

CHAPTER 5

SYSTEMIC MILIEU

- Systemic Proinflammatory State
 - § Role of Infection
 - § Link to Thrombosis
 - § Anti inflammatory Treatment

- Systemic Procoagulant State
 - § Markers of Procoagulant State
 - § Thrombin Generation and Activity
 - § Fibrinolytic System

- Changes in the internal environment (systemic milieu) can contribute to the instability of ASO plaques, disruption of the plaque, formation of coronary thrombus, persistence of thrombus and its growth to total occlusion.
- In ACS there are generalized systemic proinflammatory and prothrombotic states.
- The local vascular inflammatory and thrombotic activity are potentiated by the adverse changes in the systemic milieu.
- Pharmacologic therapy targeting the systemic milieu can attenuate both the proinflammatory and procoagulant states, help in ASO plaque stabilization and limit coronary thrombus formation and extension.
- ASA, statins, ACE-inhibitors and antibiotics target the proinflammatory state while anticoagulants target the prothrombotic state.

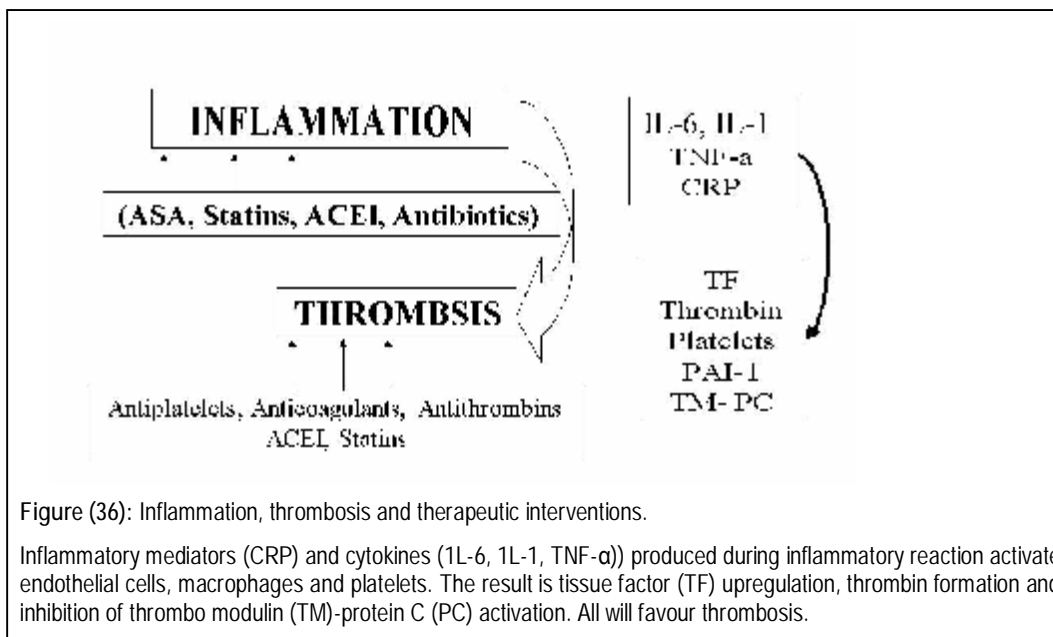


Figure (36): Inflammation, thrombosis and therapeutic interventions.

Inflammatory mediators (CRP) and cytokines (1L-6, 1L-1, TNF- α) produced during inflammatory reaction activate endothelial cells, macrophages and platelets. The result is tissue factor (TF) upregulation, thrombin formation and inhibition of thrombo modulin (TM)-protein C (PC) activation. All will favour thrombosis.

SYSTEMIC PROINFLAMMATORY STATE

- Systemic proinflammatory state can be detected clinically by elevated plasma levels of inflammatory markers.
- The inflammatory mechanisms that underline development and instability of the ASO plaque involve both:
 - Immediate locality of the plaque.
 - Circulating cells and cell products (inflammatory markers).

Plasma Inflammatory Markers

- Acute phase proteins:
 - CRP
 - Fibrinogen.
 - Serum amyloid A.
- Inflammatory cytokines
 - IL-6.
 - IL-2.
 - IF- γ .
 - TNF- α
 - IL-1B
- Other inflammatory moderators
 - MCP-1
 - Lipoprotein-associated phospholipase A₂ (LP-PLA₂).
 - Pregnancy-associated plasma protein-A (PAPP-A)
 - Myeloperoxidase.
 - Adhesion molecules.

