Capturing the Pathophysiology of Acute Coronary Syndromes With Circulating Biomarkers

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There have been considerable advances in the evaluation of suspected acute coronary syndromes (ACS): sophistication of the clinical examination, electrocardiography, risk prediction scores, multiple blood biomarkers, and rapid cardiovascular imaging. Integration of information remains a formidable challenge for the physician in the setting of time-sensitive clinical decision making. In addition to conventional panels of biomarkers, there are novel entities that may be able to signal different stages of the acute event, including plaque disruption, atherothrombosis, ischemic damage, tissue hypoxia, and oxidative stress. The natriuretic peptides are normal myocyte products that reflect myocardial tissue response to neurohormonal and mechanical forces that rapidly change during an ACS event. This article summarizes major advancements in the integrative use of multiple blood biomarkers and cardiovascular imaging in the diagnosis, prognosis, and management of ACS.
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Key words: B-type natriuretic peptide • N-terminal prohormone B-type natriuretic peptide • Acute coronary syndrome • Acute myocardial infarction • Diagnosis • Complications • Prognosis • Proteomic • Labile iron • Mortality

There have been considerable advances in the diagnosis and management of patients presenting with suspected acute coronary syndromes (ACS). Coupled with prompt therapy, monitoring, and management of complications, the mortality rate among ACS patients has markedly dropped over the past several decades. The evaluation of chest discomfort, dyspnea, diaphoresis, and the constellation of symptoms that raise suspicion for ACS, one of the most common adult presentations to emergency departments worldwide, remains a

clinical challenge with a high degree of variability among institutions with respect to use of the clinical laboratory, stress testing, computed tomography, and coronary angiography. In addition to the presenting symptoms, past medical history, and electrocardiogram, blood biomarkers have played a pivotal role in the diagnosis, prognosis, and management of patients with suspected ACS.[1] This article provides an update on the use of biomarkers alone and in combination in the transformational phases of coronary atherosclerosis, including plaque destabilization, intraplaque hemorrhage, exposure of subendothelial cellular debris and lipid material to the bloodstream, the development of an occlusive thrombus, and the downstream embolization of platelet-fibrin material. The ensuring wave of oxidative tissue injury due to tissue hypoxia will be a key step for future biomarker and therapeutic development. This supplement of *Reviews in Cardiovascular Diseases* summarizes major advancements in the integrative use of multiple blood biomarkers and cardiovascular imaging in the diagnosis, prognosis, and management of ACS.

Deposition of Lipid Material and Recruitment of Lymphocytes Into the Subintimal Space

It is beyond the scope of this article to review the complicated pathobiology that is responsible for the genesis of atherosclerosis. However, deposition of lipid material, most notably low-density lipoprotein cholesterol (LDL-C), into the subendothelial space is considered both necessary and sufficient for the creation of atherosclerosis. This fundamental step and its magnitude are reflected partially by the serum concentrations of LDL-C, the non–high-density lipoprotein (HDL), and apolipoprotein (apo) B. As demonstrated in Table 1, there are many factors that are believed to drive the next steps in atheroma formation, including oxidation of lipid material in the artery wall, attraction and ingress of monocytes, conversion to macrophages and foam cells, and proteolytic degradation of atheromatous material and the development of the necrotic core. Neovascularization of the atheroma may lead to both growth of the plaque and outward remodeling, but also may play a role in intraplaque hemorrhage that can

Table 1
Blood Biomarkers Associated With Developmental Stages and Critical Events in Atherosclerosis

