Current Concepts of the Pathogenesis of the Acute Coronary Syndromes

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The last decade has witnessed a major reassessment of our perceptions about the acute coronary syndromes. Today, we recognize that thrombosis underlies most acute complications of atherosclerosis, notably unstable angina and acute myocardial infarction. A consensus has emerged that inflammation plays a decisive role in the pathophysiology of these acute thrombotic events (Figure 1). Knowledge of the underlying mechanisms has increased substantially since this topic was last reviewed in these pages 6 years ago. The present article provides an update of this rapidly moving field.

Most coronary thromboses result from a fracture in the protective fibrous cap of the plaque (Figure 1, cross section 5). Ample evidence now supports the concept that the protective fibrous cap, far from being fixed and static, actually can undergo continuous and dynamic remodeling and displays considerable metabolic activity.1 Fibrils of interstitial collagen confer biomechanical strength on the fibrous cap. The balance between synthetic and degradative processes closely controlled by inflammatory mediators regulates the level of collagen in this structure. For example, the lymphokine gamma interferon (IFN-γ) can inhibit de novo synthesis of interstitial collagen by smooth muscle cells, the major source of this extracellular matrix protein in the artery wall.2 Proinflammatory cytokines induce the expression of enzymes capable of breaking down constituents of the arterial extracellular matrix. In particular, matrix metalloproteinases, including interstitial collagenases and gelatinases, can degrade the collagen fibrils that lend strength to the plaque’s fibrous cap.3–6 Recent work has established that certain elastolytic cathepsins, also regulated by inflammatory mediators and expressed in atheroma, can weaken elastin, another important component of the arterial extracellular matrix. Examples include the sulfhydryl-dependent proteinases cathepsins S and K.7,8

The plaque’s smooth muscle cell population also influences the level of extracellular matrix. Sites of fatal thrombosis where plaques fail mechanically and rupture typically have few smooth muscle cells.9,10 Death of these cells, a critical source of extracellular matrix macromolecules in the artery wall, can occur in atherosclerotic lesions. Inflammatory stimuli such as cytokines and fas ligand, factors overexpressed in atherosclerotic plaques, can trigger the complex mechanisms of apoptosis.11 Absence of smooth muscle cells jeopardizes the integrity of the fibrous cap because these cells repair and maintain the all-important collagenous matrix of the fibrous cap. Indeed, plaques that rupture have thin and friable fibrous caps because of the lack of collagen.12,13

In a minority of cases, fatal thrombosis in coronary arteries results from a superficial erosion of the intima without a frank rupture through the plaque fibrous cap (Figure 1, cross section 7).10,14 Inflammation may also contribute to this mechanism of coronary thrombosis. Endothelial cells, like smooth muscle cells, may undergo apoptosis in response to inflammatory mediators.15 Loss of endothelial cells can uncover the thrombogenic subendothelial matrix. Endothelial cells can also express proteinases regulated by inflammatory cytokines and oxidized lipoproteins.16–18 One of these proteinases, membrane type 1 matrix metalloproteinase, can activate matrix metalloproteinase-2, a type IV collagenase. Type IV collagen, a key constituent of the subendothelial matrix, provides an important substrate for adherence of endothelial cells to the intimal surface. Thus, activation of proteases in response to inflammatory stimuli can sever the tethersthat hold the endothelial cell to its underlying matrix, promoting desquamative injury to the intima, a possible prelude to local thrombosis resulting from superficial erosion.

Even in the absence of actual sloughing of endothelial cells, an altered balance between prothrombotic and fibrinolytic properties of the endothelium may underlie thrombosis in situ. Endothelial cells express tissue factor procoagulant in response to inflammatory mediators and bacterial products such as endotoxin.19 The fibrinolytic pathway in endothelial cells also fluctuates, depending on the inflammatory milieu.20 For example, the expression of plasminogen activator inhibitor-1 (PAI-1) can vary in the presence of inflammatory mediators.21

Vasospasm may also contribute to impaired arterial flow in the presence of inflammation. Endothelial cells in atherosclerotic arteries show impaired vasodilator function. This may result in part from decreased production of nitric oxide. Also, augmented release of superoxide anion (O2−) may annihilate nitric oxide radical, neutralizing its
vasodilator capacity. In addition to producing vasodilation, nitric oxide can impair platelet aggregation. Nitric oxide also has a direct anti-inflammatory effect, augmenting production of the inhibitor of nuclear factor kappa B (NF-κB), a transcription factor involved in the expression of the genes encoding many proinflammatory functions of vascular wall cells and infiltrating leukocytes. These various findings all highlight the central role of inflammation as a determinant of the biology underlying the acute thrombotic complications of atherosclerosis.

