of a Continuous Infusion of TNF- α on LV Structure



Evidence of cytokine hypothesis

- Myocardial wall stress, ischemia , oxidative stress, bacterial endotoxin promote inflammatory cytokine (TNF-α, IL-6, IL-1β, MCP-1, IL-8) production in heart failure

- Inflammatory cytokines play a pathogenic role by effect on both myocyte and nonmyocyte.

- The relative importance of the stimuli for cytokine production in various forms of CHF is uncertain.

Overview

- Evidence of cytokine hypothesis
- **Characteristics of inflammatory markers in heart failure**
- Immune modulation in heart failure

Inflammatory Mediators in Heart Failure

- Inflammatory Cytokines
  - ✓ TNF-α
  - ✓ IL-6, IL-1β vs IL-10
  - ✓ Cardiotrophin
- C-reactive protein
- Adhesion molecule
  - ✓ ICAM, VCAM, Integrin, Selectin
- Nitric oxide
- Leukocyte subsets : CD3+, CD68+

TNF-α

- First described in 1975,
- Cachectin
- 2 TNF-α receptors :

✓ Expressed by almost all nucleated cells

✓ TNFR1

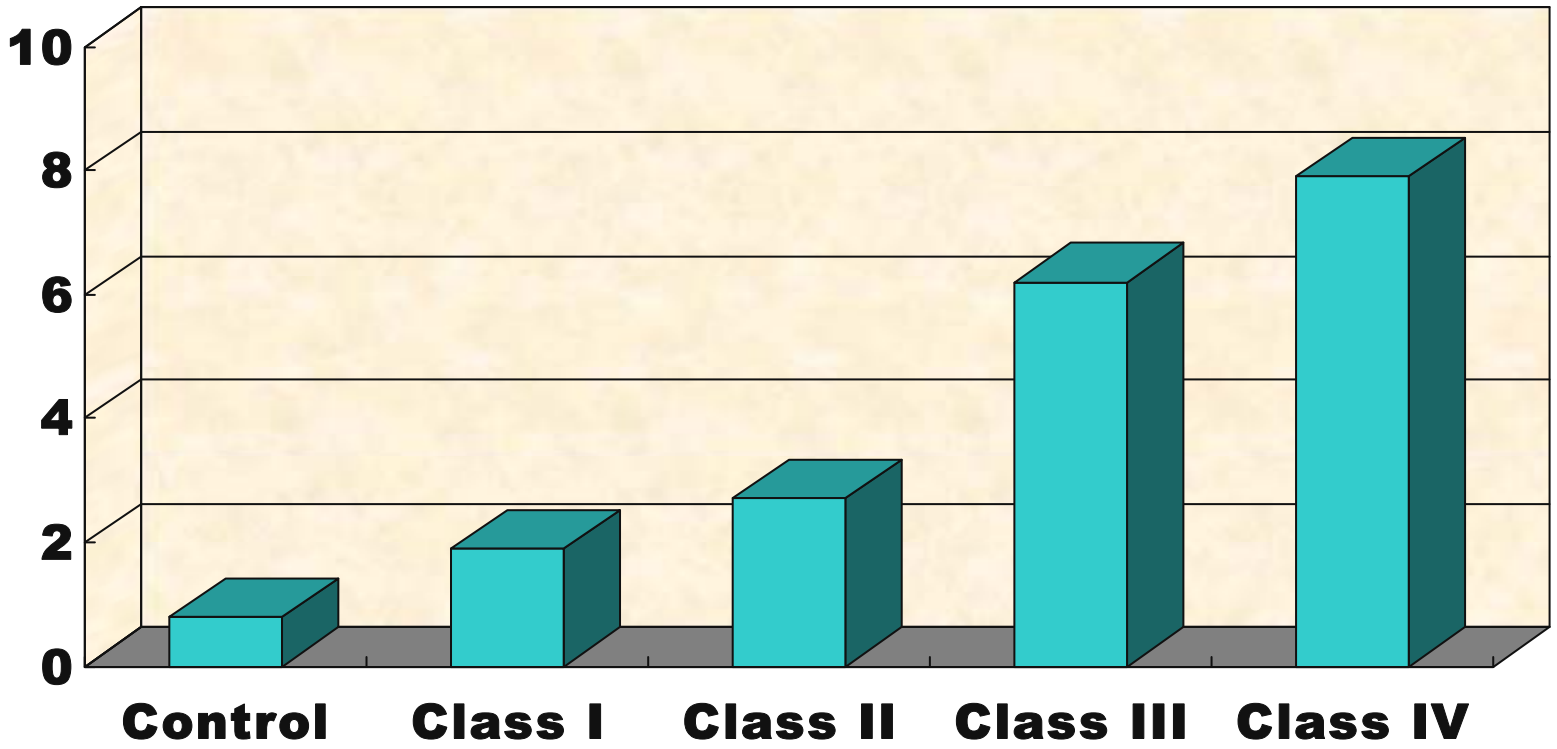
- main signalling receptor
- deleteroious effect

✓ TNFR2

- Appears to have protective role

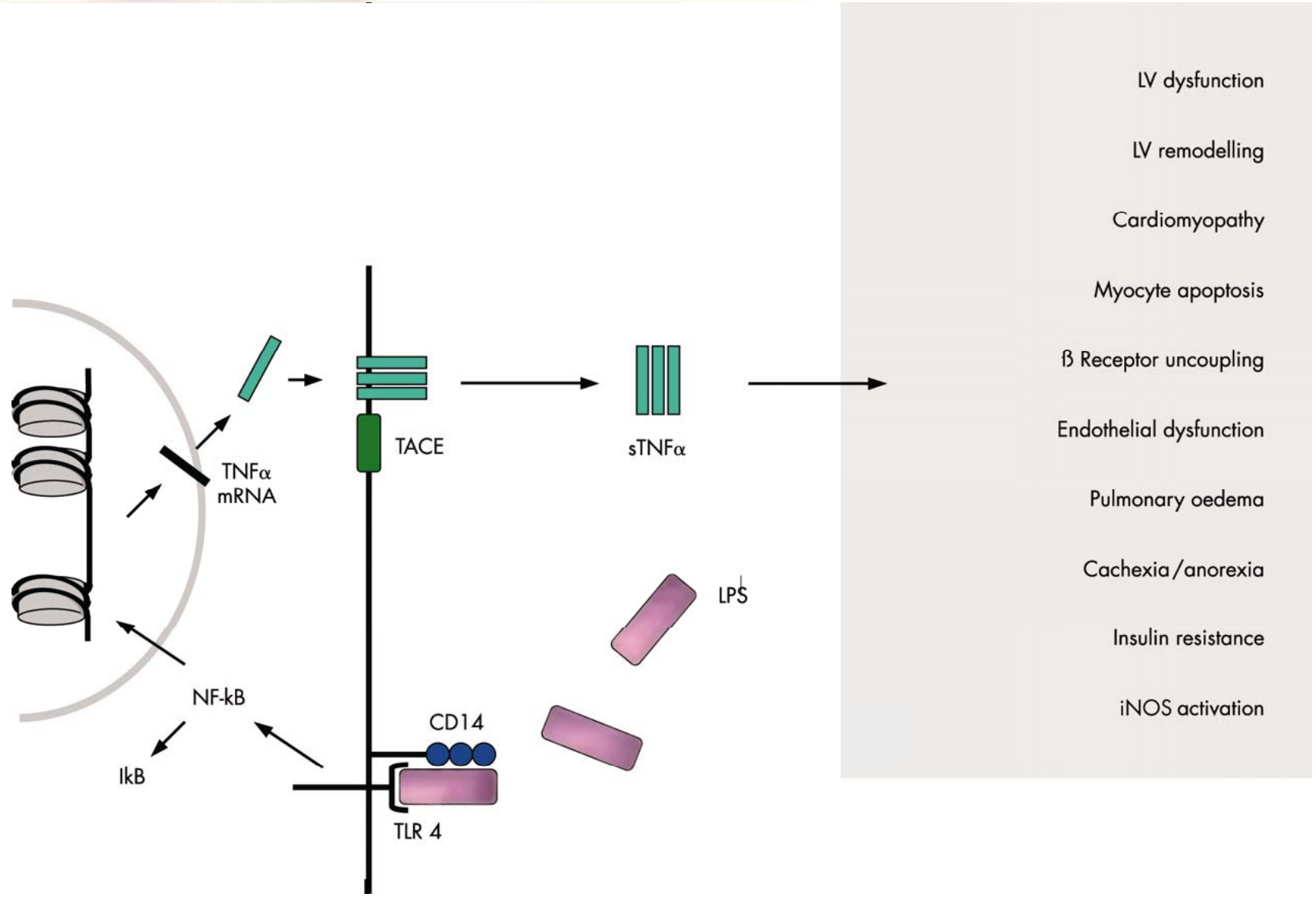
- Soluble TNF receptors : predict prognosis better than TNFα

Levels of TNF-α according to NYHA functional clas



Seta Y. *J Card Fail.* 1996;2:243–249

TNF-α signaling pathway and TNF- α mediated effects



Interleukin-6

- Released in direct response to TNFa : linear correlation
- Induce hypertrophic response of myocyte and block cardiac myocyte apoptosis
- While increased concentrations of IL-6 were found to be associated with a poorer prognosis in CHF patients, those of the soluble IL-6 receptor (IL-6R) were not.