Event	Biomarker
Deposition of LDL-C and atherogenic lipoproteins	LDL-C, non-HDL-C, Apo B
Ingress of monocytes	ICAM, VCAM, monocyte chemoattractant protein-1, interleukin-1 and -18, sE-selectin, sP-selectin
Oxidation of lipid material within atheroma	Oxidized LDL
Macrophage activity (lipid uptake and proteolytic degradation of atheromatous material)	Phospholipase-associated A2, secretory phospholipases
Adiposity-associated cardiometabolic secreted proteins from the liver	Interleukin-6, tumor necrosis factor α, hs-CRP, amyloid-associated protein
Neovascularization of plaque	Vascular endothelium-derived growth factor, placental growth factor, hepatocyte growth factor
Plaque destabilization and rupture	Myeloperoxidase, metalloproteinase-1, -2, and -9, tissue inhibitors of metalloproteinases, pregnancy-associated plasma protein A, catalytic iron
Acute coronary thrombosis with platelet adhesion	Soluble CD40 ligand, sP-selection, thrombus precursor proteins
Acceleration/amplification of thrombosis	von Willebrand factor, fibrinogen, PAI-1, Lp(a)
Myocyte hypoxic ischemia	Ischemia-modified albumin, unbound free fatty acids, choline, heart-type fatty acid-binding protein
Myocyte oxidative, proteolytic necrosis	Troponin I, troponin T, CK-MB, myoglobin, creatine phosphokinase, glycogen phosphorylase isoenzyme BB
Increased wall tension of myocardium	ANP, BNP, NT-proBNP

ANP, atrial natriuretic peptide; Apo, apolipoprotein; CK-MB, creatine kinase-myocardial band; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; ICAM, intercellular adhesion molecule; LDL-C, low-density lipoprotein cholesterol; Lp, lipoprotein; NT-proBNP, N-terminal prohormone B-type natriuretic peptide; PAI, plasminogen activator inhibitor; VCAM, vascular cell adhesion molecule.

lead to plaque destabilization due to a rise in intraplaque pressure. Atherosclerosis is a dynamic progression with processes working to stabilize and destabilize the lesion. Of note, deposition of collagen by fibroblasts, smooth muscle cell migration to the fibrous cap, and osteogenic transformation of smooth muscle cells (inciting the deposition of calcium hydroxyapatite within the atheroma and the vascular media), are all believed to be stabilizing processes that work to reduce the risk of luminal plaque rupture as outward aneurysmal dilatation.[2]

Enzymatic Destabilization of the Fibrous Cap

Despite considerable attention to the concept of "inflammation" in the pathogenesis of coronary atherosclerosis, there is little to suggest that the classic features of inflammation are responsible for coronary events. The classic components of inflammation are (1) leukocyte migration (typically polymorphonuclear leukocytes), (2) increased cytokine signaling, (3) augmented antibody interaction, and (4) complement activation. Of these 4, only cellular activity (monocytes, macrophages) and cytokines, most notably tumor necrosis factor α, and some interleukins, have been associated with ACS events.[3,4]

There has been a tendency to use the term *inflammation* interchangeably with the hepatic secretion of several proteins related to intra-abdominal adiposity (cardiometabolic factors), including high-sensitivity C-reactive protein, serum amyloid protein A, and fibrinogen. The basic mechanistic evidence supporting the role of these hepatic proteins in atherosclerosis remains to be fully elucidated.

A better concept is that atherosclerosis is marked by enzymatic activity within the fibrous cap, necrotic core, and cellular regions of the atheroma. The key event in plaque rupture is loss of structural integrity of the fibrous cap due to enzymatic activity within the cells of the atheroma overlying the lipid pool of cholesterol crystals and the necrotic core. When the blood and its procoagulant substances are exposed to the necrotic core, 4 possibilities could result: (1) asymptomatic complete occlusion with collateralization or silent infarction; (2) asymptomatic partial occlusion with organization, resolution, and healing, resulting in the generation of a residual stenosis; (3) complete occlusion resulting in symptomatic ACS; and (4) thrombus formation without occlusion but with downstream embolization, and again, symptomatic ACS.[5] Thus, plaque rupture itself is necessary but probably not sufficient in the pathogenesis of ACS.

