Inflammation & Allergy - Drug Targets, 2008, 7, 136-144

The Role of Inflammation and Allergy in Acute Coronary Syndromes

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Abstract: It is well known that inflammatory mechanisms play a crucial role in the pathogenesis of atherosclerosis and coronary artery disease. In recent years, allergic episodes have been shown to be associated with acute coronary syndromes. Mast cells release certain inflammatory mediators including histamine and neutral proteases during an allergic episode and these inflammatory mediators are implied to induce coronary artery spasm and/or atheromatous plaque erosion or rupture. As the inflammatory component of acute coronary syndromes is a potential therapeutic target, drugs that stabilize mast cell membrane and monoclonal antibodies that protect mast cell surface may be effective in preventing allergy associated acute coronary syndromes. In this review, we will mention the role of inflammation and allergy and anti-inflammatory therapeutic modalities in acute coronary syndromes.

INTRODUCTION

Acute coronary syndromes (ACS) result from an imbalance between myocardial oxygen demand and supply. In most of the cases; it is due to reduced myocardial perfusion resulting from a nonocclusive thrombus developed over a ruptured atherosclerotic plaque [1]. It is now known that arterial inflammation plays a role in atherosclerotic process and is responsible for thrombogenesis in ACS [2]. Apart from the extensive evidence to support the pathogenic role of inflammation in ACS, there is also evidence that increased concentrations of inflammatory markers can identify patients at high risk and predict clinical outcomes in ACS [3].

Coronary vasoconstriction and dynamic obstruction of the coronary flow is another cause of ACS. Histamine is an endogenous vasoconstrictor, which can result in coronary spasm and contribute to the clinical syndrome. Plasma histamine concentration in coronary circulation was found to be elevated in patients with variant angina [4] and infiltration of activated mast cells at the site of erosion or rupture was shown in patients with recent acute myocardial infarction (MI) [5]. Mast cells are activated also during hypersensitivity or allergic reactions, and release histamine and other endogenous vasoconstrictors. These mediators may cause coronary vasospasm acting on coronary vascular smooth muscle [6]. The concurrence of ACS with conditions associated with mast cell activation including allergic or hypersensitivity reactions is termed as "Kounis syndrome".

Prevention of the atherosclerotic plaque erosion or rupture should become the primary target in primary or secondary prevention of ACS. Progress in the understanding of the inflammatory pathways in ACS may provide new treatment modalities and preventive strategies. Similarly in cases of allergy associated ACS, drugs that stabilize mast cell membrane and monoclonal antibodies that protect mast cell surface may emerge as novel therapeutic modalities.

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THE ROLE OF INFLAMMATION IN ACUTE CORONARY SYNDROMES

The majority of cases of ACS are the result of combined coronary artery spasm and atheromatous plaque erosion or disruption, with consequent platelet aggregation and thrombosis [7]. During years, alterations occur on the plaque surface including fissuring, erosion, ulceration, and rupture of the plaque surface [8]. These changes involve disruption of the endothelium and the underlying connective tissue of the plaque capsule. Once the fibrous capsule is sufficiently weakened, the plaque is susceptible to sudden rupture, thereby exposing an intensely prothrombotic subsurface. Although the exact mechanisms responsible for plaque weakening and rupture have not been clearly elucidated, there is extensive evidence implicating an inflammatory process in the pathogenesis of ACS and indicating that the intensity of the inflammatory response influences clinical outcome in ACS [9].

Inflammation plays a role in destabilizing the fibrous cap tissue. Local inflammatory cells can release cytokines, which may reduce matrix synthesis and increase its degradation, favoring plaque rupture. These inflammatory cytokines may also activate the endothelium, change its natural antiadhesive and anticoagulant properties, and enhance the risk of coronary thrombosis. Cytokines also enhance synthesis of endothelin in endothelial cells and macrophages, resulting in increased smooth muscle cell reactivity to local vasoconstrictors (Fig. 1).

Although lipid rich atheromatous plaques that have a thin fibrous capsule are more prone to disruption [10], the cellular composition at the lesion site is more consistent [11]. Unstable or ruptured atherosclerotic plaques are histologically characterized by the presence of foam cells, macrophages, lymphocytes, and mast cells [12]. Macrophages and T lymphocytes, the dominant cell type at the site of plaque rupture [11], are activated and there is abundant expression of HLA-DR II antigens on both leucocytes and adjacent smooth muscle cells, indicating ongoing inflammation at the site of plaque disruption. Macrophages within atherosclerotic plaques express matrix metalloproteinases. These matrix

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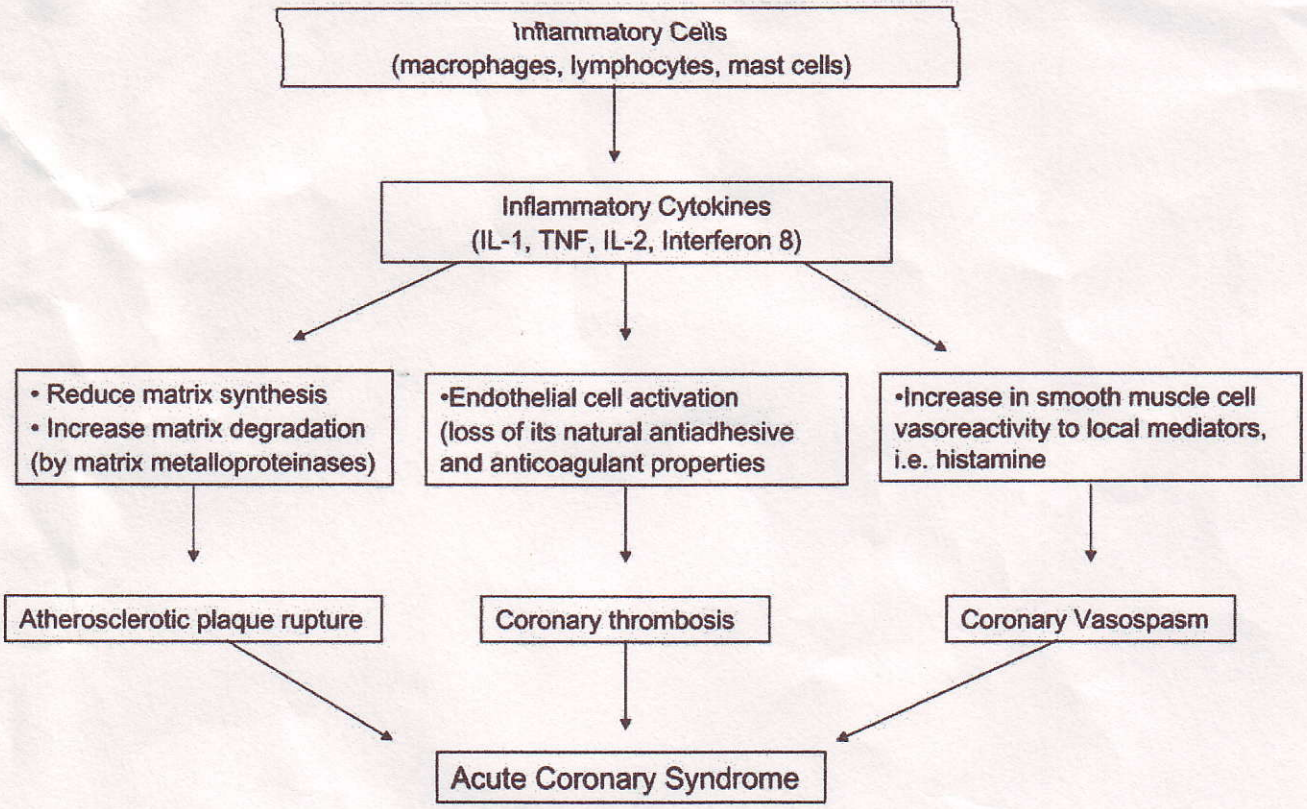

Fig. (1). The Role of inflammation in acute coronary syndrome (IL-1: interleukin 1; TNF: tumour necrosis factor, IL-2: interleukin 2).

metalloproteinases degrade collagen and extracellular matrix resulting in a weaker plaque and are upregulated by interleukin 1 (IL-1) and tumour necrosis factor (TNF) [13]. Proliferation of smooth muscle cells, which migrate to the intima and synthesize collagen, causes the arterial fatty streak to evolve to a more complex lesion. Continued release of cytokines (such as monocyte chemoattractant protein 1) by activated endothelial cells, T-cells and foam cells encourages and sustains inflammation and lipid accumulation within the atheroma and also influences further smooth muscle cell activity. Activated transcription factor nuclear factor B (NF-B) is demonstrated in the intima and media of atherosclerotic human vessels and it can activate monocyte chemoattractant protein 1 and metalloproteinase genes [14].