Significance

- Plasma levels of proinflammatory cytokines are elevated in patients with ACS.
- CRP levels are elevated in ACS and provide important short-and long-term prognostic information. It predicts recurrent ischemia and increased risk of MI.
- Elevated CRP is associated with increased risk of future cardiac events in both healthy men and women.
- Elevated MCP-1 plasma levels are present in patients with AMI and remain elevated for many weeks after the acute event.

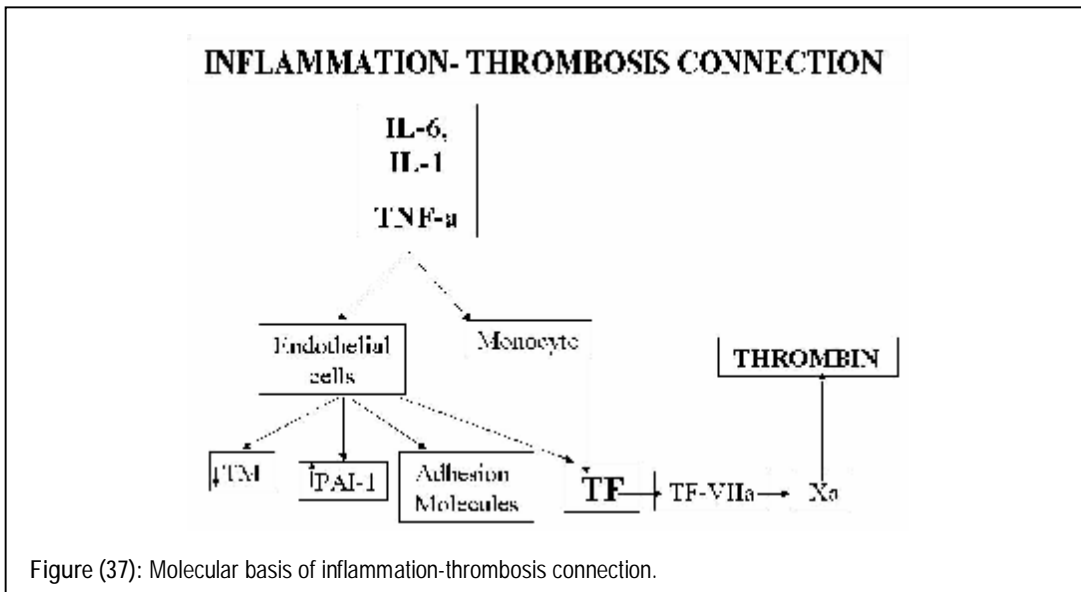
Role of Infection

- Infectious agents implicated in ASO plaque development and instability include:
 - Chlamydia pneumonia.
 - Cytomegalovirus (CMV).
 - Helicobacter pylore.
 - H-influenza.
- Infection, can through inflammatory mechanisms, lead to endothelial injury, expression of adhesion molecules and TF.
- Chronic rather than acute infection may be a potential proatherogenic factor in genetically susceptible individuals.
- Chronic infection (e.g. gingivitis, prostatitis, bronchitis, etc.) can augment production of inflammatory cytokines that may accelerate the evolution of atherosclerotic lesions.
- Infections can induce acute inflammatory responses that lead to ASO plaque destabilization and acute thrombosis.

- Chlamydia when present in the arterial plaque, may release lipopolysaccharide (endotoxin) that can stimulate the production of proinflammatory mediators by endothelial cells, VSMCs and infiltrating macrophages.
- The antibody titers for C pneumoniae, H pylori, H influenza and CMV are related to the extent of atherosclerosis.

Link to Thrombosis (Figs 36, 37)

- Both systemic and local vascular inflammation are associated with increased thrombogenesis.
- Inflammatory cytokines increase platelet activity and activate the coagulation cascade.
- Inflammation increases tissue factor (TF) production by monocytes and increase fibrinogen production.
- Inflammation reduces the actions of endogenous anticoagulants.
- Inflammatory cytokines (IL-6, IL-1 and TNF- α) through their action on endothelial cells decrease expression of thrombomodulin (TM), increase generation of PAI-1 and TF (Fig 37).
- Inflammation can:
 - Promote thrombus formation.
 - Enhance clot stability by inhibiting endogenous fibrinolysis.
 - Activated inflammatory cells –macrophages- are a very important source of the chief procoagulant TF.
 - CRP can activate coagulation through TF induction.
 - Fibrinogen and plasminogen activator inhibitor generated during inflammation acute phase response promote thrombosis.