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There are very strong lines of evidence that some of the 24 known metalloproteinases (MMPs) are active within the collagen and fibrin matrix of the plaque, especially MMPs-1, -2, and -9, which are forms of gelatinase. Secreted by macrophages, MMPs have been shown to be concentrated in the shoulder region of the plaque.[6] Once a fissure in the plaque begins, it is possible that adherent platelets, activated through CD40 and its ligand (CD40L), attract T cells that also have MMP-9 activity. It unclear to what extent T cells acutely participate in rupture of coronary plaques given that their density on histopathological specimens is small. More likely, T cells participate in the pathogenesis of atherosclerosis in the chronic phase, and their conversion to enzymatically active macrophages is the mechanism by which there is an immune system contribution to this process. Both MMP-9, produced by macrophages, and CD40 (and CD40L), produced by platelets and endothelial cells, can be measured in serum and together can be viewed as potential early markers of the future risk of plaque rupture.[7]

Pregnancy-associated plasma protein A (PAPP-A) is an insulin-like growth factor that binds to MMPs and, in theory, could participate in the enzymatic destabilization of plaque. It is thought to be released when neovascularization occurs and thus may be a marker of incipient plaque rupture as a result of intraplaque hemorrhage.[8,9] PAPP-A, demonstrated to elevate in ACS, is in the form of a homodimer and is not the same protein that is seen in pregnancy. Because heparin, commonly given in confirmed ACS, binds to PAPP-A, this marker is useful only as an exclusion marker measured in the early pretreatment window in patients with suspected ACS.

Placental growth factor (PlGF), which stimulates angiogenesis in the placenta, is produced by platelets and may serve as a monocyte chemoattractant and promote vascular permeability (via the FLT-1 receptor) involved in cellular recruitment and entry into the plaque. In the randomized, placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina (CAPTURE), which recruited 544 patients with ST-elevation myocardial infarction (STEMI), PlGF

(with an adjusted hazard ratio [HR] of 3.3) along with CD40L, and cardiac troponin T (cTnT), were independent predictors for myocardial infarction (MI) and death at 30 days.[10] Much more information is needed on this marker in order for it to move forward in clinical development.

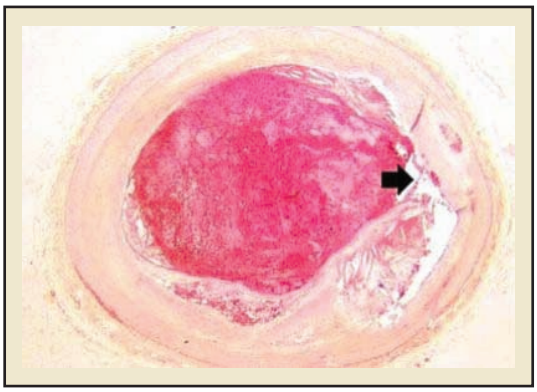
Choline is produced by cleavage of membrane phospholipids and may be a signal of plaque rupture that is measurable in whole blood or plasma. There appears to be nothing specific about choline and atherosclerosis; therefore, this marker may be a more generalized indicator of tissue injury. Early work indicates its main value may be assisting in the exclusion of MI.[11]

An important concept in plaque rupture is that the crystallization of cholesterol creates mechanical forces within the atheroma that may lead to expansion, lancination, and disruption of the cap from within. Abela and coworkers[5] have clearly shown the presence of cholesterol crystals in the setting of culprit plaques causing MI and stroke. Temperature, and perhaps other physiochemical forces such as saturation, hydration, and pH in the necrotic lipid core, may be determinants of the crystallization of free cholesterol. These factors may explain some of the temporal and environmental patterns observed in the epidemiology of ACS.[12]

Atherothrombosis

Approximately 90% of patients with STEMI and 30% of those with non-STEMI have a completely occluded epicardial vessel, as shown in Figure 1.[13] It is beyond the scope of this article to discuss the intricacies of coagulation and fibrinolysis. However, it is important to realize that acute changes in rheology hold out hope for diagnostic strategies to detect the presence of developing thrombosis.