In patients with unstable angina expression of HLA-D is enhanced in both CD4+ and CD8+ lymphocytes, indicating that T lymphocytes are activated during the acute phase of unstable angina. The activation of T cells is further supported by the increased serum concentration of interleukin 2 receptor among patients with unstable angina. Postmortem studies of patients who died of ACS have demonstrated an increase in the percentage of interleukin 2 receptor (CD25) positive T lymphocytes in culprit lesions correlating with the severity of the ischemic syndrome (less in stable angina whereas more in acute myocardial infarction) [15]. Proinflammatory cytokines and interferon (INF-8) released from activated T cells in the plaque destabilize atherosclerotic plaques by inhibiting the proliferation and inducing the apoptosis of vascular smooth muscle cells and decreasing their synthesis of collagen in atherosclerotic plaques [16, 17]. Activated T-cells secrete cytokines that influence macrophage activity. CD40/CD40-ligand binding between activated T-cells and macrophages results in the expression of tissue factor, matrix metalloproteinases and proinflammatory cytokines, which all act to perpetuate and increase the inflammatory response.

Mast cells have also been implicated in the pathogenesis of coronary heart disease [18]. High number of activated mast cells has been shown at the vulnerable shoulder regions of stable atherosclerotic plaques and at the site of erosion or rupture in patients with recent MI [5, 19-21]. Their number in the adventitia of coronary arteries increases with the progression of atherosclerosis. Higher mast cell counts are seen in coronary arteries containing both fresh and organizing thrombi and lower counts are observed in association with fully organized thrombi [22]. Mast cells can induce matrix degeneration by release of tryptase and chymase and can actively contribute to plaque destabilization preceding rupture [23]. Mast cells have to be stimulated to secrete these neutral proteases. Activated T lymphocytes or macrophages also seem to play a role in the pathway leading to degranulation of mast cells at the site of plaque rupture [24-26]. However, the best known immunologic stimulus leading to degranulation of human mast cells is their activation when the immunoglobulin E (IgE) molecules on their surfaces bind a relevant antigen [27]. Recently, we have demonstrated that the level of IgE significantly increased during the acute phase of ACS and then gradually decreased [26, 28]. Cytokines including interleukin 4 and 13, secreted by Th-2 cells provide the first signal to B cells to switch to the production of the IgE isotype [29]. Secreted IgE molecules bind to mast cells and stimulate them to release histamine, leukotrienes, and other endogenous vasoconstrictors, which can cause contraction of vascular smooth muscle

cells and result in coronary spasm and contribute to ACS [29-32]. The concentration of histamine in the coronary circulation is elevated shortly before coronary spasm with ensuing attacks of angina [4]. When histamine binds to histamine-1 receptors on smooth muscle cells in the medial layer, especially in atherosclerotic segments where the opposing vasodilatory action is diminished, it will cause vasoconstriction [33, 34].

Endothelial cells also become activated during ACS. In response to tissue injury, endothelial cells express cell adhesion molecules that mediate the binding of activated leucocytes and platelets to the endothelial surface. The process of leukocyte binding and extravasation is critically dependent on both selectin and immunoglobulin adhesion molecules on endothelial cells interacting with integrin receptors on leucocytes. Immunohistochemical analysis of human atherosclerotic coronary arteries shows expression of intercellular adhesion molecule-1 (ICAM-1) on endothelial cells, macrophages, and smooth muscle cells within the plaque [35]. Increased concentrations of soluble ICAM-1, VCAM-1 and soluble P-selectin were reported in patients with acute coronary syndromes [36-38].

There is serological evidence that infection with organisms such as *Chlamydia pneumoniae* (*C. pneumoniae*), virulent strains of Helicobacter pylori, herpes simplex virus, and cytomegalovirus (CMV) are common in patients with chronic atherosclerosis and ACS [39-42]. It has been postulated that organisms induce the production of cytokines, such as TNF and several interleukins, which may unfavorably alter local lipid metabolism, destabilize coronary plaques, stimulate platelet activation, and enhance thrombus formation. CMV has also been implicated in restenosis following coronary intervention [43] and in graft atherosclerosis in cardiac transplant recipients [44]. High concentrations of antibodies to human heat shock protein 60 and C. pneumoniae are shown to be independent risk factors for coronary atherosclerosis and their simultaneous presence significantly increases the risk of disease [45].

There is not only a local inflammatory process at the site of plaque rupture but also a systemic inflammation is present in patients with ACS. Circulating lymphocytes from patients with unstable angina can induce tissue factor activity in cultured monocytes, which can activate the coagulation cascade [46, 47]. Circulating neutrophils in patients with unstable angina and acute myocardial infarction have low myeloperoxidase content, which then returns to its normal concentrations with the resolution of unstable angina [48]. Both the local and systemic inflammatory process precedes the acute coronary event and persists despite the resolution of clinical symptoms indicated by the ongoing increased concentrations of sICAM-1, sVCAM-1, sE selectin, and sP selectin following ACS [49, 50]. Serum CRP concentrations were reported to remain increased at the time of discharge and at three months' follow up in up to 50% of patients with unstable angina [51]. Furthermore, the persistent increase of CRP in patients with unstable angina was associated with frequent hospital readmission for recurrent instability. Thus, there is a potential link between recurrent ischemic episodes and persistent inflammatory stimuli.

The demonstration of the activation of macrophages, lymphocytes, mast cells, monocytes, and endothelial cells and increased inflammatory cytokines all confirm the critical pathological role of both local and systemic inflammation in ACS and further suggest that the intensity of the inflammatory reaction influences clinical outcome in ACS [52].

INFLAMMATORY MARKERS IN ACUTE CORONARY SYNDROMES

C-reactive protein (CRP) and serum amyloid A are markers of acute inflammation. The acute phase response of CRP and serum amyloid A is a non-specific phenomenon reflecting cytokine mediated hepatic production triggered by inflammation, infection, and tissue injury. Activated macrophages secrete interleukin 6 (IL-6) and IL 1, which determine the production of acute-phase reactant proteins in the liver [53]. CRP is also produced by human coronary artery smooth muscle cells [54].

CRP is an independent risk factor in atherosclerotic disease and even small rises in baseline CRP concentrations in patients without biochemical evidence of myocardial necrosis are associated with an increased risk of an adverse event [55, 56]. It seems to reflect an inflammatory reaction of the arterial wall and might therefore indicate an ongoing inflammation-mediated atherosclerotic process [55-58]. Although initially considered only a "marker" of inflammation, CRP itself has been shown to possess proinflammatory and proatherogenic properties. It stimulates endothelial cells to express adhesion molecules and secrete cytokines [59, 60] and it decreases the expression of endothelial NO synthase [61, 62]. CRP accumulates in macrophage-rich regions of nascent atherosclerotic lesions and activates the macrophages to express cytokines and tissue factor, while enhancing macrophage uptake of LDL [63]. It also amplifies proinflammatory effects of several other mediators including endotoxin [64, 65]. However, many other factors including metabolic syndrome, type 2 diabetes, insulin resistance, abdominal obesity, renal failure and smoking affect CRP levels [66-70].