ANTI INFLAMMATORY TREATMENT

- Aspirin.
- Statins.
- ACE-Inhibitors.
- Antibiotics.

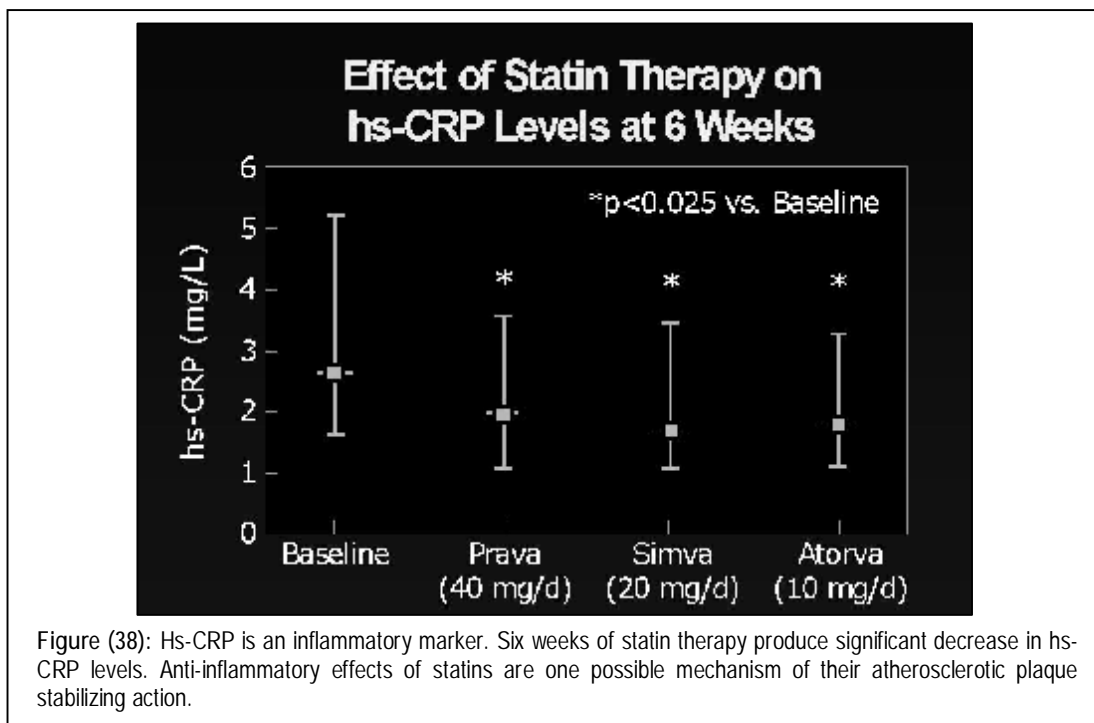
Aspirin (ASA)

- Aspirin inhibit:
 1. Cyclo oxygenase enzyme.
 2. NF-kB (transcription factor regulating inflammatory gene transcription): it reduces plasma level of macrophages colony stimulating factor (MCSF), IL-6 and CRP in patients with CAD.
- Benefit of ASA in prevention of MI among apparently healthy individuals is seen in patients with elevated CRP level.

Statins

Statins produce their anti-inflammatory action through:

- Reduction in LDL-C and oxidized LDL-C production: ox-LDL has proinflammatory actions.
- Non-lipid related mechanisms: reduction in macrophage accumulation and metalloproteinase expression in ASO plaques.
- Statins reduce hs-CRP levels in patients with CAD (Fig 38).



ACE-inhibitors

- Anti-inflammatory actions of ACE-inhibitors are established.
- Administration of ACE-I (enalapril) to patients with AMI significantly decreased the plasma level of MCP-1 which is a monocyte and macrophage chemotactic and activating factor and a marker of inflammation.