Interleukin-1

- Pro-inflammatory cytokines, not much known
- Demonstrated in in patients with DCM and it depresses myocardial contractility in a dose dependent fashion.
- Being involved in myocardial apoptosis, hypertrophy, and arrhythmogenesis

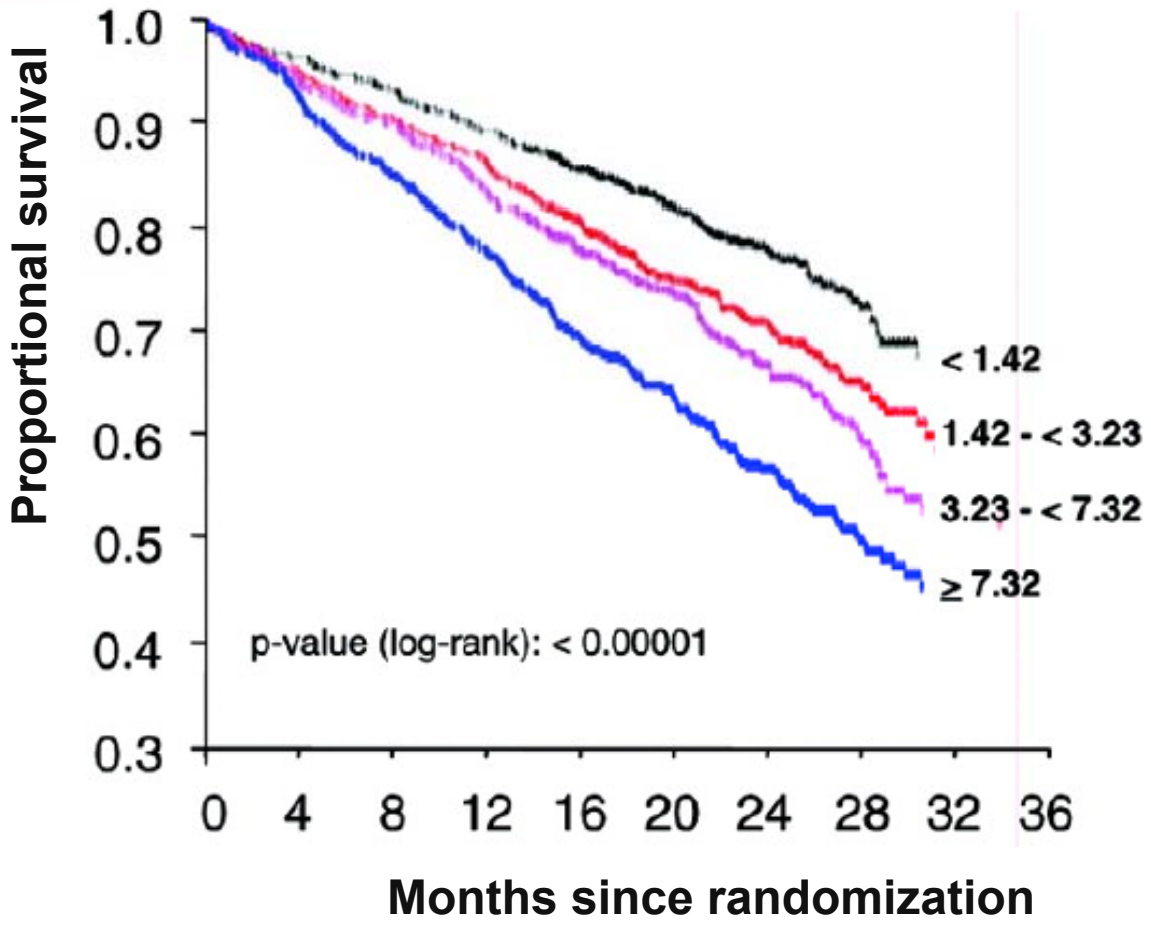
C-reactive protein

- Found in 1930.
- Reacts with the somatic C polysaccharide of Streptococcus pneumoniae

→Activate classical complement pathways

- Exclusively produced in the liver
- Secreted in increased amounts within six hours of an inflammatory stimulus and is therefore regarded as a marker of acute inflammation.

Val-HeFT : Plasma CRP level and survival



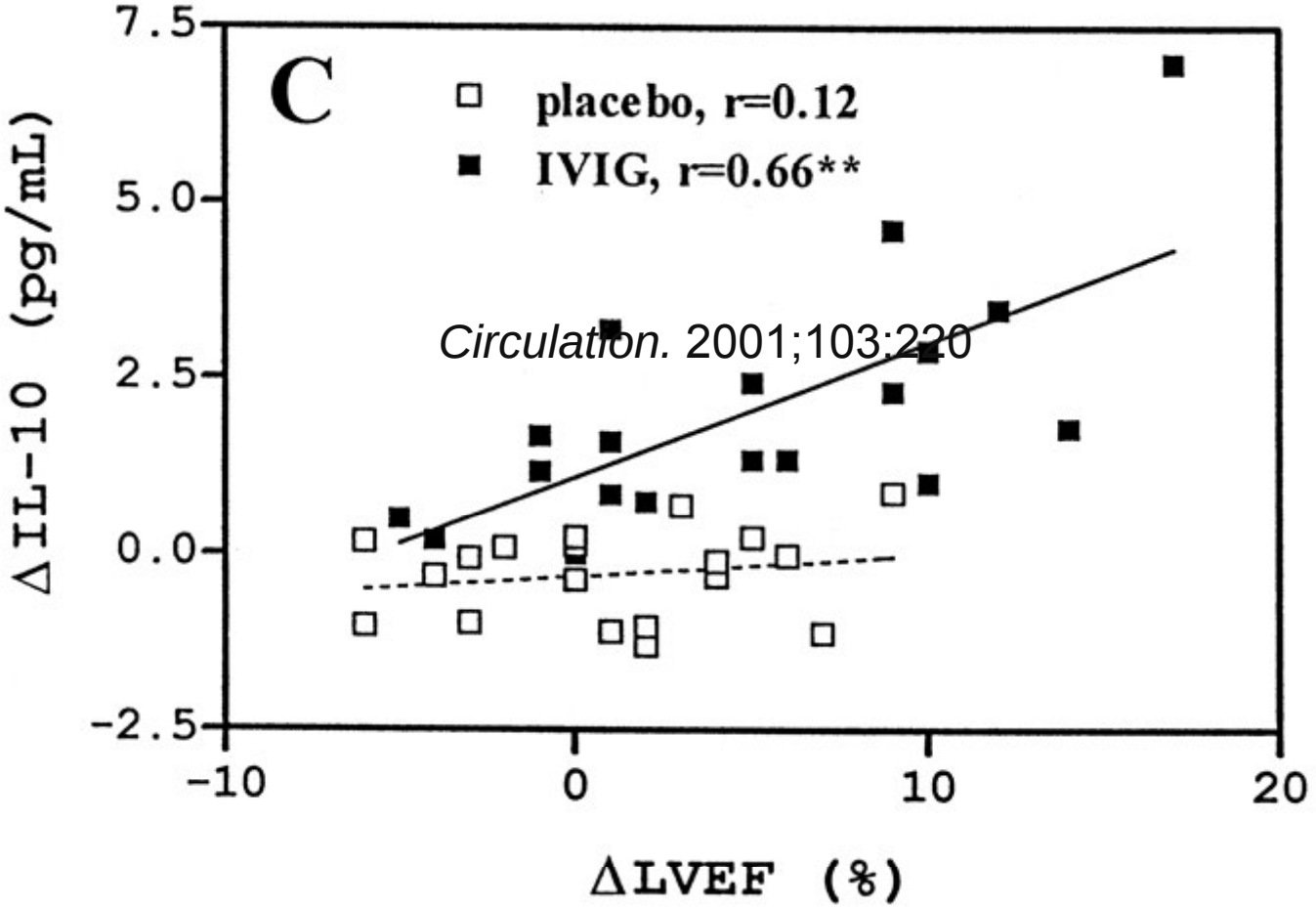
Anand IS, *Circulation 2005: 112;148*

Interleukin-10

- IL-10 is one of the most important anti-inflammatory cytokines down regulating the production of TNFa, IL-1, and IL-6, respectively.
- IL-10 also enhances the release of soluble TNFR which contributes to the reduction of TNFa activity.
- Increased or decreased in CHF patients
- IVIG → Increase IL-10 → improved LVEF

