Cytokines and Cardiovascular disease: Exploring Inflammation & Clinical Outcomes

London, August 31 2015 – 12:45-13:45 hrs
ExCel Conference Centre – Room DAMASCUS – VILLAGE 5

Inflammation and Thrombosis

Raffaele De Caterina
August 31 2015 - 13:10-13:25 hrs
15 min + Disc.
Inflammation, atherosclerosis, and CV risk

• Markers of inflammation – such as CRP, myeloperoxidase and leukocyte count – are strong predictors of CV death, MI, and stroke.

• Individuals with chronic inflammatory conditions, such as rheumatoid arthritis, systemic lupus erythematosus or psoriasis, are at higher CV risk.

Inflammation and atherothrombosis

Inflammation plays a pivotal role in all stages of atherosclerosis:

- endothelial dysfunction
- recruitment of immune cells
- LDL modifications
- foam cell formation
- foam cell apoptosis
- plaque rupture
- ...
- thrombosis??

Peter Libby, *A Fire Within* Scientific American, May 2002
Does inflammation cause thrombosis only through an atherogenic mechanism or ALSO directly?
INFLAMMATION AND THROMBOSIS
- clues from different thrombotic phenotypes

ARTERIAL THROMBOSIS:
- white clot
- atherosclerosis

VENOUS THROMBOSIS:
- red clot
- Virchow’s Triad
INFLAMMATION-INDUCED THROMBOSIS

Venous thromboembolism should be now considered as part of a *pan-cardiovascular syndrome* that includes coronary artery disease, cerebrovascular disease, and peripheral artery disease.

Patients with arterial thrombosis are also at increased risk for venous thrombosis and overlapping risk factors have been found to be associated with both arterial and venous thrombotic events.

Inflammation is involved in the pathogenesis of both arterial and venous thrombosis→**INFLAMMATION-INDUCED THROMBOSIS**

Increased frequency in patients with chronic inflammatory disorders such as rheumatoid arthritis

Holmqvist et al. Risk of venous thromboembolism in patients with rheumatoid arthritis and association with disease duration and hospitalization. JAMA 2012; 308: 1350-6
Increased levels of inflammatory biomarker C-reactive protein (CRP) have been linked to the risk risk of venous thromboembolism

VENOUS THROMBOEMBOLISM in JUPITER

The occurrence of venous thromboembolism (vte) was a protocol-specified secondary end point of the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial, testing whether treatment with 20 mg of rosuvastatin daily, as compared with placebo, would reduce the rate of first major cardiovascular events.

Therefore the benefits of statins on VTE might occur not only through the effects of statins on lipid levels (venous and arterial thrombosis share some risk factors),

... but also through their influence on inflammation-related thrombosis
A Randomized Trial of Rosuvastatin in the Prevention of Venous Thromboembolism

INFLAMMATION-INDUCED THROMBOSIS – POTENTIAL MECHANISMS

- Endothelial cell dysfunction
- Platelet activation
- Tissue factor-mediated coagulation
- Hyperfibrinogenemia
- Suppressed fibrinolytic activity
- Impaired function of anticoagulants
INFLAMMATION-INDUCED THROMBOSIS – POTENTIAL MECHANISMS

- Endothelial cell dysfunction
INFLAMMATION-INDUCED THROMBOSIS – POTENTIAL MECHANISMS

- Platelet activation

INFLAMMATION-INDUCED THROMBOSIS – POTENTIAL MECHANISMS

- Tissue factor (TF)-mediated activation of coagulation

• Hyperfibrinogenemia

✓ fibrinogen is a soluble glycoprotein synthesized by hepatocytes. In pathological conditions, such as after injury, vascular disruption, infection, or inflammation, blood concentrations of fibrinogen increase several fold → fibrinogen is considered an acute-phase reactant

✓ hyperfibrinogenemia significantly increases the risk of arterial and venous thrombosis, and this risk is proportional to fibrinogen levels

✓ several studies have correlated increased risk of thrombosis with increased fibrin network density and increased resistance of plasma clots to fibrinolysis; fibrin network structure reflects the fibrinogen concentration, and the presence of elevated fibrinogen increases fibrin network density, clot stiffness, and the resistance of clots to fibrinolysis
INFLAMMATION-INDUCED THROMBOSIS

Using an intravenous infusion strategy to increase levels of circulating fibrinogen in mice, hyperfibrinogenemnic mice featured a shorter time to vessel occlusion, increased thrombus fibrin content, and increased resistance of thrombi to thrombolysis compared to controls.

INFLAMMATION-INDUCED THROMBOSIS – POTENTIAL MECHANISMS

• Impaired function of anticoagulants (antithrombin, protein C system; tissue factor pathway inhibitor)

  • decreased synthesis
  • increased consumption (due to activation of the coagulation cascade)
  • increased degradation by proteolytic enzymes (elastase from activated neutrophils)
  • impaired function (reduced synthesis of glycosaminoglycans and thrombomodulin)
INFLAMMATION-INDUCED THROMBOSIS – POTENTIAL MECHANISMS

- Impaired fibrinolytic activity
Ongoing large randomized controlled trials designed to evaluate the effect of anti-inflammatory drugs on atherosclerosis, including CANTOS and CIRT, also assess the impact of antiinflammatory therapy on incident VTE, will shed light on the hypothesis of inflammation-mediated thrombosis.