**Mechanisms by Which Lipid Lowering May Mitigate Thrombotic Complications of Atherosclerosis**

A consistent body of evidence from large clinical trials has established beyond doubt that lipid lowering can reduce the...
Lipid Lowering Improves Features of Experimental Atheroma Associated With Plaque Stability

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incidence of coronary events and stroke in a broad spectrum of individuals. Curiously, lipid lowering produces rather modest improvements in the luminal caliber of fixed atherosclerotic lesions. This finding suggests that qualitative changes in plaques, rather than improvements in the degree of stenosis, must contribute importantly to the striking reduction in clinical events produced by lipid lowering. In view of the central role in inflammation in the pathophysiology of these events, we have advanced the hypothesis that lipid lowering acts as an anti-inflammatory intervention, modifying the biology of plaque instability. A considerable corpus of experimental data now support this contention (the Table). In animals with experimental atherosclerosis, lipid lowering reduces the number of inflammatory cells and various inflammatory mediators. Concomitant with the decrease in macrophage number, the levels of collagenolytic enzymes such as matrix metalloproteinase-1 decrease. In addition, levels of tissue factor decline. Tissue factor owes its procoagulant effect to the ability to bind factor VIIa and augment its enzymatic activity many fold. Along with decreased levels of tissue factor antigen, lipid lowering decreases factor VIIa and X binding activity in rabbit arteries. Thus, lipid lowering not only yields an increased level of interstitial collagen in the atherosclerotic intima but also decreases the thrombotic potential of the lesion. Such improvements in features of plaques associated with stability or reduced thrombogenicity occur both with dietary and statin-induced lipid lowering and with lesions resulting from either dietary or endogenous hypercholesterolemia. No studies yet available address directly the possible contributions of non-lipid-lowering effects of statins on these variables. These qualitative changes in the atheroma should yield a more stable plaque, one less likely to cause thrombosis if it were to rupture.

More recent work has demonstrated a reduction in markers of endothelial activation, such as expression of the leukocyte adhesion molecule, vascular cell adhesion molecule-1 (VCAM-1), as a consequence of lipid lowering (M. Aikawa, 2001, submitted). Moreover, animals subjected to lipid lowering show a less abundant plexus of microvessels in the intima. Plaque microvessels serve as a portal for leukocyte trafficking. The neovessels in the plaque, like those in the diabetic retina, may be fragile and prone to leakage or hemorrhage. Thrombosis in situ caused by microvascular disruption may provide one pathway of plaque growth. Mediators released or generated during clot formation, such as platelet-derived growth factor and thrombin, may promote smooth muscle cell migration and proliferation. Additionally, intraplaque hemorrhage resulting from microvascular disruption could cause sudden expansion of lesions. In this manner, reduced neovascularization during lipid lowering may further stabilize atherosclerotic plaques. Moreover, as the microvessels in plaques may contribute to plaque growth, reduced neovascularization resulting from lipid lowering may, like other antiangiogenic strategies, limit plaque progression.

The foregoing experimental studies support the view that lipid lowering can reduce inflammation. Emerging clinical data support the validity of this concept in humans. For example, lipid lowering with pravastatin in the Cholesterol and Recurrent Events (CARE) study showed a significant decline in the levels of C-reactive protein (CRP). Multiple studies have validated CRP as an index of inflammation that correlates closely with prospective cardiovascular risk (see below).

Possible “Pleiotropic” Effects of Statins

At high concentrations, inhibitors of HMG CoA reductase (statins) can restrict many cellular processes. This enzyme catalyzes the rate-limiting step in the synthesis of cholesterol. The pathway leading to cholesterol also produces other less well-known compounds such as the polyisoprenoids farnesyl phosphate and geranylgeranyl phosphate. These polyisoprenoids can link to proteins (prenylation), altering their functions in important ways. Inhibition by statins of prenylation of a family of intracellular signaling molecules known as small G proteins, among others, may have direct effects on cells independent of systemic lipid lowering. In vitro studies showing such so-called “pleiotropic effects” of statins abound. Yet there is uncertainty that the concentrations used in most such cell culture studies can apply to humans treated with clinically relevant doses of these drugs. Various statins currently marketed vary widely in their direct effects on cells. However, in humans, no consistent evidence available establishes differences between various statins in regard to such putative pleiotropic effects. Various clinical trials currently underway may illuminate this issue. To date, appropriately powered studies have shown benefits on clinical end points of all statins tested. Hence, effects on lipid levels likely account for much of the clinical benefits of this class of drugs.