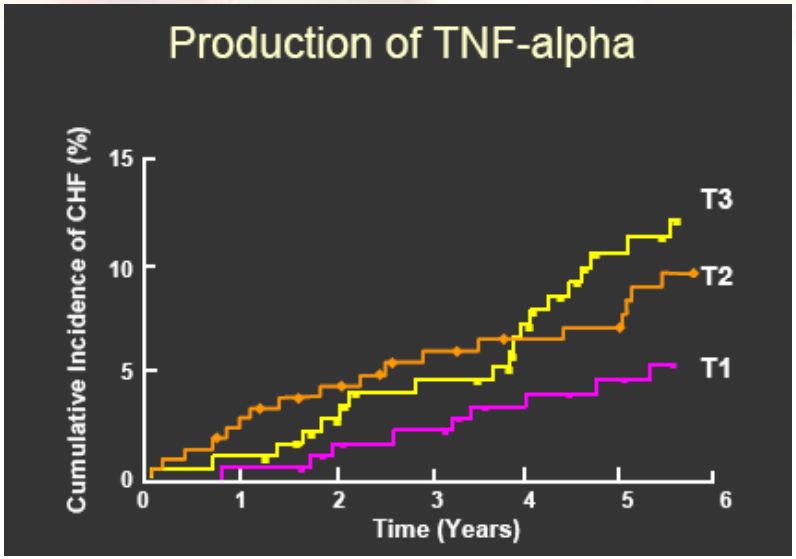
: may offer therapeutic potentials in CHF

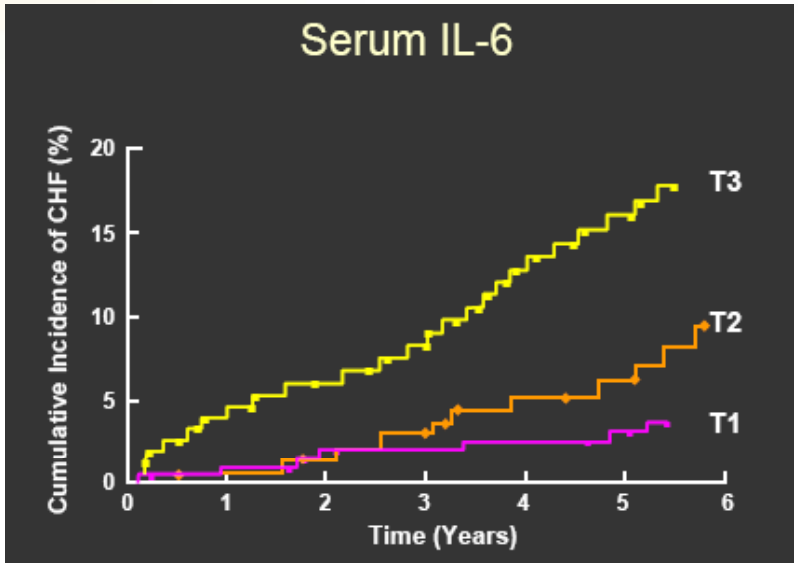
Correlations between absolute change in LVEF and IL-10 after use of IVIG

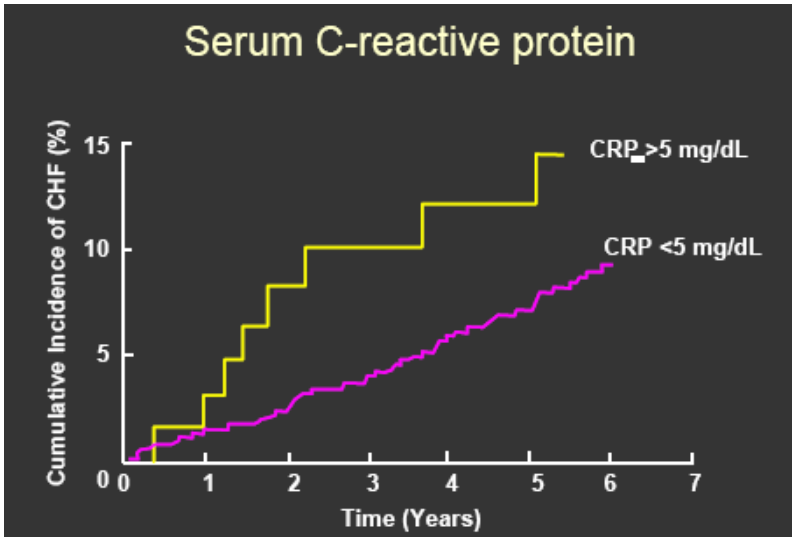


Lars Gullestad , *Circulation.* 2001;103:220

Framingham Heart Study : Inflammatory markers and risk of new onset heart failure