Concentrations of CRP [71, 72], serum amyloid A and IL 6 [73] are increased in patients with unstable angina and can predict the risk of adverse outcomes in patients with unstable angina [74, 75]. Liuzzo *et al.* [74] have shown that concentrations of CRP and serum amyloid A in unstable angina increase independently of myocardial cell injury. They also reported that higher concentrations of CRP at the time of hospital admission (> 3.0 mg/l) were predictive of a poor outcome in unstable angina. In ACS patients who are treated with very early revascularization, CRP is a strong independent predictor of both short-term and long-term mortality [76].

IL-6 is the major cytokine of the acute phase response and is intimately involved in the pathogenesis of ACS [77]. It stimulates production of fibrinogen and CRP, triggers the expression of adhesion molecules and TNF, stimulates macrophages to produce tissue factor and matrix metalloproteinases, and stimulates vascular smooth muscle cell proliferation and platelet aggregation. Circulating levels of IL-6 are a strong independent marker of increased mortality among patients with unstable angina [73].

TNF-α is a cytokine produced by a variety of cells, including macrophages, endothelial cells and smooth muscle cells. It has an essential role in the amplification of the inflammatory cascade. High levels of TNF-α identify stable patients with CAD at risk for recurrent cardiovascular events [78], but its

short plasma half-life has limited its clinical utility as a screening tool.

Soluble CD40 ligand (sCD40L) is released from both activated lymphocytes and activated platelets [79-81]. Both membrane-bound and soluble CD40L can interact with the CD40 receptor, which is expressed on B-lymphocytes, macrophages, endothelial cells, vascular smooth muscle cells and activated platelets. CD40-CD40L interaction plays a pathogenic role in inflammatory disorders, as well as in coronary disease progression and plaque destabilization [82, 83]. Stimulation of endothelial cells by CD40L causes increased expression of adhesion molecules and cytokines. Membrane-bound and sCD40L may promote matrix metalloproteinase expression in vascular smooth muscle cells and macrophages. The CD40-CD40L interaction induces expression of procoagulant tissue factor from monocytes, endothelial cells and smooth muscle cells [84, 85]. Elevation of sCD40L is detectable in the serum of patients with ACS [86] and serves as a prognostic marker, with higher levels indicating a significantly increased risk of death or MI.

Lysophospholipids and arachidonic acid derivatives (prostaglandins and leukotrienes) participate in inflammation and smooth muscle cell proliferation. Lipoprotein associated phospholipase A2 (Lp-PLA2), which hydrolyze phospholipids to generate lysophospholipids and arachidonic acid, has been shown to be a strong independent predictor for cardiovascular events [87-89]. Hirsh *et al.* [90] reported that local release of thromboxane B2 into the coronary circulation was associated with recent episodes of ischemic chest pain in unstable angina. Increased urinary excretion of leukotrienes D4 and E4 was observed in patients with unstable angina.

Matrix metalloproteinases degrade collagen and extracellular matrix and weaken the plaque stability. Matrix metalloproteinase activity, which is upregulated by inflammatory mediators including TNF-α, CD40L and IL-1, is elevated in ACS [91-93]. Pregnancy-associated plasma protein-A, which is a metalloproteinase enzyme and a specific activator of insulin-like growth factor, is also a mediator of atherosclerosis and is increased in patients with ACS correlating highly with CRP [94].

Increased surface expression of adhesion molecules, such as E-selectin, ICAM-1 and VCAM-1, is involved in arresting leukocyte rolling and promoting adhesion. The extracellular portion of these adhesion molecules is cleaved and detected in serum as soluble cell adhesion molecule. The soluble forms of adhesion molecules are increased in patients with ACS [36-38]. It is reported that the increase in concentrations of sVCAM-1 provides prognostic information similar to increased concentration of CRP in ACS [95].

Activated neutrophils secrete myeloperoxidase, which deplete nitric oxide and convert low-density lipoprotein into a form for rapid uptake by macrophages, leading to increased foam cell formation. High levels of leukocyte and blood myeloperoxidase has been shown to be significant predictors for the risk of coronary artery disease [96].

THE ROLE OF ALLERGY IN ACUTE CORONARY SYNDROMES

The role of inflammation and mast cell activation has been well established in atherosclerotic plaque destabilization and rupture in ACS. Similarly, hypersensitivity or allergic reactions may cause ACS. Since the same substances from the same cells are present in both acute allergic episodes and ACS, it is not surprising to have an ACS during an allergic episode. It has been shown that patients suffering from IgE mediated hypersensitivity reactions or anaphylaxis may exhibit cardiovascular symptoms and mast cell activation and degranulation are responsible for the cardiovascular alterations [6].

During allergic episodes; mast cells are activated by IgE mediated cross linking of Fce receptor I [27], histamine releasing factors secreted by macrophages and T lymphocytes [24, 25] and anaphylatoxin components of the complement system (C3a, C5a) [97]. When activated, mast cells rapidly release several vasoconstricting and collagen degrading inflammatory mediators including histamine, neutral proteases (such as tryptase and chymase), arachidonic acid products (leukotrienes by lipoxygenase pathway and prostaglandins by cycloxygenase pathway), platelet activating factor and a variety of cytokines and chemokines (Fig. 2).

Histamine and serotonin are powerful coronary vasoconstrictors and induce coronary artery spasm. Histamine can also induce proinflammatory cytokine production from endothelial cells [98]. Histamine can activate platelets and potentiate their aggregation [99]. Histamine can induce tissue factor expression and activity in human aortic endothelial cells and vascular smooth muscle cells [100]. In addition to histamine released from mast cells, monocytes also express tissue factor on their surfaces and can specifically activate the coagulation cascade after exposure to an immune stimulus [46]. Tryptase and chymase are metalloproteinase activators that can trigger degradation of collagen and induce weakening of the atheromatous plaque and its erosion or rupture [101]. Chymase also converts angiotensin I to angiotensin II, which can act synergistically with histamine and aggravate coronary spasm [20]. Leukotrienes are powerful arterial vasoconstrictors while thromboxane is a potent mediator of platelet aggregation in addition to its vasoconstricting properties. Thus all these mediators released during an allergic insult may fascilitate initiation of an ACS.

The coincidental occurrence of chest pain with characteristic clinical symptoms, signs, and laboratory findings of angina pectoris together with an allergic, hypersensitivity or anaphylactic reaction is named as "allergic angina" [102]. Allergic angina can progress to acute MI, which is named as allergic MI [103, 104]. Allergic angina and allergic MI are now referred as "Kounis Syndrome" [105-107]. Kounis syndrome is described as the concurrence of ACS associated with mast cell activation including allergic or hypersensitivity reactions as well as anaphylactic or anaphylactoid reactions.

In allergic ACS, ACS may develop within the first 24 hours following the onset of allergic symptoms. The concept of allergic ACS is based on the release of inflammatory mediators from activated mast cells and leukocytes that induce coronary spasm or digest the upper layer of the plaque facilitating plaque rupture. Two variants of this syndrome have been described according to the findings of coronary angiography [6, 108, 109]. Type I variant includes patients having normal coronary angiography with no predisposing risk