One potentially relevant pleiotropic effect of statins is attenuation of proliferation of cultured smooth muscle cells, an action caused part to by interference with G protein-mediated cell cycle regulation. With respect to plaque progression and evolution, limitation of smooth muscle proliferation might slow lesion growth. However, in the context of atheroma stability, a reduction in the population of smooth muscle cells might favor plaque disruption. As noted above, the smooth muscle cell synthesizes virtually all of the interstitial collagen responsible for the strength of the plaque’s fibrous cap. Plaques that clinically rupture and cause fatal thrombosis have relatively few smooth muscle cells. For this reason, a direct inhibitory effect of statins on smooth muscle growth could conceivably render lesions less stable. However, this concern probably does not apply clinically, because concentrations of statins required to inhibit smooth muscle proliferation in vitro are rarely, if ever, achieved in vivo.
Statins can also increase vascular cell functions related to thrombus formation and stability. For example, these agents can increase the expression of plasminogen activator and decrease the expression of its inhibitor, PAI-1. In addition to the effects on smooth muscle cell and endothelial functions alluded to earlier, statins can alter macrophage metabolism. Indeed, statins can inhibit tissue factor expression. Once again, however, these direct effects of statins on cellular function require concentrations of the drugs beyond those likely to have clinical relevance. However, some of the so-called pleiotropic effects of statins clearly do pertain in vivo. For example, treatment of mice with statins can improve cerebral blood flow and reduce stroke size by increasing endothelial nitric oxide synthase activity. Animals lacking nitric oxide synthase because of targeted gene manipulation do not have increased cerebral flow or decreased stroke size after treatment with statins.

**Plaque Stabilization by Lipid Lowering: Beyond LDL**

Over the last several years, a remarkably consistent body of controlled clinical trials has established the efficacy of lowering LDL in improving clinical outcomes. However, most adverse events still occur in patients at risk despite substantial lowering of LDL by statin treatment. Thus, our goals for the coming decade should include further reductions in cardiovascular risk by addressing other risk factors. Certain recent studies provide guides in this regard. In the Veterans Affairs HDL Intervention Trial (VA-HIT), treatment of individuals with established atherosclerosis with gemfibrozil significantly reduced cardiovascular events in the absence of a change in LDL level. The Lyon Heart Study showed that a Mediterranean diet could likewise reduce coronary risk without substantially altering levels of LDL. Both of these interventions may alter a more recently recognized mechanism for controlling vascular gene expression. The drug gemfibrozil, a member of the fibrate class, acts by binding the nuclear receptor peroxisomal proliferation activating receptor-α (PPAR-α). Polyunsaturated fatty acids, increased in the Mediterranean diet, may also activate PPAR-α.

PPAR-α acts as part of a transcription factor complex that regulates the expression of a number of genes implicated in atherogenesis and plaque stability (Figure 2). Notably, PPAR-α agonism can limit cytokine-induced activation of inflammatory functions of vascular endothelial cells, eg, expression of VCAM-1 in response to tumor necrosis factor-α and tissue factor gene expression in these cells. Thus, the results of the VA-HIT and Lyon Heart Study might derive in part from an anti-inflammatory action. Because these interventions act by a mechanism distinct from LDL lowering, combining statin therapy with the Mediterranean diet or PPAR-α agonists might have additive effects on reducing cardiovascular risk. Because oxidized phospholipids may augment certain cytokines via PPAR-α activation, under some circumstances, this nuclear receptor may play a proinflammatory role.