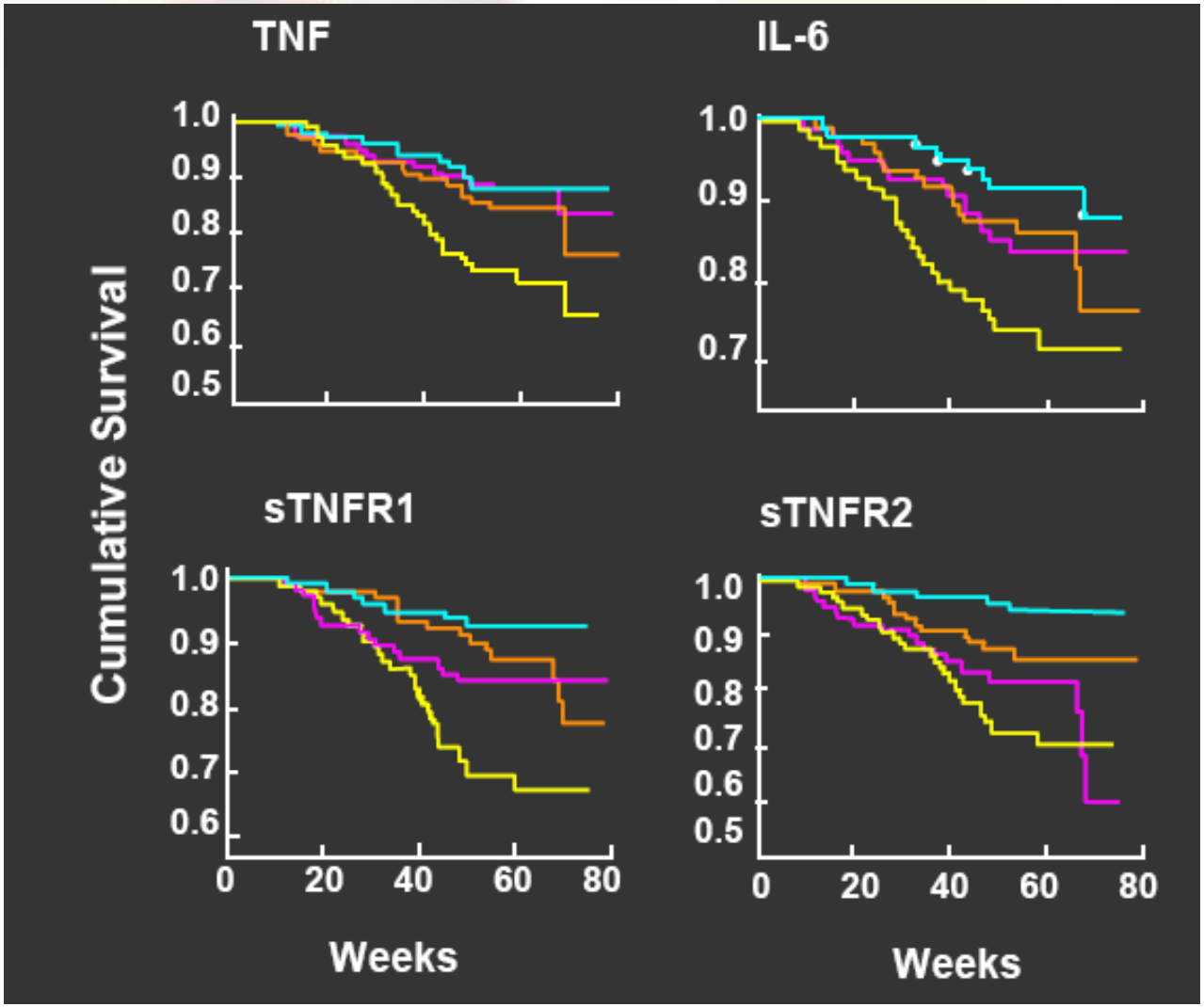






Vasan RS , Circulation 2003;107:1486

VEST : Plasma level of inflammatory mediator and survival



Deswal A et al, Circulation 2001;103:2055

Characteristics of inflammatory markers in heart failure

- While unable to establish cause and effect relationship inflammatory markers appear to be elevated relatively early in the disease process NYHA class I or II → potential role of the use of such markers to predict new-onset HF.

- A variety of studies have demonstrated that inflammatory cytokines are elevated in patients with HF in concordance with disease severity

- TNF-α, IL-6, TNFR1, and TNFR2 were all significant independent predictors of long-term mortality.In this analysis, the soluble TNF-α receptors, TNFR1 and TNFR2, were the most powerful predictors of longterm mortality,

Overview

- Evidence of cytokine hypothesis
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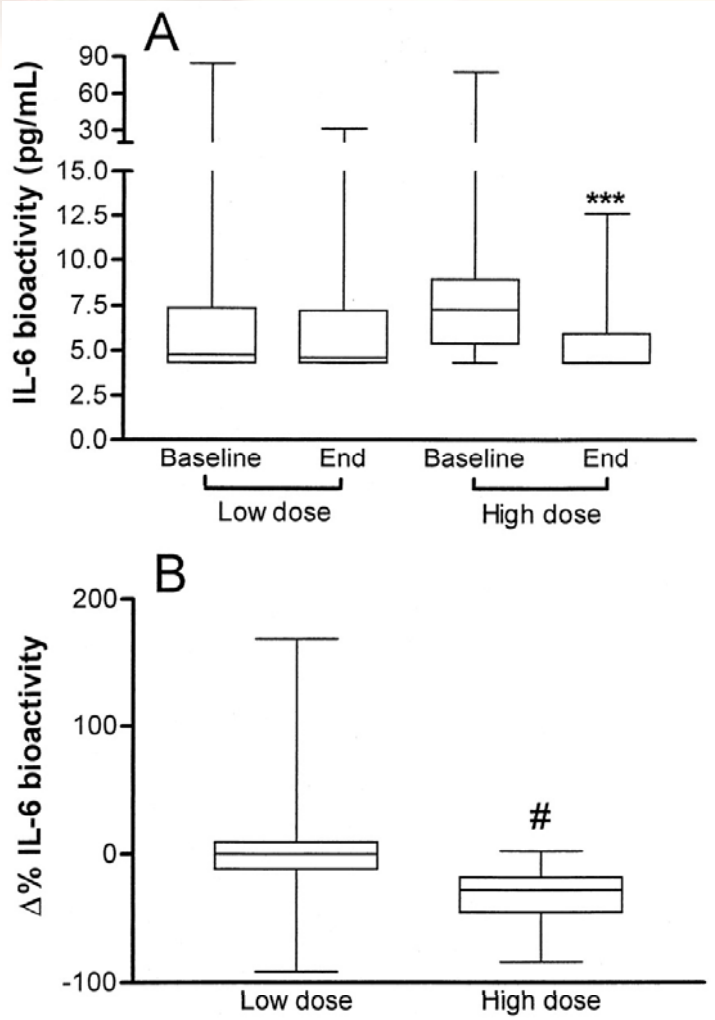
- **Immune modulation in heart failure**

Modulation of inflammation in CHF

- B-blocker, ACE-I, Statins on inflammatory markers in HF
- Recombinant human soluble TNFR (etanercept)
- Monoclonal antibody to TNFα (infliximab)
- Pentoxifylline : inhibition of TNF α production
- Intravenous immunoglobulin (IVIG)
- Celacade TM : Immune Modulation Therapy

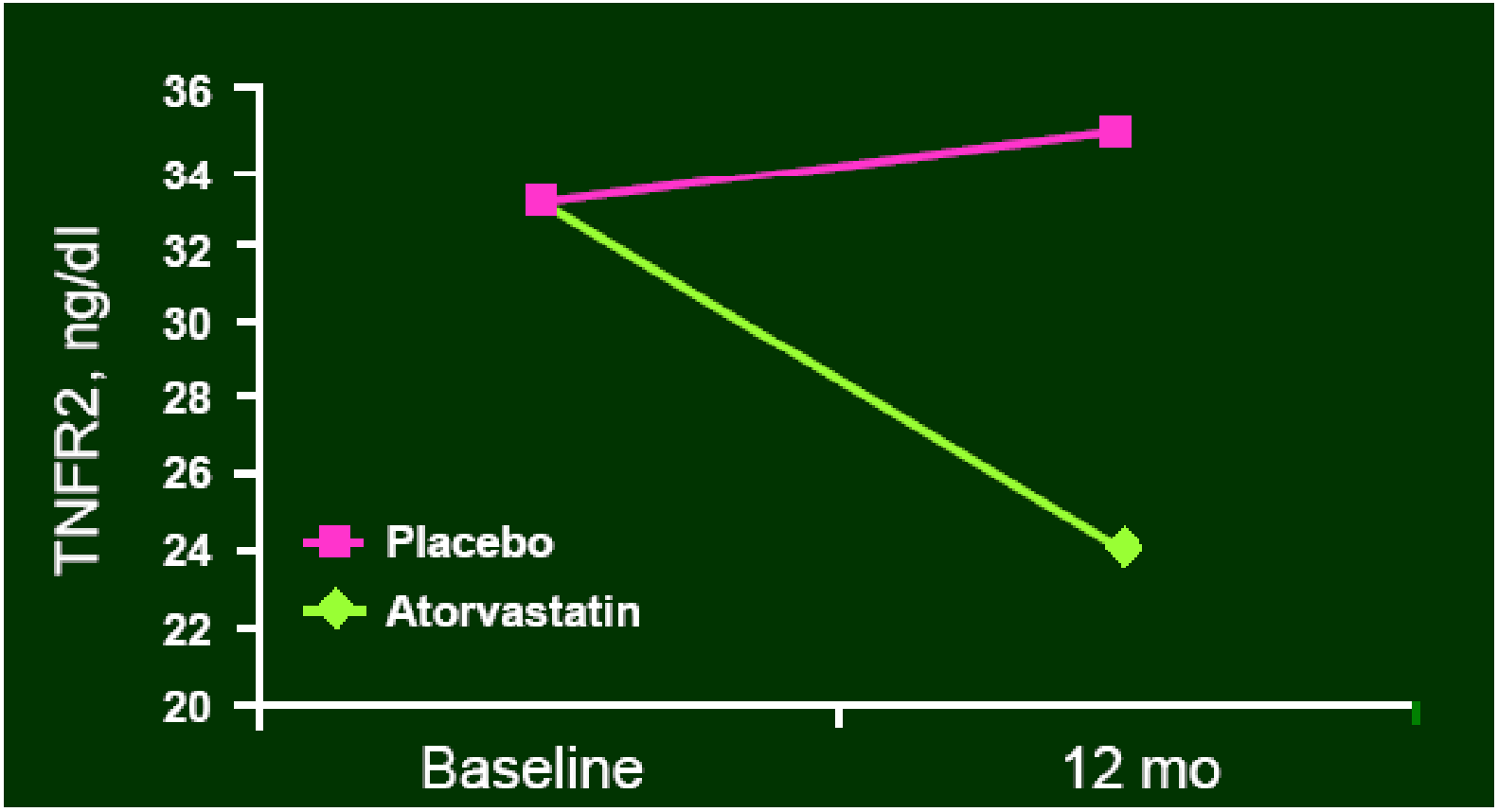
ACE inhibitors on inflammatory cytokines in CHF