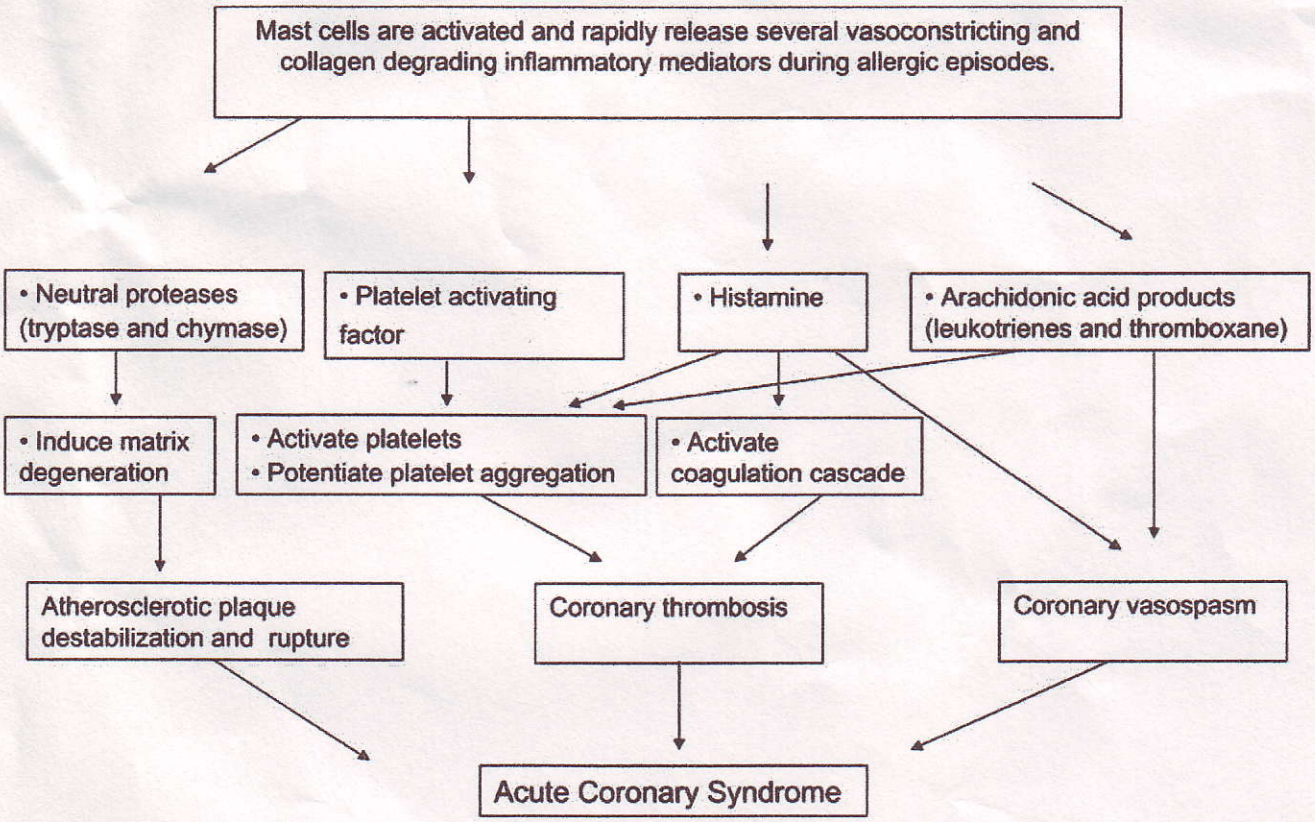

Fig. (2). The role of allergy in acute coronary syndrome.

factors for coronary artery disease. In type I variant acute allergic reaction may cause coronary artery spasm and vasospastic angina with no rise in cardiac enzymes or it may progress to acute MI. This variant may reflect an endothelial dysfunction or microvascular angina. On the other hand, type II variant includes patients with quiescent preexisting atheromatous disease. In type II variant, allergic reaction triggers atheromatous plaque disruption and thus manifests as an acute MI. Several reports have shown that type I variant of Kounis syndrome has better prognosis than type II variant [110]. However, in both types the prognosis depends on the magnitude of the initial allergic response, the patient's sensitivity, the patient's comorbidity, the site of antibody-antigen reaction, the allergen concentration and the route of allergen entrance [108].

Although allergic episodes are common in daily practice, only few patients develop chest pain and ACS. It seems likely that atopic individuals are at high risk of ACS than normal people [111]. It is hypothesized that there is a threshold level of mast cell content above which it can provoke coronary artery spasm and plaque rupture [108]. The exact frequency of ACS associated with acute allergic reactions is not known; but it is increasingly encountered in clinical practice than anticipated. There are several conditions and drugs reported to be responsible for Kounis syndrome. So far, it is reported that certain environmental exposures including poisons, ant, bee or wasp stings, jelly fish sting, grass cutting, latex contact and viper venoms; conditions such as angioedema, bronchial asthma, exercise-induced anaphylaxis, food allergy, idiopathic anaphylaxis, serum sickness, urticaria, and mastocytosis; and drugs such as antibiotics (penicillin), analgesics, intravenous anesthetics, antineoplastics, contrast media, corticosteroids, dextran, nonsteroidal antiinflammatory drugs, skin disinfectants, thrombolytics (streptokinase and urokinase), lepirudin, tetanus toxoid, glaphenine, and zomepirac [104, 105] result in Kounis syndrome.

ANTI-INFLAMMATORY THERAPY IN ACUTE CORONARY SYNDROMES

As the role of inflammation in ACS is more understood, management of ACS is more focused on the anti-inflammatory aspects. Among the non medical approach, cessation of cigarette smoking and weight loss take the lead. Cigarette smoking and obesity have been shown to increase CRP, IL-6 and soluble ICAM-1. Physical exercise has also been shown to have a beneficial effect in terms of reducing the concentration of several inflammatory markers [112, 113].

Anti-inflammatory therapy begins to form the basis for the management of patients with ACS. Current ACS therapy includes the use of drugs involving aspirin, statins, clopidogrel, angiotensin-converting enzyme inhibitors. In addition to these well known drugs, attempts have been made to counteract the actions of inflammatory mediators by using, experimentally, mediator antagonists, inhibitors of mediator biosynthesis and mediator receptor blockers [114]. It has been suggested that the increased leukocyte adhesiveness observed in some patients with unstable angina identifies those who will benefit from treatment with anti-inflammatory agents [115].

Aspirin is the most widely used drug in ACS. It is a platelet anti-aggregating agent through inhibition of the cyclooxygenase-1 (COX-1) enzyme. It also has anti-inflammatory properties. In primary prevention, the magnitude of risk reduction attributable to aspirin appears to be greatest among those with elevated CRP, again reemphasizing the importance of the vascular inflammatory state [55]. On the other hand, cyclooxygenase-2 (COX-2) is a highly inducible enzyme responsible for the generation of inflammatory prostaglandins at sites of inflammation, including the vascular walls. Selective inhibition of COX-2 with specific COX-2 inhibitors showed a potential clinical benefit in coronary disease [116, 117]. However, additional research is needed to further clarify the selective inhibition of COX-2 due to the reports about its adverse effects [118, 119].

Statins are also widely used in ACS due to their anti-inflammatory effects in addition to reduction LDL cholesterol. Statins have been shown to reduce CRP levels irrespective of the magnitude of LDL reduction. Clinical risk reduction with statin therapy is particularly large in patients with elevated CRP levels [120]. Statins have been shown to improve endothelial function [121]. These beneficial effects of statins are believed to involve the inhibition of Rho-kinase pathway. Rho-kinase has proatherogenic effects, including causing a decrease in nitric oxide synthase and plasminogen activator inhibitor-1 (PAI-1). Statins can block integrins and decrease matrix metalloproteinase secretion [122-124].

The benefit of pretreatment of clopidogrel prior to coronary interventions is shown to be more pronounced especially in patients with a high baseline CRP [125]. The combination of aspirin and clopidogrel may have a synergistic effect on inhibition of inflammation and platelet activation [126, 127].

Angiotensin-converting enzyme (ACE) inhibitors may provide anti-inflammatory protection by inhibiting the synthesis and release of IL 6, which is enhanced by angiotensin II [128]. ACE has been found in the shoulder region of the atherosclerotic plaque at sites of clustered macrophages, and ACE activity appears enhanced in unstable human plaques compared to stable lesions [129, 130]. ACE inhibition in patients with documented coronary disease has been shown to reduce the incidence of acute ischemic cardiovascular events [106-108].

Thiazolidinediones are oral insulin sensitizers that enhance glucose uptake by skeletal muscle. They may block growth and migration of vascular smooth muscle cells and inhibit the expression of VCAM-1 and ICAM-1 in activated endothelial cells and significantly decrease the homing of macrophages and monocytes to atherosclerotic plaques [131].