PPAR-γ, a close relative of PPAR-α, binds a distinct series of ligands and controls a separate set of genes involved in cardiovascular and metabolic diseases. Notably, mutations that alter the function of PPAR-γ cause a syndrome of insulin resistance, hypertension, and dyslipidemia characteristic of the cardiovascular dysmetabolic syndrome. PPAR-γ agonists include the insulin-sensitizing thiazolidinedione family of antidiabetic drugs (the glitazones). In vitro, PPAR-γ agonists can decrease proinflammatory functions of macrophages and smooth muscle cells. However, PPAR-γ agonism can also augment endothelial PAI-1 production and expression of the scavenger receptor for modified lipoprotein CD36 on mononuclear phagocytes. These in vitro observations cannot predict the net effects of PPAR-γ agonism in the intact organism. However, they certainly underscore the importance of careful consideration of cardiovascular risk as an outcome in future clinical studies of this new class of pharmacological agents.

**ACE Inhibition as Anti-Inflammatory Therapy: An Additional Avenue for Reducing Atherosclerotic Events**

Multiple clinical studies have substantiated an initially unexpected reduction in acute coronary events in patients treated...
with ACE inhibitors. Emerging evidence suggests that ACE inhibitor therapy may possess benefits beyond blood pressure lowering (Figure 3). For example, in the recent Heart Outcomes Prevention Evaluation (HOPE) trial, ACE inhibitor therapy produced little reduction in blood pressure but strikingly diminished cardiovascular events. How can one fit these unanticipated clinical findings with ACE inhibition into the current concepts of the role of inflammation in plaque biology? Indeed, angiotensin II activates inflammatory functions of vascular wall cells. For example, angiotensin II can augment interleukin-6, macrophage chemoattractant protein-1 elaboration by human smooth muscle cells in culture. Administration of ACE inhibitors can reduce cytokine levels and indexes of activation of NF-κB in rabbits with experimentally induced atherosclerosis. Angiotensin II also alters fibrinolytic balance by augmenting PAI-1 expression, a function it shares with more classically recognized proinflammatory cytokines. Activation of the renin-angiotensin system also spurs the production of reactive oxygen species from vascular cells, a property increasingly well understood at the molecular level.

These various data suggest that inhibition of angiotensin II signaling by ACE inhibitors or angiotensin II receptor blockers might actually act as anti-inflammatory therapy. Angiotensin II increases levels of the peptide mediator bradykinin and interrupts angiotensin II production. Bradykinin, an endothelial-dependent vasodilator, augments local production of nitric oxide. As noted earlier, in addition to its vasodilatory properties, nitric oxide may mitigate atherosclerosis because of its anti-inflammatory properties mediated by interference with the NF-κB transcriptional control pathway. Bradykinin also elevates intracellular levels of the second messenger cGMP. The increased cGMP may contribute to some of the beneficial actions of ACE inhibitors, eg, by promoting vasodilatation resulting from smooth muscle relaxation. In this regard, bifunctional inhibitors of ACE and the neutral endopeptidase that catabolizes certain other peptide hormones, including atrial and brain natriuretic peptides, should also augment intracellular cGMP levels. Future studies should evaluate the effect of angiotensin receptor blockers and the bifunctional peptidase inhibitors on cardiovascular outcomes as well.

**Figure 3. Angiotensin II (A II) is inflammatory mediator. Angiotensin II can be considered an “honorary” proinflammatory cytokine, in addition to its well-known vasoconstrictor properties. Angiotensin II augments expression of leukocyte adhesion molecules such as VCAM-1. It can also stimulate expression of leukocyte chemoattractant protein-1 (MCP-1). Angiotensin II stimulates expression of interleukin-6 (IL-6), instigator of acute-phase response, provoking elaboration of CRP, serum amyloid A, and fibrinogen from hepatocyte. Angiotensin II also augments production of reactive oxygen species by vascular cells augmenting oxidative stress, which is potent proinflammatory stimulus.**

**Infections and Atheroma: Will Antibiotics Prevent Acute Coronary Syndromes?**

Recent results have rekindled interest in the possible role of infectious agents in atheroma. Mechanisms by which infections such as *Chlamydia pneumonia* or cytomegalovirus may aggravate or initiate atherosclerosis have been previously reviewed in these pages. Indeed, this complex topic merits a separate discussion but warrants here a brief summary of the current state of this association. Prospective and well-controlled seroepidemiological studies have failed to support a consistent link between infections and coronary events. However, almost half of the human plaques studied show evidence of the presence of *C pneumonia*. Chlamydial products, including its heat shock protein 60, and endotoxin can promote inflammation of vascular cells and the activation of atherogenic functions of macrophages. These findings render it plausible that Chlamydia might potentiate the complication of existing atheroma. Various pilot studies of antibiotic treatment for secondary prevention of coronary events lack power to provide a definitive answer. Large randomized trials now in progress should reveal whether antibiotic treatment can forestall recurrent coronary events.