- n=75
- High dose ; Enalapril 40 mg
  Low dose ; Enalapril 5 mg%

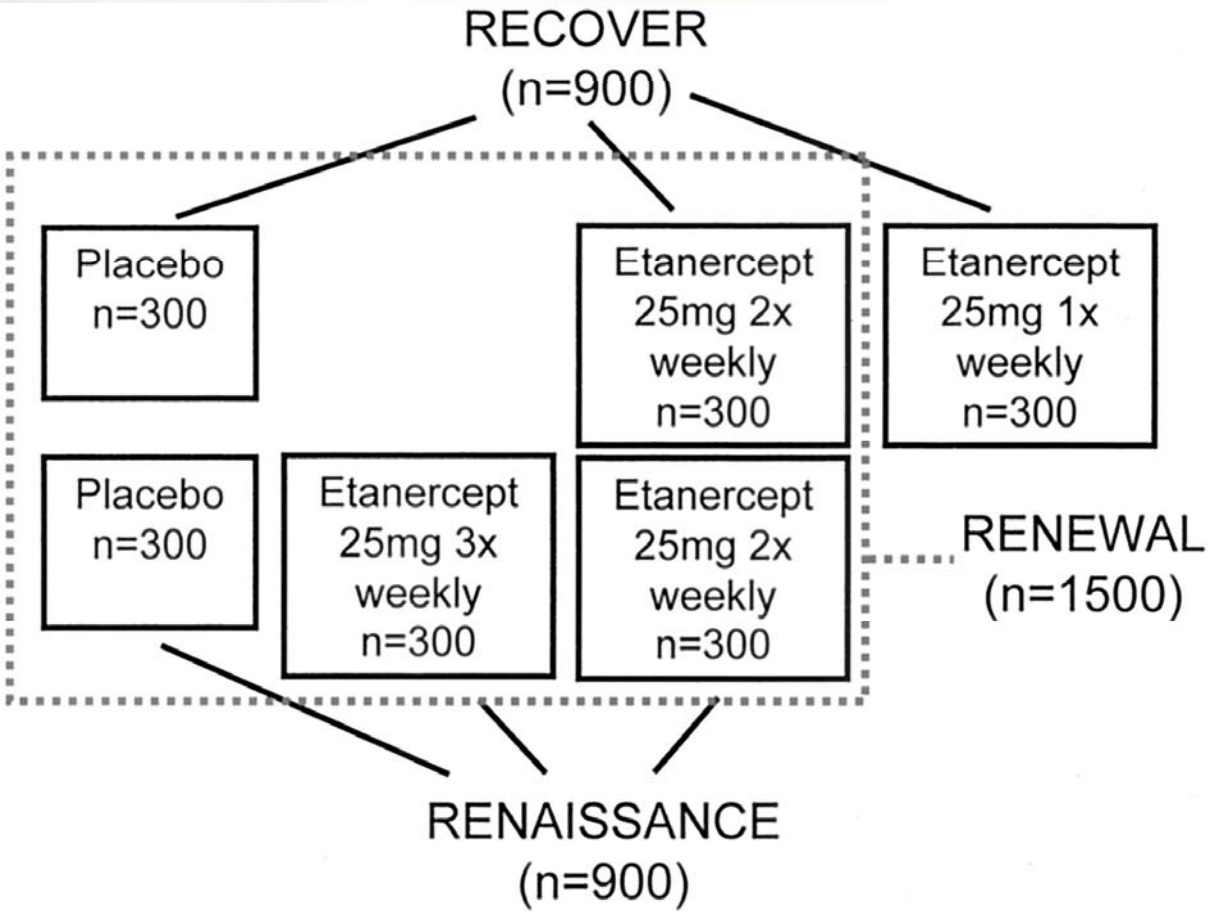
Gullestad, J Am Coll Cardiol.1999;34:2061–2067

Statins on inflammatory cytokines in CHF



Sola S, JACC 2006;47:332

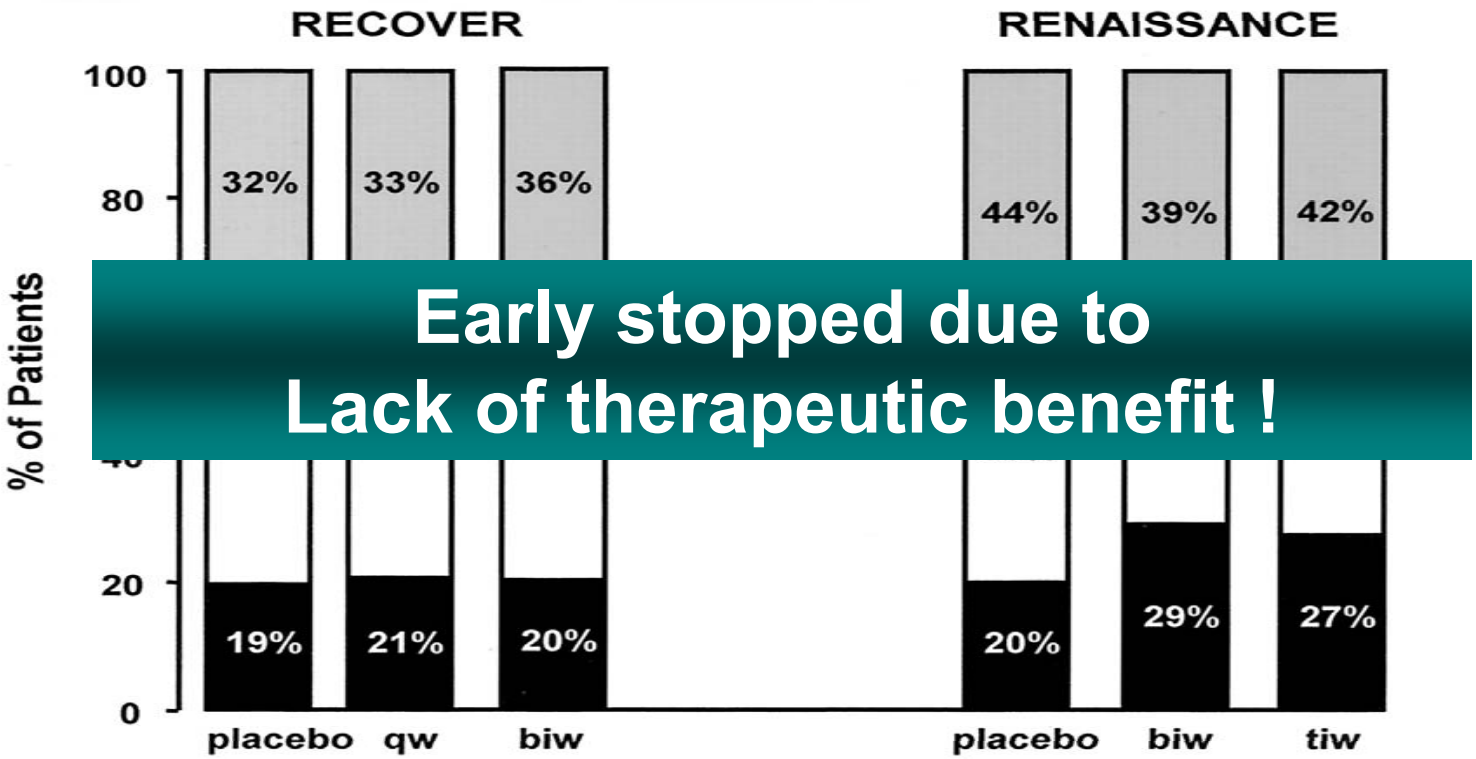
Recombinant human soluble TNF Receptor (etanercept)



Primary end point : clinical status after 24 week treatment

***Mann DL , Circulation.* 2004;109:1594–1602.**

Recombinant human soluble TNF Receptor (etanercept)



Early stopped due to Lack of therapeutic benefit !