Current research on the infective etiology of coronary disease has focused mainly on the chlamydia pneumonia and helicobacter pylori organisms. Two small studies suggest that macrolide antibiotics reduce the incidence of recurrent events in patients with unstable angina [132] and acute myocardial infarction [133]. Amoxicillin is also shown to decrease CRP in patients with unstable angina [134]. Although further studies are needed to elucidate the mechanisms of benefit of antibiotics and vaccinations, suggested possible mechanisms include alteration in clotting factors, platelet aggregation, concentration of inflammatory response proteins and alteration in cytokine concentrations.

Selective mast cell surface membrane protection and stabilization is considered a potential therapeutic strategy. Since mast cell degranulation is implicated in ACS, drugs that stabilize the mast cell membrane (mast cell stabilizators) are suggested to be useful in prevention of ACS [23], at least in some instances such as atopic patients or patients who have already experienced a first Kounis syndrome. Sodium nedocromil, sodium cromoglycate, ketotifen, and lodoxamide are currently used mast cell stabilizators in experiments. Nemmar *et al.* [135] managed to abrogate late thrombotic events by inhibition of mast cell degranulation with sodium cromoglycate. In a recent study [136], anti-IgE therapy with humanized IgG1 monoclonal antibodies masked the region of mast cell surface responsible for IgE binding and protected against mast cell degranulation. Treatment with anti-IL-4Rα antibodies is also suggested in atopic patients, who produce large amounts of interleukin-4 and interleukin-13 [137].

The action of histamine *via* histamine-1 (H-1) receptors on smooth muscle cells in the medial layer of coronary arteries is mainly vasoconstriction [33]. The vasoconstrictive response to histamine is vigorous, especially in atherosclerotic segments because the damaged endothelium is incapable of synthesizing and secreting sufficient amounts of vasodilatory mediators [34]. Since there is a predominant role of mast cell and its mediator histamine on the process of ACS, especially during the early period of the event when the action of histamine is suspected to be the greatest, the use of antihistaminics might be helpful in blocking its effects. In a prospective clinical study [138], we explored the anti-ischemic additive effect of a selective H-1 receptor blocker antihistaminic, loratidine, in patients who have recently suffered an acute MI. We demonstrated that adding loratidine to an anti-ischemic regimen significantly improved ischemic parameters induced by an exercise stress testing performed 2 and 3 weeks after the event. We believed that the anti-ischemic effect of loratidine did not depend on the time related self-healing process of myocardial ischemia. We also suggest that anti-inflammatory drugs, antihistaminics, or mast cell stabilizators suppress the acute short term inflammatory reaction to stent implantation and might yield some beneficial effect in decreasing the restenosis rate [28].

Leukotrienes have vasoconstrictor effects in diseased arteries, increase vascular permeability and smooth muscle cell proliferation, facilitate neutrophil adhesion to endothelial cells and regulate angiotensin-II mediated vascular effects. Antileukotriene drugs are being searched in treatment of vascular diseases [139]. Similarly Toll-like receptor 4 (TLR4), which also induces proinflammatory cytokine production when activated, is a potential candidate in the search for new ways to inhibit the development of atherosclerotic vascular disease [140]. Experimental animal studies suggest the use of anti-CD40L antibody in stabilizing atheromatous plaques [80]. There is also considerable evidence today that polyphenolic plant compounds such as flavonoids may block basophils and mast cells and inhibit mediator release [141].

CONCLUSION

Inflammation plays a mjor role in atherosclerotic process and ACS. Inflammation is responsible for the degeneration

of plaques that leads to their sudden rupture and coronary vasospasm. Since the pathways and mediators are similar, allergic or hypersensitivity reactions also may cause ACS. Many drugs or conditions may cause allergy associated ACS, so it will certainly be lifesaving to the sufferer if those complications be minded, evaluated and intervened earlier.

In addition to classic traditional risk factors, inflammatory related risk factors and inflammatory markers such as CRP should be used in predicting the absolute risk of a cardiovascular event in individual patients. Now, treating inflammation and inhibiting the activation of inflammatory cells or the action of the inflammatory mediators gain more importance in the management of atherosclerosis and ACS. New agents targeting various mediators and trigger-points in inflammation-related pathways are being investigated to reduce clinical events.