Figure 1. *Complete coronary occlusion with thrombus. Plaque rupture is evident at the shoulder region of the plaque with minimal intraplaque hemorrhage into the necrotic core of cholesterol crystals (arrow).*



During the past decade, several markers of coagulation have been evaluated in the setting of ACS, including fibrinogen, D-dimer, and fibrinopeptide A. Fibrinogen has been studied as a predictor of future cardiovascular events in patients with stable cardiovascular disease; yet, as an acute-phase reactant, it can reflect systemic inflammation rather than coagulation and thrombosis.[14] D-dimer has been evaluated in the post-ACS population, and increased levels have been associated with recurrent cardiac events. Unfortunately, D-dimer has very little specificity and its main use in clinical practice is being a negative predictor in suspected venous thromboembolism in low-risk patients.[15] Fibrinopeptide A concentrations have been found to be increased in patients with ACS; however, it has a half-life of 3 to 4 minutes in circulation and is thereby associated with widely fluctuating levels, making potential clinical decision making with this marker difficult.

In contrast to fibrinopeptide A, a soluble fibrin polymer such as thrombus precursor protein is a particularly attractive marker of fibrin formation. Thrombus precursor protein has a longer plasma half-life (5-6 hours) and involves the step of the activated coagulation cascade immediately preceding the formation of fibrin. In limited studies of ACS to date, its adjusted HR for mortality has not been high (~ 1.5); hence, this marker in its current form is not a biologically strong signal of intracoronary thrombus. This is possibly because of the relative size of the thrombus compared with the blood pool, which is always maintaining a balance of coagulation and antithrombosis.[16]

Acute Ischemic Injury and Loss of Myocyte Cellular Integrity

Deposition of cholesterol in the subintimal space, oxidation of lipid material, recruitment of monocytes with conversion to macrophages and foam cells, and the build-up of a lipid-rich core is an accepted sequence for coronary artery disease. Enzymatic activity within the fibrous cap is believed to result in plaque instability. Conversely, intraplaque hemorrhage and increased tension on the cap from within may occur to bring a plaque to a stage of rupture. Hemodynamic erosion of the plaque