Mann DL , Circulation. **2004;109:1594–1602.**

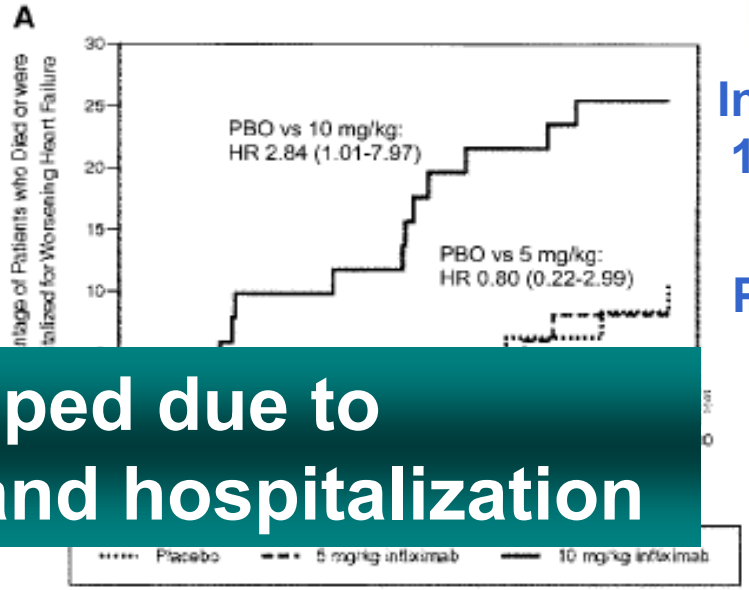
Monoclonal antibody to TNFα (infliximab)

- One hundred fifty patients with stable New York Heart Association class III or IV heart failure and left ventricular ejection fraction 25%

- rando
  placebo (n49),
  infliximab 5 mg/kg (n50),
  infliximab 10 mg/kg (n51)

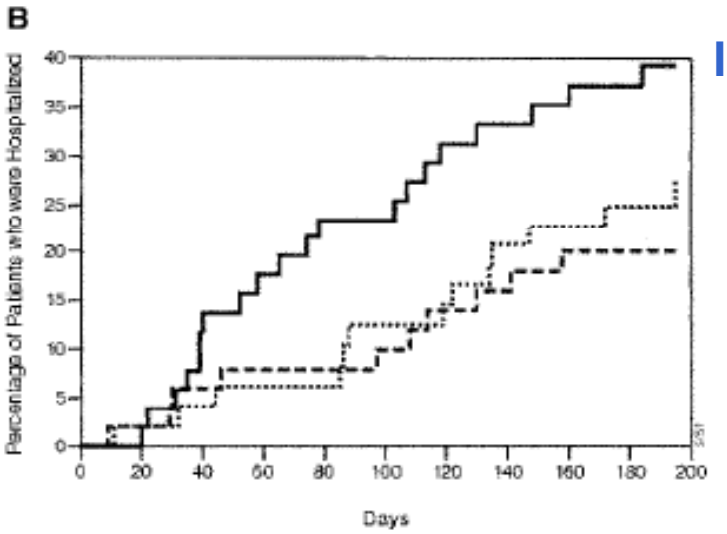
- at 0, 2, and 6 weeks after randomization and were followed-up prospectively for 28 weeks.

Early stopped due to increased death and hospitalization



Infliximab 10 mg/kg

Placebo



Infliximab 10 mg/kg

Placebo

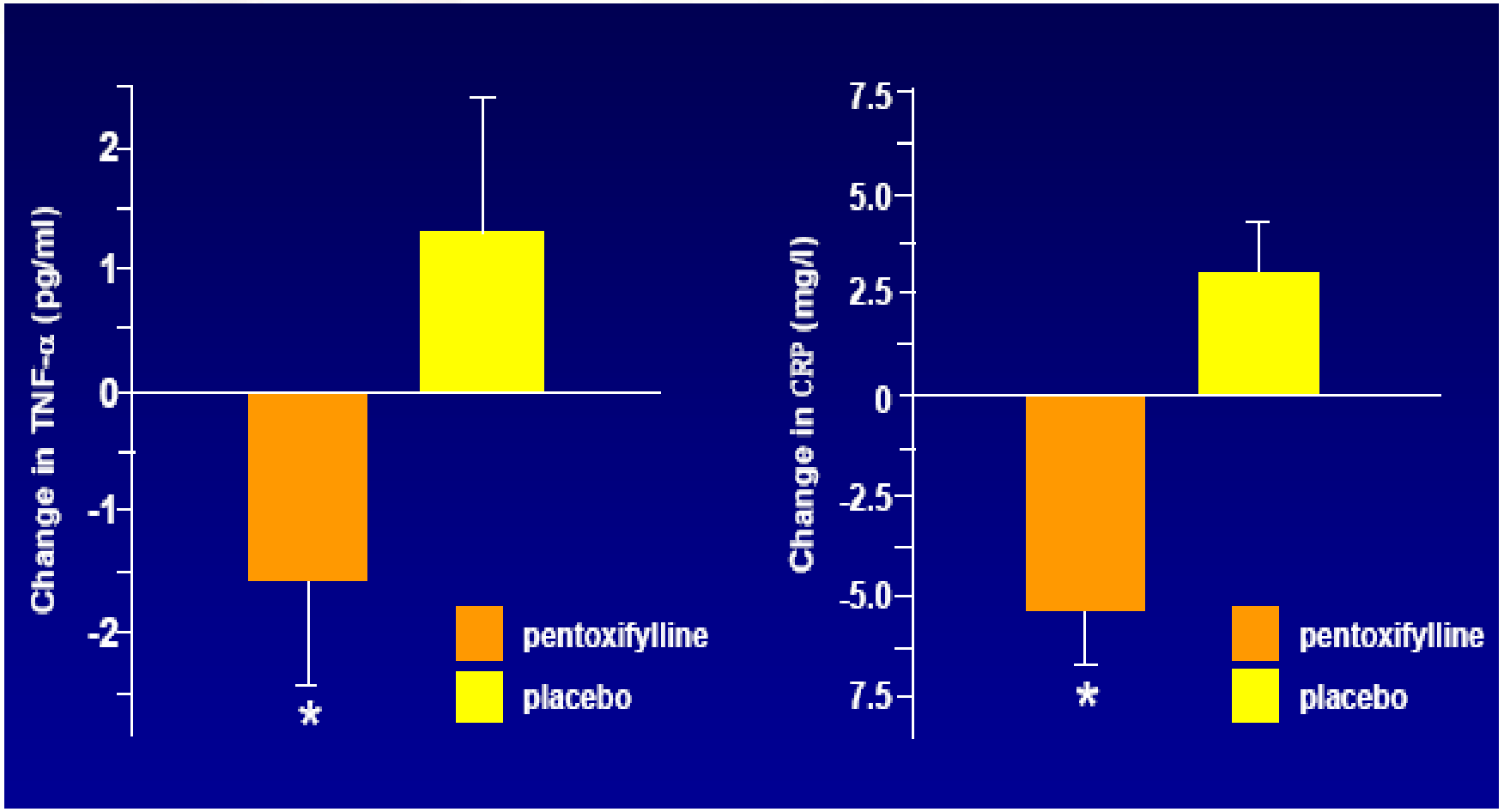
Possible Causes of Failure

- In addition, due to the redundancy of the cytokine cascade, it is possible that intervention on a single cytokine (such as TNF-α) may be insufficient to favorably impact the progression of HF.

- specific groups of patients with greater degrees of inflammation may receive more benefit from immune-directed therapies.

- Specific biologic attributes of etanercept and infliximab may have increased the biologic half-life of TNF-α or resulted in the fixation of complement to cardiomyocytes

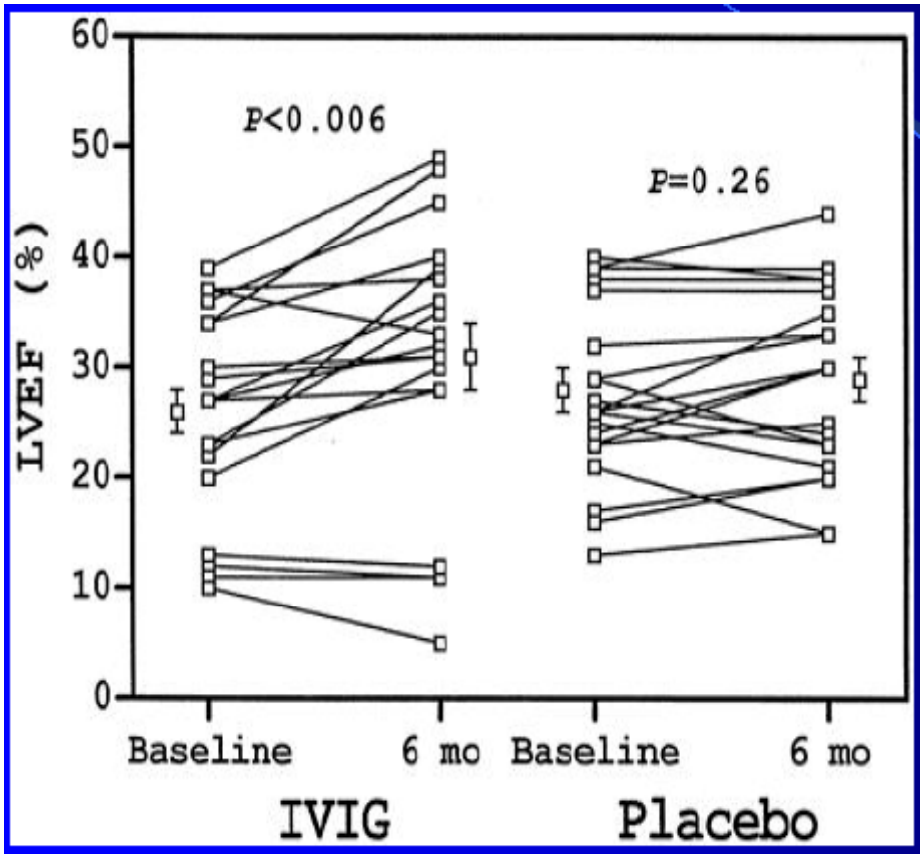
Pentoxifylline : inhibition agent of TNF production