REFERENCES

[1] Braunwald, E. *Circulation*, **1998**, *98*, 2219.
[2] Buja, L.M.; Willerson, J.T. *Circulation*, **1994**, *89*, 503.
[3] Murtagh, B.M.; Anderson, H.V. *J. Invasive Cardiol.*, **2004**, *16*, 377.
[4] Sakata, Y.; Komamura, K.; Hirayama, A.; Nanto, S.; Kitakaze, M.; Hori, M.; Kodama, K. *Am. J. Cardiol.*, **1996**, *77*, 1121.
[5] Constantinides, P. *Circulation*, **1995**, *92*, 1083.
[6] Nikolaidis, L.A.; Kounis, N.G.; Gradman, A.H. *Can. J. Cardiol.*, **2002**, *18*, 508.
[7] Fuster, V.; Badimon, L.; Badimon, J.J.; Chesebro, J.H. *N. Engl. J. Med.*, **1992**, *326*, 242.
[8] Davies, M.J.; Woolf, N.; Rowles, P.M.; Pepper, J. *Br. Heart J.*, **1988**, *60*, 459.
[9] Mulvihill, N.T.; Foley, J.B. *Heart*, **2002**, *87*, 201.
[10] Davies, M.J. *Heart*, **2000**, *83*, 361.
[11] Van der Wal, A.C.; Becker, A.E.; van der Loos, C.M.; Das, P.K. *Circulation*, **1994**, *89*, 36.
[12] Kohchi, K.; Takebayashi, S.; Hiroki, T.; Nobuyoshi, M. *Circulation*, **1985**, *71*, 709.
[13] Nikkari, S.T.; O'Brien, K.D.; Ferguson, M.; Hatsukami, T.; Welgus, H.G.; Alpers, C.E.; Clowes, A.W. *Circulation*, **1995**, *92*, 1393.
[14] Barnes, P.J.; Karin, M. *N. Engl. J. Med.*, **1997**, *336*, 1066.
[15] Van der Wal, A.C.; Piek, J.J.; de Boer, O.J.; Koch, K.T.; Teeling, P.; van der Loos, C.M.; Becker, A.E. *Heart*, **1998**, *80*, 14.
[16] Neri Serneri, G.G.; Prisco, D.; Martini, F.; Gori, A.M.; Brunelli, T.; Poggesi, L.; Rostagno, C.; Gensini, G.F.; Abbate, R. *Circulation*, **1997**, *95*, 1806.
[17] Bennett, M.R. *Cardiovasc. Res.*, **1999**, *41*, 361.
[18] Forman, M.B.; Oates, J.A.; Robertson, D.; Robertson, R.M.; Roberts, L.J. 2nd.; Virmani, R. *N. Engl. J. Med.*, **1985**, *313*, 1138.
[19] Kovanen, P.T.; Kaartinen, M.; Paavonen, T. *Circulation*, **1995**, *92*, 1084.
[20] Laine, P.; Kaartinen, M.; Penttilä, A.; Panula, P.; Paavonen, T.; Kovanen, P.T. *Circulation*, **1999**, *99*, 361.
[21] Irani, A.A.; Schechter, N.M.; Craig, S.S.; DeBlois, G.; Schwartz, L.B. *Proc. Natl. Acad. Sci. USA.*, **1986**, *83*, 4464.
[22] Pomerance, A. *J. Pathol. Bacteriol.*, **1958**, *76*, 55.
[23] Kaartinen, M.; Penttilä, A.; Kovanen, P.T. *Circulation*, **1994**, *90*, 1669.
[24] Sedgwick, J.D.; Holt, P.G.; Turner, K.J. *Clin. Exp. Immunol.*, **1981**, *45*, 409.
[25] Liu, M.C.; Proud, D.; Lichtenstein, L.M.; MacGlashan, D.W. Jr.; Schleimer, R.P.; Adkinson, N.F. Jr.; Kagey-Sobotka, A.; Schulman, E.S.; Plaut, M. *J. Immunol.*, **1986**, *136*, 2588.
[26] Erdogan, O.; Gul, C.; Altun, A.; Ozbay, G. *Angiology*, **2003**, *54*, 73.
[27] Ishizaka, T.; Ishizaka, K. *Prog. Allergy*, **1984**, *34*, 188.
[28] Erdogan, O.; Altun, A.; Gul, C.; Ozbay, G. *Jpn. Heart J.*, **2003**, *44*, 593.
[29] Busse, W.W.; Lemanske, R.F. Jr. *N. Engl. J. Med.*, **2001**, *344*, 350.
[30] Szczeklik, A.; Sladek, K.; Szczerba, A.; Dropinski, J. *Circulation*, **1988**, *77*, 1245.
[31] Galli, S.J. *N. Engl. J. Med.*, **1993**, *328*, 257.
[32] Ginsburg, R.; Bristow, M.R.; Davis, K.; Dibiase, A.; Billingham, M.E. *Circulation*, **1984**, *69*, 430.
[33] Toda, N. *Circ. Res.*, **1987**, *61*, 280.
[34] Kalsner, S.; Richards, R. *Science*, **1984**, *223*, 1435.
[35] Poston, R.N.; Haskard, D.O.; Coucher, J.R.; Gall, N.P.; Johnson-Tidey, R.R. *Am. J. Pathol.*, **1992**, *140*, 665.
[36] Shyu, K.G.; Chang, H.; Lin, C.C.; Kuan, P. *Chest*, **1996**, *109*, 1627.
[37] Ikeda, H.; Takajo, Y.; Ichiki, K.; Ueno, T.; Maki, S.; Noda, T.; Sugi, K.; Imaizumi, T. *Circulation*, **1995**, *92*, 1693.
[38] Mulvihill, N.; Foley, J.B.; Ghaisas, N.; Murphy, R.; Crean, P.; Walsh, M. *Am. J. Cardiol.*, **1999**, *83*, 1265.
[39] Muhlestein, J.B.; Hammond, E.H.; Carlquist, J.F.; Radicke, E.; Thomson, M.J.; Karagounis, L.A.; Woods, M.L.; Anderson, J.L. *J. Am. Coll. Cardiol.*, **1996**, *27*, 1555.
[40] Pasceri, V.; Cammarota, G.; Patti, G.; Cuoco, L.; Gasbarrini, A.; Grillo, R.L.; Fedeli, G.; Gasbarrini, G.; Maseri, A. *Circulation*, **1998**, *97*, 1675.
[41] Mehta, J.L.; Saldeen, T.G.; Rand, K. *J. Am. Coll. Cardiol.*, **1998**, *31*, 1217.
[42] Hendrix, M.G.; Salimans, M.M.; van Boven, C.P.; Bruggeman, C.A. *Am. J. Pathol.*, **1990**, *136*, 23.
[43] Zhou, Y.F.; Leon, M.B.; Waclawiw, M.A.; Popma, J.J.; Yu, Z.X.; Finkel, T.; Epstein, S.E. *N. Engl. J. Med.*, **1996**, *335*, 624.
[44] Grattan, M.T.; Moreno-Cabral, C.E.; Starnes, V.A.; Oyer, P.E.; Stinson, E.B.; Shumway, N.E. *JAMA*, **1989**, *261*, 3561.
[45] Burian, K.; Kis, Z.; Virok, D.; Endresz, V.; Prohaszka, Z.; Duba, J.; Berencsi, K.; Boda, K.; Horvath, L.; Romics, L.; Fust, G.; Gonczol, E. *Circulation*, **2001**, *103*, 1503.
[46] Rickles, F.R.; Levin, J.; Hardin, J.A.; Barr, C.F.; Conrad, M.E. Jr. *J. Lab. Clin. Med.*, **1977**, *89*, 792.
[47] Serneri, G.G.; Abbate, R.; Gori, A.M.; Attanasio, M.; Martini, F.; Giusti, B.; Dabizzi, P.; Poggesi, L.; Modesti, P.A.; Trotta, F. *Circulation*, **1992**, *86*, 790.
[48] Biasucci, L.M.; D'Onofrio, G.; Liuzzo, G.; Zini, G.; Monaco, C.; Caligiuri, G.; Tommasi, M.; Rebuzzi, A.G.; Maseri, A. *J. Am. Coll. Cardiol.*, **1996**, *27*, 611.
[49] Ault, K.A.; Cannon, C.P.; Mitchell, J.; McCahan, J.; Tracy, R.P.; Novotny, W.F.; Reimann, J.D.; Braunwald, E. *J. Am. Coll. Cardiol.*, **1999**, *33*, 634.
[50] Mulvihill, N.T.; Foley, J.B.; Murphy, R.; Crean, P.; Walsh, M. *J. Am. Coll. Cardiol.*, **2000**, *36*, 1210.
[51] Biasucci, L.M.; Liuzzo, G.; Grillo, R.L.; Caligiuri, G.; Rebuzzi, A.G.; Buffon, A.; Summaria, F.; Ginnetti, F.; Fadda, G.; Maseri, A. *Circulation*, **1999**, *99*, 855.
[52] Ridker, P.M. *Circulation*, **1998**, *97*, 1671.
[53] Libby, P.; Warner, S.J.; Friedman, G.B. *J. Clin. Invest.*, **1988**, *81*, 487.
[54] Calabró, P.; Willerson, J.T.; Yeh, E.T. *Circulation*, **2003**, *108*, 1930.
[55] Ridker, P.M.; Cushman, M.; Stampfer, M.J.; Tracy, R.P.; Hennekens, C.H. *N. Engl. J. Med.*, **1997**, *336*, 973.
[56] Ridker, P.M.; Buring, J.E.; Shih, J.; Matias, M.; Hennekens, C.H. *Circulation*, **1998**, *98*, 731.
[57] van der Wal, A.C.; Becker, A.E.; Koch, K.T.; Piek, J.J.; Teeling, P.; van der Loos, C.M.; David, G.K. *Heart*, **1996**, 76, 312.
[58] Kuller, L.H.; Tracy, R.P.; Shaten, J.; Meilahn, E.N. *Am. J. Epidemiol.*, **1996**, *144*, 537.
[59] Pasceri, V.; Willerson, J.T.; Yeh, E.T. *Circulation*, **2000**, *102*, 2165.
[60] Pasceri, V.; Cheng, J.S.; Willerson, J.T.; Yeh, E.T. *Circulation*, **2001**, *103*, 2531.
[61] Verma, S.; Wang, C.H.; Li, S.H.; Dumont, A.S.; Fedak, P.W.; Badiwala, M.V.; Dhillon, B.; Weisel, R.D.; Li, R.K.; Mickle, D.A.; Stewart, D.J. *Circulation*, **2002**, *106*, 913.
[62] Venugopal, S.K.; Devaraj, S.; Yuhanna, I.; Shaul, P.; Jialal, I. *Circulation*, **2002**, *106*, 1439.
[63] Zwaka, T.P.; Hombach, V.; Torzewski, J. *Circulation*, **2001**, *103*, 1194.
[64] Yeh, E.T.; Anderson, H.V.; Pasceri, V.; Willerson, J.T. *Circulation*, **2001**, *104*, 974.
[65] Nakagomi, A.; Freedman, S.B.; Geczy, C.L. *Circulation*, **2000**, *101*, 1785.
[66] Ridker, P.M.; Buring, J.E.; Cook, N.R.; Rifai, N. *Circulation*, **2003**, *107*, 391.

[67] Jager, A.; van Hinsbergh, V.W.; Kostense, P.J.; Emeis, J.J.; Yudkin, J.S.; Nijpels, G.; Dekker, J.M.; Heine, R.J.; Bouter, L.M.; Stehouwer, C.D. *Arterioscler. Thromb. Vasc. Biol.*, **1999**, *19*, 3071.