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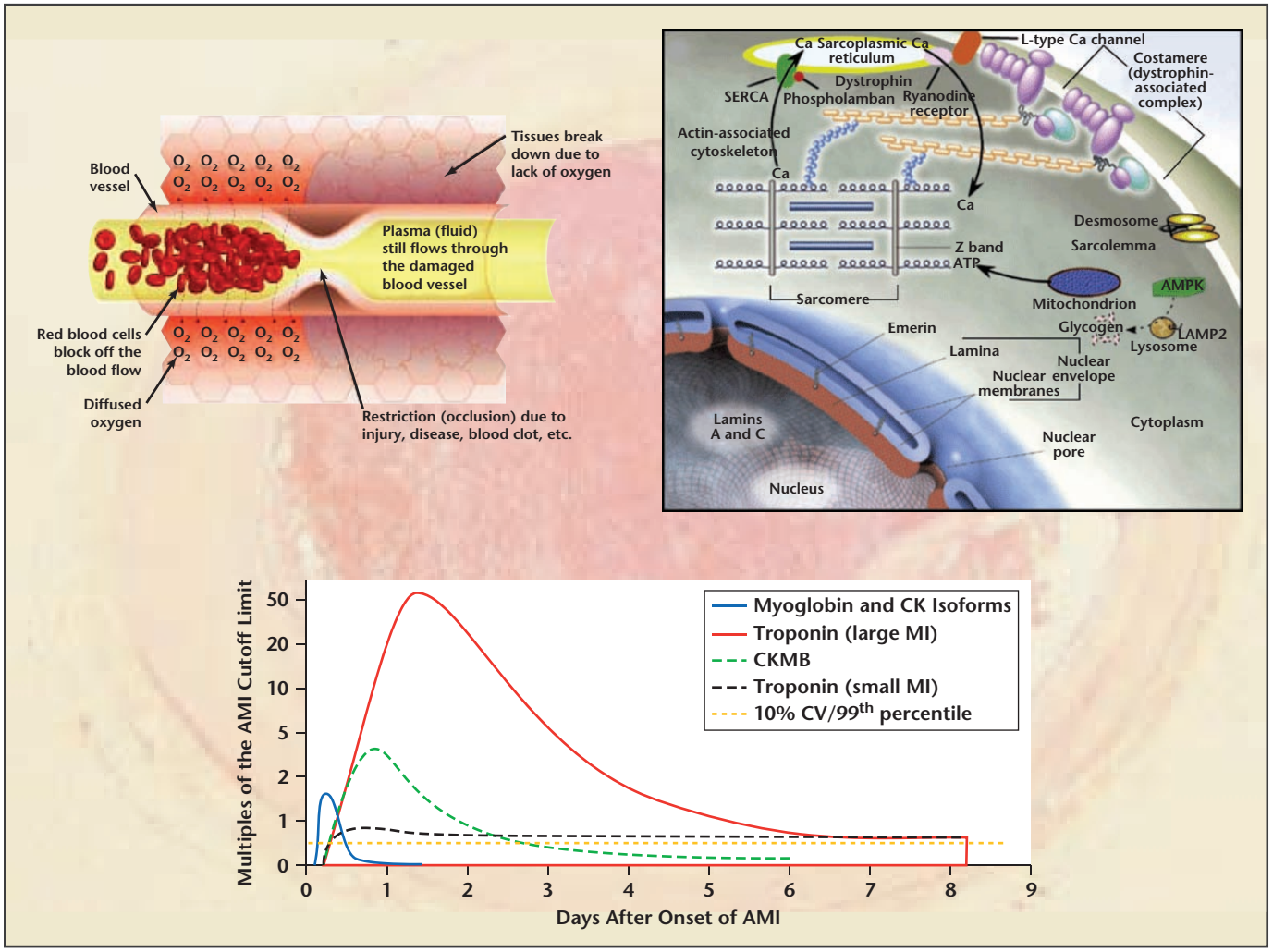
from the luminal side is yet another putative mechanism of plaque rupture. Finally, puncture of the fibrosis cap by cholesterol crystals within the lipid-rich core may be the mechanism of plaque rupture in some individuals. Likely, it is a combination of processes that lead to the critical rent in the fibrous plaque and exposure of blood to lipid-rich cellular debris beneath the cap. Ultimately, it is the subsequent development of thrombosis, and the degree to which impairment of blood flow occurs, that is believed to be the major determinant of a symptomatic ACS. In the setting of abrupt loss of oxygen and nutrient delivery to cardiomyocytes due to either occlusion of an epicardial vessel, downstream embolization of platelet-fibrin thrombus, microvascular constriction, or excessive myocardial demand in the setting of a high-grade, flow-limiting stenosis, there is a sequence of events that liberates a variety of substances into the pericellular space and ultimately the bloodstream, as shown in Figure 2. Because there are likely differential degrees to which occlusion, embolization, and myocardial demand contribute to ischemia and infarction, it is unlikely any single marker will elucidate the pathophysiology occurring within an individual; thus, a panel of blood tests offers the best opportunity to better understand the mechanisms at work in any given case of ACS.

There are over 200 putative blood biomarkers of myocyte injury corresponding to myocyte structural and contractile proteins, components of the sarcolemma, and cytosolic proteins. Other sources of potential

Figure 2. *Acute myocardial infarction (AMI) with disruption of cellular elements and the release of classic markers of myocardial necrosis used in the diagnosis of acute coronary syndromes. AMPK, adenosine monophosphate-activated protein kinase; ATP, adenosine triphosphate; Ca, calcium; CK-MB, creatine kinase-myocardial band; LAMP2, lysosomal-associated membrane protein 2; MI, myocardial infarction; SERCA, Sarco/endoplasmic reticulum Ca^{2+}-ATPase.*



markers include myeloperoxidase, an enzyme released by neutrophil degranulation, which is measurable in the bloodstream within minutes of myocyte injury. Studies to date have found it to be poorly specific and not of sufficient sensitivity for diagnosis in patients presenting with suspected acute coronary syndromes, although it may have greater utility in long-term risk management. Alternatively, albumin (a bystander blood protein) can be damaged by ischemia and oxidative myocardial tissue injury, therefore reducing its ability to bind cobalt (termed *ischemia-modified albumin*). Despite high sensitivity, ischemia-modified albumin has not been found to be sufficiently specific for it to move forward in clinical practice despite having regulatory approval.[17] Fatty acid-binding protein is rapidly released by myocytes after infarction and could be positioned as an early marker of injury. However, it lacks cardiac specificity and may indicate damage to other organs including the kidneys. In a recent study, this marker outperformed ischemia modified albumin in the prediction of ACS among patients presenting with acute chest pain.[18]