SliwaK et al *Circulation.* 2004;109:750-755

Immunomodulatory Strategies IVIG

- Increase in LVEF (p<0.01) independent of the cause of heart failure



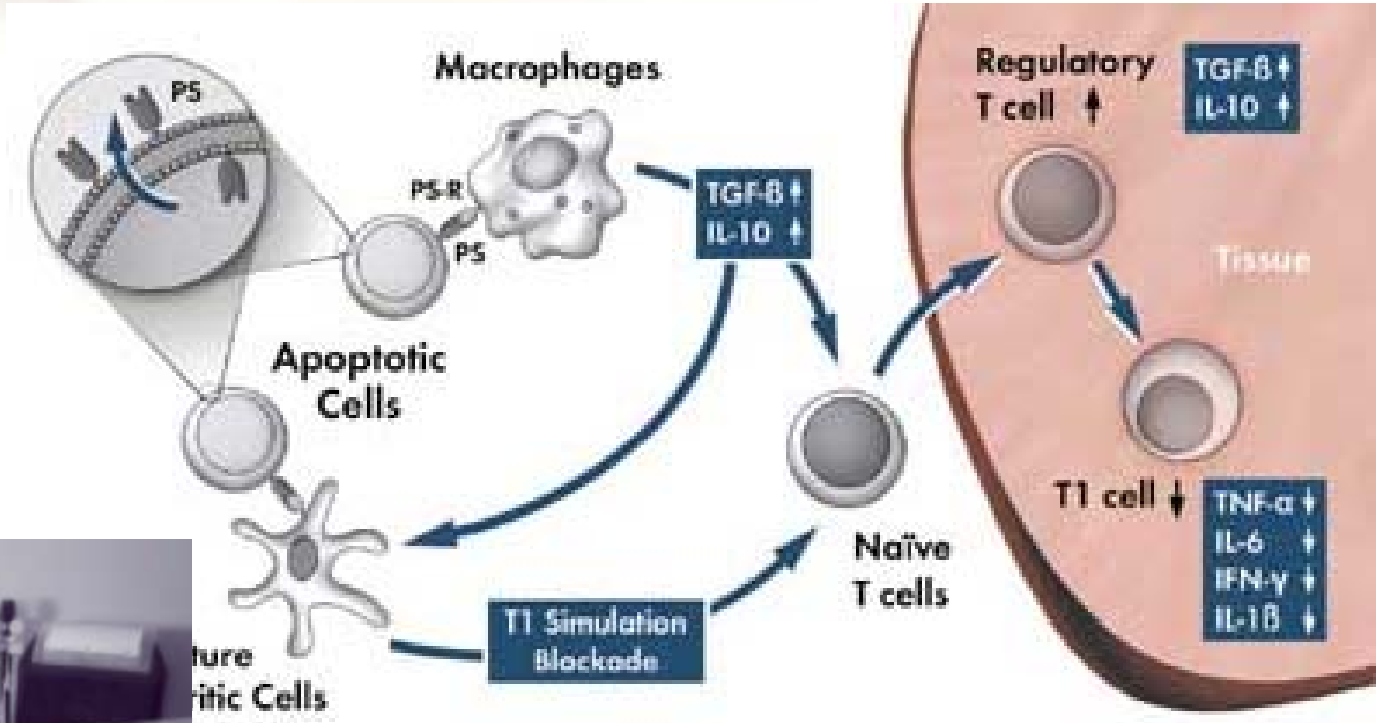
Gullestadet al Circulation 2001;103:220-225

Immune Modulation Therapy : Celacade TM

Guillermo Torre-Amione , J Am Coll Cardiol, 2004; 44:1181-1186

- Immune Modulation Therapy uses a medical device (VC7000 Blood Treatment System, Vasogen Inc) to expose a sample of blood to a combination of physiochemical stressors ex-vivo
- Oxidative stress is known to induce senescence of the white blood cells
- The treated blood sample is administered intramuscularly into the same patient from whom the sample is obtained.
- Vasogen has completed a multi-center phase II clinical trial investigating the safety and efficacy of Celacade™in chronic heart failure patients
- 73 patients, randomized into two groups, each of which received either Celacade™or placebo treatments
- Had a relatively advanced degree of heart failure as depicted by NYHA Class (III or IV), a low (22%) left ventricular ejection fraction (LVEF), and limited exercise capacity (<300m)

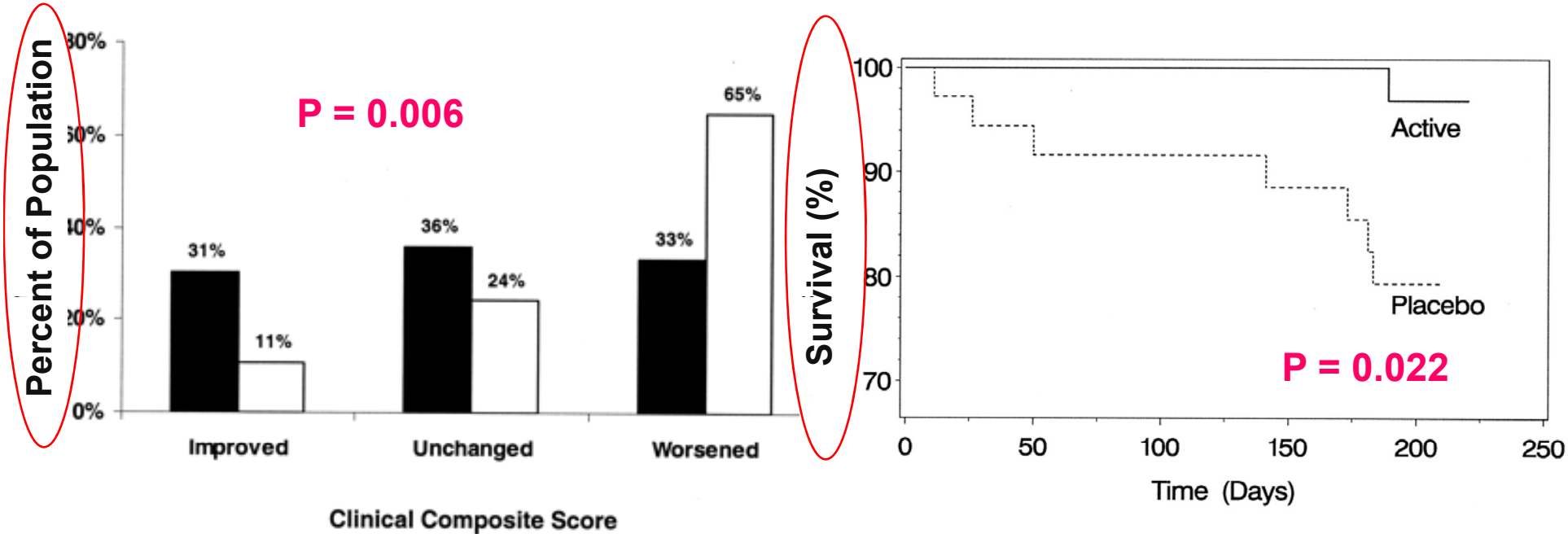
Immune respone to apototic cell



From www.vasogen.com

Result of IMT with Celacade TM (pilot , n=78)