[68] Festa, A.; D'Agostino, R. Jr.; Howard, G.; Mykkänen, L.; Tracy, R.P.; Haffner, S.M. *Circulation*, **2000**, *102*, 42.

[69] Visser, M.; Bouter, L.M.; McQuillan, G.M.; Wener, M.H.; Harris, T.B. *JAMA*, **1999**, *282*, 2131.

[70] Shlipak, M.G.; Fried, L.F.; Crump, C.; Bleyer, A.J.; Manolio, T.A.; Tracy, R.P.; Furberg, C.D.; Psaty, B.M. *Circulation*, **2003**, *107*, 87.

[71] Berk, B.C.; Weintraub, W.S.; Alexander, R.W. *Am. J. Cardiol.*, **1990**, *65*, 168.

[72] de Beer, F.C.; Hind, C.R.; Fox, K.M.; Allan, R.M.; Maseri, A.; Pepys, M.B. *Br. Heart J.*, **1982**, *47*, 239.

[73] Biasucci, L.M.; Liuzzo, G.; Fantuzzi, G.; Caligiuri, G.; Rebuzzi, A.G.; Ginnetti, F.; Dinarello, C.A.; Maseri, A. *Circulation*, **1999**, *99*, 2079.

[74] Liuzzo, G.; Biasucci, L.M.; Gallimore, J.R.; Grillo, R.L.; Rebuzzi, A.G.; Pepys, M.B.; Maseri, A. *N. Engl. J. Med.*, **1994**, *331*, 417.

[75] Morrow, D.A.; Rifai, N.; Antman, E.M.; Weiner, D.L.; McCabe, C.H.; Cannon, C.P.; Braunwald, E. *J. Am. Coll. Cardiol.*, **1998**, *31*, 1460.

[76] Mueller, C.; Buettner, H.J.; Hodgson, J.M.; Marsch, S.; Perruchoud, A.P.; Roskamm, H.; Neumann, F.J. *Circulation*, **2002**, *105*, 1412.

[77] Ridker, P.M.; Rifai, N.; Stampfer, M.J.; Hennekens, C.H. *Circulation*, **2000**, *101*, 1767.

[78] Ridker, P.M.; Rifai, N.; Pfeffer, M.; Sacks, F.; Lepage, S.; Braunwald, E. *Circulation*, **2000**, *101*, 2149.

[79] Lee, Y.; Lee, W.H.; Lee, S.C.; Ahn, K.J.; Choi, Y.H.; Park, S.W.; Seo, J.D.; Park, J.E. *Cardiology*, **1999**, *92*, 11.

[80] Henn, V.; Steinbach, S.; Büchner, K.; Presek, P.; Kroczek, R.A. *Blood*, **2001**, *98*, 1047.

[81] Henn, V.; Slupsky, J.R.; Gräfe, M.; Anagnostopoulos, I.; Förster, R.; Müller-Berghaus, G.; Kroczek, R.A. *Nature*, **1998**, *391*, 591.

[82] Mach, F.; Schönbeck, U.; Sukhova, G.K.; Atkinson, E.; Libby, P. *Nature*, **1998**, *394*, 200.

[83] Schönbeck, U.; Varo, N.; Libby, P.; Buring, J.; Ridker, P.M. *Circulation*, **2001**, *104*, 2266.

[84] Mach, F.; Schönbeck, U.; Bonnefoy, J.Y.; Pober, J.S.; Libby, P. *Circulation*, **1997**, *96*, 396.

[85] Urbich, C.; Mallat, Z.; Tedgui, A.; Clauss, M.; Zeiher, A.M.; Dimmeler, S. *J. Clin. Invest.*, **2001**, *108*, 1451.

[86] Aukrust, P.; Müller, F.; Ueland, T.; Berget, T.; Aaser, E.; Brunsvig, A.; Solum, N.O.; Forfang, K.; Frøland, S.S.; Gullestad, L. *Circulation*, **1999**, *100*, 614.

[87] Packard, C.J.; O'Reilly, D.S.; Caslake, M.J.; McMahon, A.D.; Ford, I.; Cooney, J.; Macphee, C.H.; Suckling, K.E.; Krishna, M.; Wilkinson, F.E.; Rumley, A.; Lowe, G.D. *N. Engl. J. Med.*, **2000**, *343*, 1148.

[88] Blake, G.J.; Dada, N.; Fox, J.C.; Manson, J.E.; Ridker, P.M. *J. Am. Coll. Cardiol.*, **2001**, *38*, 1302.

[89] Ballantyne, C.M.; Hoogeveen, R.C.; Bang, H.; Coresh, J.; Folsom, A.R.; Heiss, G.; Sharrett, A.R. *Circulation*, **2004**, *109*, 837.

[90] Hirsh, P.D.; Hillis, L.D.; Campbell, W.B.; Firth, B.G.; Willerson, J.T. *N. Engl. J. Med.*, **1981**, *304*, 685.

[91] Kai, H.; Ikeda, H.; Yasukawa, H.; Kai, M.; Seki, Y.; Kuwahara, F.; Ueno, T.; Sugi, K.; Imaizumi, T. *J. Am. Coll. Cardiol.*, **1998**, *32*, 368.

[92] Inokubo, Y.; Hanada, H.; Ishizaka, H.; Fukushi, T.; Kamada, T.; Okumura, K. *Am. Heart J.*, **2001**, *141*, 211.

[93] Hojo, Y.; Ikeda, U.; Ueno, S.; Arakawa, H.; Shimada, K. *Jpn. Circ. J.*, **2001**, *65*, 71.

[94] Bayes-Genis, A.; Conover, C.A.; Overgaard, M.T.; Bailey, K.R.; Christiansen, M.; Holmes, D.R. Jr.; Virmani, R.; Oxvig, C.; Schwartz, R.S. *N. Engl. J. Med.*, **2001**, *345*, 1022.

[95] Mulvihill, N.T.; Foley, J.B.; Murphy, R.T.; Curtin, R.; Crean, P.A.; Walsh, M. *Heart*, **2001**, *85*, 623.

[96] Zhang, R.; Brennan, M.L.; Fu, X.; Aviles, R.J.; Pearce, G.L.; Penn, M.S.; Topol, E.J.; Sprecher, D.L.; Hazen, S.L. *JAMA*, **2001**, *286*, 2136.

[97] Metcalfe, D.D.; Kaliner, M.; Donlon, M.A. *Crit. Rev. Immunol.*, **1981**, *3*, 23.

[98] Li, Y.; Chi, L.; Stechschulte, D.J.; Dileepan, K.N. *Microvasc. Res.*, **2001**, *61*, 253.

[99] Masini, E.; Di Bello, M.G.; Raspanti, S.; Fomusi Ndisang, J.; Baronti, R.; Cappugi, P.; Mannaioni, P.F. *Inflamm. Res.*, **1998**, *47*, 211.

[100] Steffel, J.; Akhmedov, A.; Greutert, H.; Lüscher, T.F.; Tanner, F.C. *Circulation*, **2005**, *112*, 341.

[101] Johnson, J.L.; Jackson, C.L.; Angelini, G.D.; George, S.J. *Arterioscler. Thromb. Vasc. Biol.*, **1998**, *18*, 1707.

[102] Kounis, N.G.; Zavras, G.M. *Br. J. Clin. Pract.*, **1991**, *45*, 121.

[103] Kounis, N.G.; Zavras, G.M. *Circulation*, **1996**, *94*, 1789.

[104] Kounis, N.G.; Grapsas, N.D.; Goudevenos, J.A. *Circulation*, **1999**, *100*, e156.

[105] Zavras, G.M.; Papadaki, P.J.; Kokkinis, C.E.; Kalokairinov, K.; Kouni, S.N.; Batsolaki, M.; Gouvelou-Deligianni, G.V.; Koutsojannis, C. *Int. J. Clin. Pract.*, **2003**, *57*, 622.