**Markers and Surrogates of Atherosclerotic Risk**

Recent clinical trials with statins have vindicated the cholesterol hypothesis, establishing beyond doubt the efficacy of LDL lowering in reducing cardiovascular risk in a broad swath of the population. The foregoing discussion has highlighted other interventions on the horizon that may further limit the risk of acute complications of atherosclerosis. Our ability to modify the natural history of atherosclerosis may well have outstripped our ability to predict who might benefit from therapy. Contemporary clinical trials show that benefits of lipid lowering can accrue to patients not currently eligible for treatment on the basis of current guidelines. For example, the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) showed reductions in cardiovascular events in individuals with average LDL levels not eligible for treatment on the basis of the National Cholesterol Education Adult Treatment Panel II Guidelines. This finding illustrates the urgent need to identify approaches to risk stratification that add to the utility of the lipoprotein profile.
Help in this regard should come from two directions. First, the clinical application of the surge in understanding of the role of inflammation in atherosclerotic events has led to multiple studies that have validated inflammatory markers such as CRP as a marker for risk of future cardiovascular events. Other inflammatory markers, including soluble intercellular adhesion molecule-1 and soluble E-selectin, for example, may also predict risk of atherosclerotic complications. However, the high sensitivity assay of CRP is well standardized, widely available, and reproducible and adds to the predictive value of traditional risk factors, including the lipoprotein profile. Addition of a small panel of such serum markers of risk, including those linked to inflammation, should hone our ability to target therapy in the future.

Also, the recent solution of the human genome will enable the flowering of functional genomics. In coming years, we will see delineation of polymorphisms in the human genome, some of which will doubtless predict an individual’s cardiovascular risk. Clearly, application of this knowledge will require careful consideration of ethical issues and confidentiality. However, we already make public health recommendations based on genotyping. For example, screening for phenylketonuria at birth leads to dietary recommendations broadcast widely on containers of diet cola and other products sweetened with aspartame. This example illustrates the principle of making an individualized recommendation for control of a risk factor on the basis of a genetic predisposition tested for at birth.

I believe that in the future we will target our preventive therapies by a combination of a panel of few serum tests, including traditional and a few nontraditional markers. I foresee the utility of only a small number of serum markers, because it will become increasingly difficult to demonstrate additive information over established markers, such as the lipoprotein profile and CRP. These markers will provide an integrated assessment of the interaction between genotype and the environment, including individual behaviors (eg, smoking and diet). Genotyping, probably accomplished by high-throughput screening early in life, will identify genetic markers (eg, single nucleotide polymorphisms and haplotypes) that should predict individual responses to risk factors. The combination of the serum markers and hereditary predisposition revealed by genetic analysis should sharpen our ability to make a prescription for management of risks in individuals in a rational manner.

Conclusions

Our view of the mechanisms underlying the acute complications of atherosclerosis has shifted remarkably in the last decade. In the past era, we relied on flow-limiting arterial stenoses and functional indexes of end-organ ischemia to guide our therapies. We held high-grade arterial stenoses responsible for the bulk of acute ischemic complications of atherosclerosis. Considerable clinical data have compelled a reassessment of these concepts. Current findings establish the importance of qualitative aspects of plaques as decisive determinants of their propensity to cause acute complications. Among these functional features of plaques associated with vulnerability, inflammation has emerged as a leading pathophysiologic mechanism, providing new potential therapeutic targets and novel avenues to risk assessment.

In addition to local effects of inflammation at the level of the atherosclerotic lesion itself, systemic aspects of the inflammatory response may alter thrombotic risk. Inflammation upsets the prevailing homeostatic balance. Increased fibrinogen and plasminogen activator inhibitor circulate at higher concentrations in inflammatory states. A given plaque disruption could have a greater chance to produce an occlusive thrombus under such conditions.

Our newfound understanding of the role of inflammation in acute complications of atherosclerosis helps us to comprehend the mechanisms by which a variety of interventions can reduce clinical events. Exercise reduces cardiovascular risk. By increasing nitric oxide production, elevating HDL, and augmenting insulin sensitivity, exercise may act in part by reducing inflammation. Dietary modifications such as increased consumption of unsaturated fatty acids may act as an anti-inflammatory therapy by altering the pattern of prosta-

References


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