- There were no between-group differences in LVEF or circulating levels of interferon-gamma, TNF-alpha, interleukin-6, interleukin-10, brain natriuretic peptide, and C-reactive protein
- No safety concerns were apparent



ACCLAIM : Advanced Chronic Heart Failure Clinical Assessment of Immune Modulation Therapy

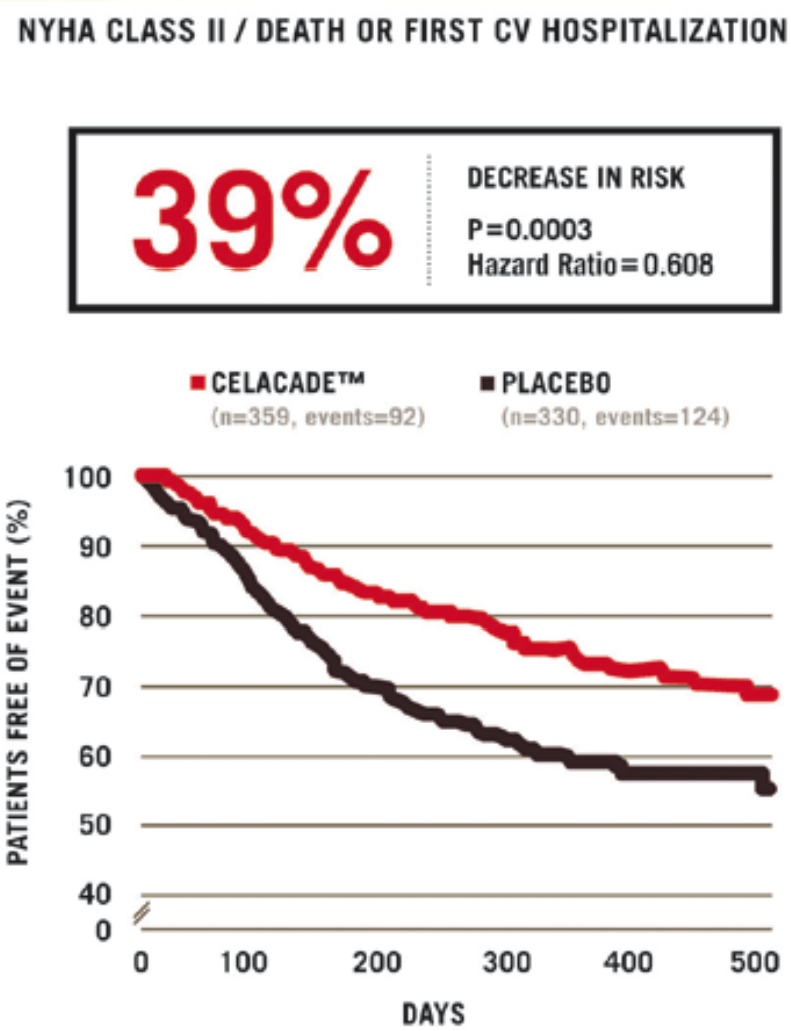
- Phase III double-blind, placebo-controlled clinical trial of Cela™ (immune mod patie chro (LVE Clas

Primary enc
all cause mortality,

Not significant diff

But .

- N=2,408



Immune modulation in heart failure

- Correction of cytokine network may represent a new therapeutic strategy approach in the management of CHF.
- However, results obtained from the first clinical trials are discouraging.
- More knowledge on inflammatory cytokine in heart failure will allow more effective therapeutic option

Summary

- Immune activation plays an important role in the pathogenesis of chronic heart failure (CHF)
- While unable to establish cause and effect relationship inflammatory markers appear to be elevated relatively early in the disease process and correlated with disease severity
- Recent clinical trials to inhibit TNF activity in CHF showed disappointing results.
- Although not necessarily the 'drugs of choice', recent studies of various anticytokine and immunomodulating agents in CHF clearly suggest a potential role for such therapies in addition to the optimal medical regimens.
- Larger placebo-controlled randomized studies are needed to confirm the results in these small studies

감사합니다

2008년 대한심장학회 춘계학술대회

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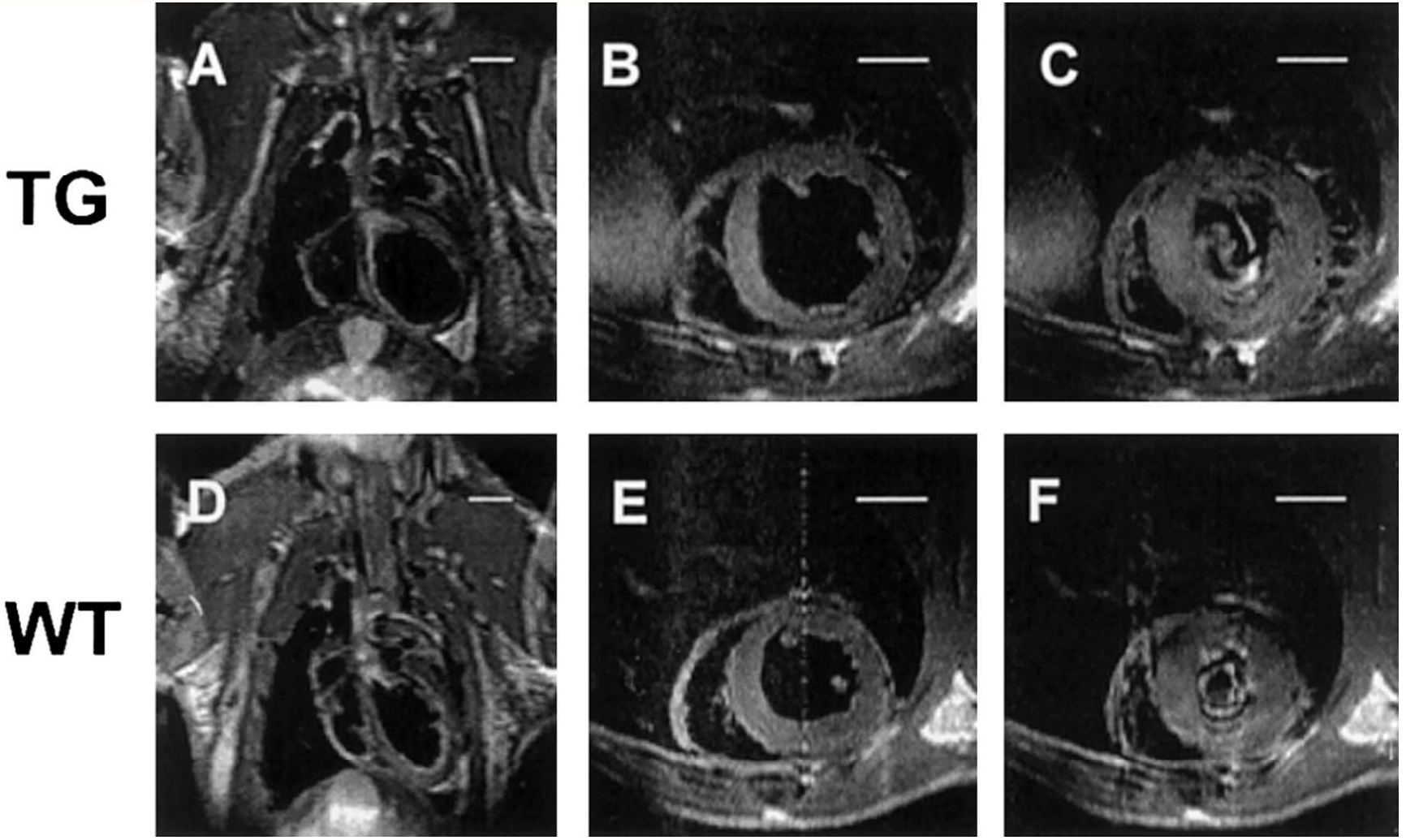
MR cardiac images of TNF-α transgenic mouse：comparison with an age-matched wild-type mouse



Circ Res. 1997;81:627–635

Effect of inflammatory mediators in LV remodelling

Alterations in the Biology of the Myocyte
- Myocyte hypertrophy
- Fetal gene expression
- Negative inotropic effects
- Increased oxidative stress

Alterations in the Biology of the Nonmyocytes
- Conversion of fibroblasts to myofibroblasts
- Upregulation of AT_1 receptors on fibroblasts
- Increased matrix metalloproteinase secretion by fibroblasts
- Alterations in the extracellular matrix
- Degradation of the matrix
- Myocardial fibrosis

Progressive Myocyte Loss
- Necrosis
- Apoptosis