Antibiotics

- Effect of antibiotic treatment in patients with stable CAD is not encouraging.
- Patients with ACS may benefit from antibiotic treatment.
- The difference in response of patients with stable CAD from those with ACS may be due to the difference in the magnitude of inflammation in the two conditions.
- Clinical trials:
 - *Clarithromycin* (Kelocid) 500 mg once daily for 3 months reduced the risks of ischemic cardiovascular events in patients presenting with acute NSTEMI or unstable angina. The beneficial effect persisted for two years (CLARIFY trial, 2002).
 - *Amoxicillin* 500 mg twice daily for one week plus metronidazole (400 mg BID) and omeperazole (200 mg BID) or *Azithromycin* (500 mg once daily) plus metronidazole and omeperazole for one week significantly reduced adverse cardiac events mainly readmission with unstable angina in patients with ACS (STAMINA trial, 2002).
 - § Risk reduction with antibiotics was significantly greater in patients with AMI.
 - § There is no significant difference in total mortality.
 - *Azithromycin* (500 mg/daily for 1 day, then 250 mg daily for 4 days) did not improve the clinical outcomes in patients with ACS.
 - *Gatifloxacin* (400 mg/day x 10 days/month for 2 years) showed no benefit when given to patients with ACS (PROVE IT trial 2004).

SYSTEMIC PROCOAGULANT STATE

- Tendency to blood coagulation and increase in plasma coagulation markers is present in patients with ACS.
- The procoagulant state persists up to 6 months after the acute event.

Makers of Procoagulants State

I. Up stream markers- Coagulation factors

1. VIIa
2. TF
3. TFPI

II. Intermediate markers – Thrombin

A. Thrombin generation

1. Prothrombin fragment 1+2 (F1+2)
2. Thrombin – antithrombin complex (TAT)

B. Thrombin activity

1. Fibrinopeptide A (FPA)
2. Soluble fibrin (SF)

III. Down stream markers – Fibrin

A. Fibrinolysis

1. T-PA
2. PAI-1

B. Fibrin turnover

D-dimer.

THROMBIN MARKERS

- *Prothrombin fragment 1+2 (F1+2)*: a polypeptide released from prothrombin during its conversion to thrombin. It is a marker for factor Xa activity.
- *Fibrinopeptide A (FPA)*: a peptide released from fibrinogen during its transition to fibrin. It is a marker of thrombin action.

Implications of elevated markers of thrombin generation and activity

- Measurements of those markers may help identifying groups of patients at high risk of adverse ischemic events or active coronary disease, however, individual risk assessment is very difficult because of the considerable interindividual dispersion.

- Plasma concentrations of F1+2 and FPA are significantly elevated in patients with unstable angina or AMI.
- Elevated plasma concentrations of F1+2 or FPA signify a hypercoagulable state.
- Persistent hypercoagulable state in patients with ACS appears to be independent of the extent of CAD or drug intake.
- Increased activity of the hemostatic mechanisms may predate the onset of ACS.
- Elevated plasma levels of markers of thrombin generation and activity as well as fibrin turnover such as F1+2, FPA and D-dimer are risk indicators for future cardiovascular events in apparently healthy men.
- Increased level of activation of the coagulation system long after clinical stabilization in patients with ACS may explain the high reoccurrence of cardiac events in patients with unstable angina and MI than in those with stable angina.
- Detection of hypercoagulable state with F1+2 assay could identify patients most likely to benefit from prolonged anticoagulant therapy.