For clinical practice, there is an accepted panel of approved cardiac markers that can be used alone or ideally in combination. Release of myoglobin, troponin (Tn), and creatine kinase-myocardial band (CK-MB), in that order, has been recognized as a sequence that can be measured with bedside devices or in the central laboratory. The relative timing and the excursions of each protein, when measured serially, give information with respect to the onset of ischemia, size of the infarction, risk of in-hospital complications, and long-term prognosis. Because cardiac tissue contains relatively large amounts of Tn compared with the other proteins measured, the characteristic rise and fall of cTnT I or T is recognized as the single best and confirmatory indicator of MI. With the introduction of more sensitive Tn assays, it is now possible to measure very low levels of Tn that are considered normal and reflective of either normal cardiomyocyte or Tn turnover in cardiac tissue. Thus, the curve elicited by serial measurements over time is critical in the diagnosis of acute MI as opposed to viewing each level as positive or negative. Reichlin and colleagues[19] published a multicenter comparative study of 4 sensitive Tn I assays in 718 consecutive patients with suspected ACS and were able to demonstrate that within 3 hours of onset of chest pain, these assays outperformed standard tests (Figure 3). The area under the receiver operating characteristic curve for the detection of acute MI ranged from 0.94 to 0.98, indicating that sensitive Tn I testing alone may be comparable with traditional multimarker approaches using myoglobin, standard Tn I, and CK-MB as an early (< 2 hours) rule-out strategy.[20,21]

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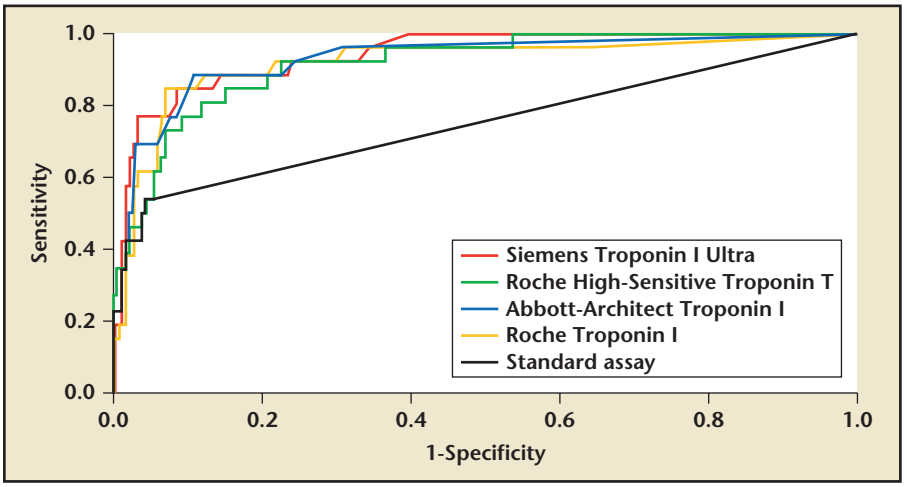
Wave of Oxidative Stress and Cellular Injury

After the initial ischemic insult, there is a secondary wave of cellular and tissue injury as a result of oxidative stress, as shown in Figure 4. Little is known about this process as it occurs within humans with acute MI. It is possible that with the disruption of cell and organelle membranes, there is the liberation of trace metals that include copper, zinc, and selenium. Among the most notable trace metals is iron, which provides the basis for the rapid transfer of oxygen and hydrogen. Free iron acting as a catalyst allows an explosive local generation of reactive oxygen