[106] Mazarakis, A.; Koutsojannis, C.M.; Kounis, N.G.; Alexopoulos, D. *Acta Cardiol.*, **2005**, *60*, 341.

[107] Koutsojannis, C.M.; Mallioris, C.N.; Kounis, N.G. *Circ. J.*, **2004**, *68*, 806.

[108] Kounis, N.G. *Int. J. Cardiol.*, **2006**, *110*, 7.

[109] Frangides, C.; Kouni, S.; Niarchos, C.; Koutsojannis, C. *Eur. J. Intern. Med.*, **2006**, *17*, 215.

[110] Mori, E.; Ikeda, H.; Ueno, T.; Kai, H.; Haramaki, N.; Hashino, T.; Ichiki, K.; Katoh, A.; Eguchi, H.; Ueyama, T.; Imaizumi, T. *Clin. Cardiol.*, **1997**, *20*, 656.

[111] Criqui, M.H.; Lee, E.R.; Hamburger, R.N.; Klauber, M.R.; Coughlin, S.S. *Am. J. Med.*, **1987**, *82*, 964.

[112] Manson, J.E.; Hu, F.B.; Rich-Edwards, J.W.; Colditz, G.A.; Stampfer, M.J.; Willett, W.C.; Speizer, F.E.; Hennekens, C.H. *N. Engl. J. Med.*, **1999**, *341*, 650.

[113] Smith, J.K.; Dykes, R.; Douglas, J.E.; Krishnaswamy, G.; Berk, S. *JAMA*, **1999**, *281*, 1722.

[114] Sebaldt, R.J.; Sheller, J.R.; Oates, J.A.; Roberts, L.J. 2nd.; FitzGerald, G.A. *Proc. Natl. Acad. Sci. USA*, **1990**, *87*, 6974.

[115] Leibovitz, E.; Hertz, Y.; Liberman, E.; Sclarovsky, S.; Berliner, S. *Clin. Cardiol.*, **1997**, *20*, 1017.

[116] Altman, R.; Luciardi, H.L.; Muntaner, J.; Del Rio, F.; Berman, S.G.; Lopez, R.; Gonzalez, C. *Circulation*, **2002**, *106*, 191.

[117] Chenevard, R.; Hürlimann, D.; Béchir, M.; Enseleit, F.; Spieker, L.; Hermann, M.; Riesen, W.; Gay, S.; Gay, R.E.; Neidhart, M.; Michel, B.; Lüscher, T.F.; Noll, G.; Ruschitzka, F. *Circulation*, **2003**, *107*, 405.

[118] Mukherjee, D.; Nissen, S.E.; Topol, E.J. *JAMA*, **2001**, *286*, 954.

[119] Pitt, B.; Pepine, C.; Willerson, J.T. *Circulation*, **2002**, *106*, 167.

[120] Ridker, P.M.; Rifai, N.; Pfeffer, M.A.; Sacks, F.M.; Moye, L.A.; Goldman, S.; Flaker, G.C.; Braunwald, E. *Circulation*, **1998**, *98*, 839.

[121] Laufs, U.; Wassmann, S.; Hilgers, S.; Ribaudo, N.; Böhm, M.; Nickenig, G. *Am. J. Cardiol.*, **2001**, *88*, 1306.

[122] Frenette, P.S. *N. Engl. J. Med.*, **2001**, *345*, 1419.

[123] Bellosta, S.; Via, D.; Canavesi, M.; Pfister, P.; Fumagalli, R.; Paoletti, R.; Bernini, F. *Arterioscler. Thromb. Vasc. Biol.*, **1998**, *18*, 1671.

[124] Ikeda, U.; Shimpo, M.; Ohki, R.; Inaba, H.; Takahashi, M.; Yamamoto, K.; Shimada, K. *Hypertension*, **2000**, *36*, 325.

[125] Chew, D.P.; Bhatt, D.L.; Robbins, M.A.; Mukherjee, D.; Roffi, M.; Schneider, J.P.; Topol, E.J.; Ellis, S.G. *Am. J. Cardiol.*, **2001**, *88*, 672.

[126] Yusuf, S.; Zhao, F.; Mehta, S.R.; Chrolavicius, S.; Tognoni, G.; Fox, K.K. *N. Engl. J. Med.*, **2001**, *345*, 494.

[127] Moshfegh, K.; Redondo, M.; Julmy, F.; Wuillemin, W.A.; Gebauer, M.U.; Haeberli, A.; Meyer, B.J. *J. Am. Coll. Cardiol.*, **2000**, *36*, 699.

[128] Schieffer, B.; Schieffer, E.; Hilfiker-Kleiner, D.; Hilfiker, A.; Kovanen, P.T.; Kaartinen, M.; Nussberger, J.; Harringer, W.; Drexler, H. *Circulation*, **2000**, *101*, 1372.

[129] Hoshida, S.; Kato, J.; Nishino, M.; Egami, Y.; Takeda, T.; Kawabata, M.; Tanouchi, J.; Yamada, Y.; Kamada, T. *Circulation*, **2001**, *103*, 630.

[130] Potter, D.D.; Sobey, C.G.; Tompkins, P.K.; Rossen, J.D.; Heistad, D.D. *Circulation*, **1998**, *98*, 800.

[131] Haffner, S.M.; Greenberg, A.S.; Weston, W.M.; Chen, H.; Williams, K.; Freed, M.I. *Circulation*, **2002**, *106*, 679.

[132] Gurfinkel, E.; Bozovich, G.; Daroca, A.; Beck, E.; Mautner, B. *Lancet*, **1997**, *350*, 404.

[133] Gupta, S.; Leatham, E.W.; Carrington, D.; Mendall, M.A.; Kaski, J.C.; Camm, A.J. *Circulation*, **1997**, *96*, 404.

[134] Stone, A.F.; Mendall, M.A.; Kaski, J.C.; Edger, T.M.; Risley, P.; Poloniecki, J.; Camm, A.J.; Northfield, T.C. *Circulation,* **2002**, *106*, 1219.
[135] Nemmar, A.; Hoet, P.H.; Vermylen, J.; Nemery, B.; Hoylaerts, M.F. *Circulation,* **2004**, *110*, 1670.
[136] Leung, D.Y.; Sampson, H.A.; Yunginger, J.W.; Burks, A.W. Jr.; Schneider, L.C.; Wortel, C.H.; Davis, F.M.; Hyun, J.D.; Shanahan, W.R. Jr. *N. Engl. J. Med.*, **2003**, *348*, 986.
[137] Finkelman, F.D.; Rothenberg, M.E.; Brandt, E.B.; Morris, S.C.; Strait, R.T. *J. Allergy Clin. Immunol.*, **2005**, *115*, 449.
[138] Erdogan, O.; Altun, A.; Gazi, S.; Ozbay, G. *Am. Heart J.*, **2004**, *148*, e24.
[139] Spanbroek, R.; Grabner, R.; Lotzer, K.; Hildner, M.; Urbach, A.; Ruhling, K.; Moos, M.P.; Kaiser, B.; Cohnert, T.U.; Wahlers, T.; Zieske, A.; Plenz, G.; Robenek, H.; Salbach, P.; Kuhn, H.; Radmark, O.; Samuelsson, B.; Habenicht, A.J. *Proc. Natl. Acad. Sci. USA*, **2003**, *100*, 1238.
[140] Vink, A.; Schoneveld, A.H.; van der Meer, J.J.; van Middelaar, B.J.; Sluijter, J.P.; Smeets, M.B.; Quax, P.H.; Lim, S.K.; Borst, C.; Pasterkamp, G.; de Kleijn, D.P. *Circulation,* **2002**, *106*, 1985.
[141] Theoharides, T.C.; Bielory, L. *Ann. Allergy Asthma Immunol.*, **2004**, *93*, S24.

Received: June 17, 2008 **Revised: July 10, 2008** **Accepted: July 13, 2008**