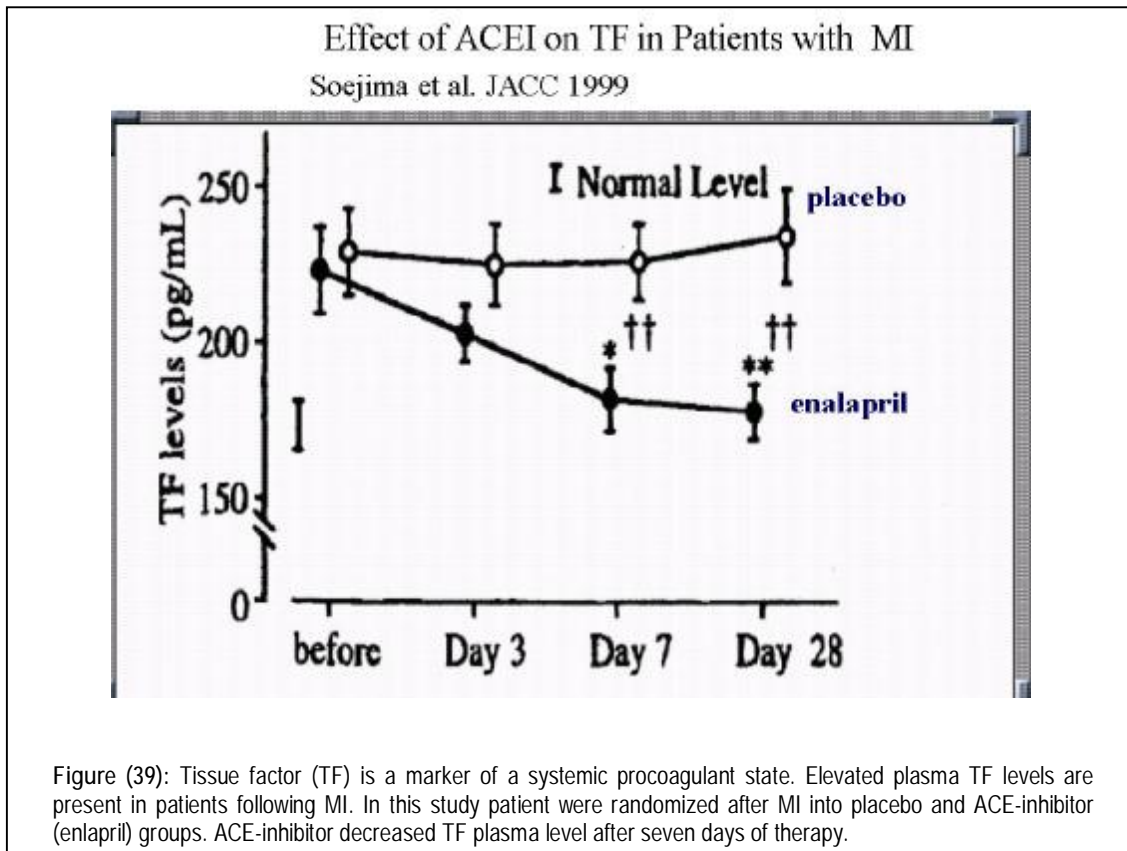
Warfarin Therapy

- Success to prevent unstable angina and AMI with warfarin therapy may result from the suppression of the persistent activation of the hemostatic mechanism.
- Much of the clinical benefit of anticoagulant treatment is lost a few days after cessation of treatment due to reactivation increase in hemostatic markers.
- Thrombin activity is increased in patients with ACS and persists after resolution of symptoms.

COAGULATION FACTORS

Tissue Factor (TF)

- Chief procoagulant glycoprotein that binds with factor VII and the resulting complex activates factors IX and X.
- Plasma TF levels are elevated in patients with MI and unstable angina.
- High TF levels contribute to the high procoagulant activity of ASO plaques in CAD.
- Blood clotting activation in patients with CAD was related to elevated TF circulating levels.
- ACE-inhibitors therapy decreases the over-expression of TF in patients with MI (Fig 39).



FIBRINOLYTIC SYSTEM

Vascular fibrinolytic activity is mainly determined by the balance between plasminogen activators, primarily t-PA and plasminogen activator inhibitor predominately PAI-1.

Source

- Both t-PA and PAI-1 are synthesized locally in the vascular wall-endothelial and smooth muscle cells.

Functions

- The fibrinolytic system serves as one of the main endogenous defense mechanisms against intravascular thrombus formation.
- A circadian association exist for plasma PAI-1 levels, which exhibit a peak in the early morning hours, coincident with the reported peak incidence of MI.

Significance

- Elevated PAI-1 level is associated with MI.
- Elevated PAI-1 levels in young survivors of MI have been associated with an increased risk of recurrent infarction.

- High concentrations of PAI-1, which are commonly found in thrombi, are an important determinant of resistance to clot lysis by TPA.
- Plasma PAI-1 is increased in patients with diabetes mellitus and is linked to the development of renal and vascular disease in diabetics.

Role of Renin-Angiotensin-System (RAS)

- RAS plays an important role in the regulation of fibrinolysis after MI, and may contribute to the ability of ACE inhibitors to reduce the incidence of ischemic coronary events in patients with LV dysfunction.
- Angiotensin II may contribute to a prothrombotic state by reducing the activity of the endogenous fibrinolytic system.
- ACE-inhibitor therapy could improve plasma fibrinolytic balance by reducing the Ang II dependent production and secretion of PAI-1, while promoting the bradykinin dependent secretion of t-PA.
- ACE-inhibitor therapy reduces plasma PAI-1 after AMI.