Figure 3. *Area under the receiver operating characteristic curve for various more sensitive troponin assays compared with a standard assay in patients presenting with chest discomfort of < 3 hours in duration. The reference standard for myocardial infarction was a review of the history, physical examination, electrocardiogram, and all clinical tests by 2 independent cardiologists at 60 days after the event. Reprinted with permission from Reichlin T et al.*[19]



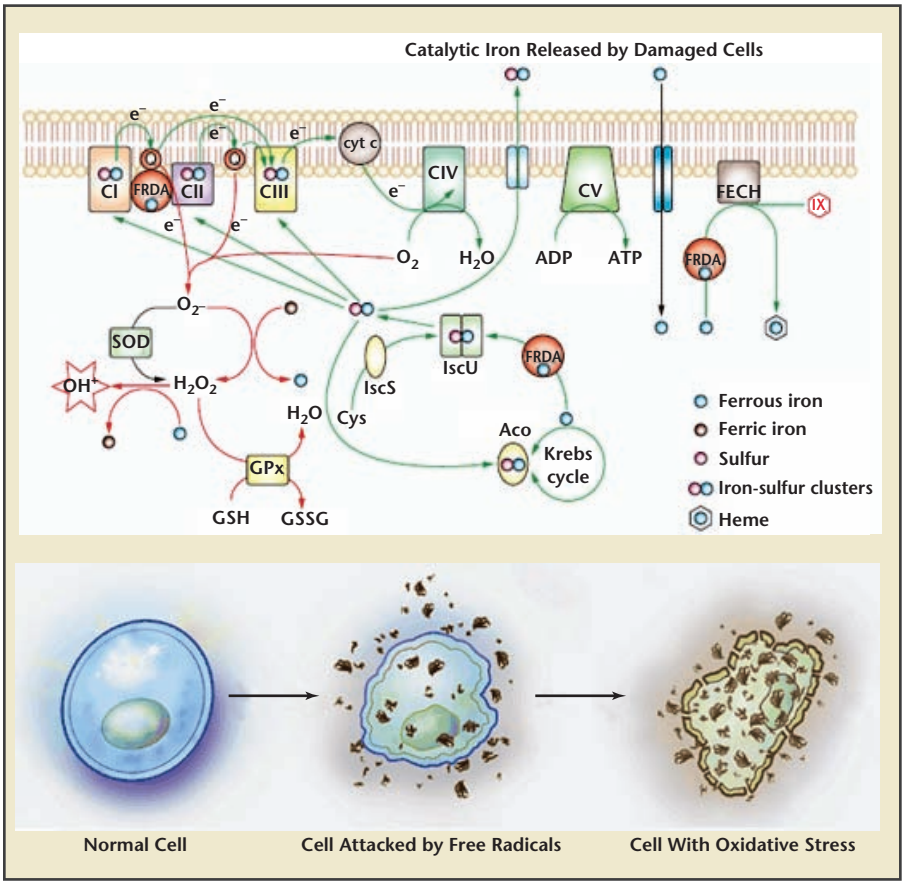


Figure 4. *Wavefront of iron-dependent of tissue oxidative injury resulting in further cell injury and death. Aco, aconitase; ADP, adenosine diphosphate; ATP, adenosine triphosphate; CI, respiratory chain complex I; CII, respiratory chain complex II; CIII, respiratory chain complex III; CIV, respiratory chain complex IV; CV, respiratory chain complex V; Cys, cysteine; cyt c, cytochrome c; e,1 electron; FECH, ferrochelatase; FRDA, frataxin; GPx, glutathione peroxidase; GSH, reduced glutathione; GSSG, oxidized glutathione; H_2O_2, hydrogen peroxide; IscS, cysteine desulfurase; IscU, iron–sulfur cluster scaffold protein; IX, protoporphyrin IX; OH, hydroxyl radical; Q, coenzyme Q; SOD, superoxide dismutase. Top panel reprinted with permission from Macmillan Publishers Ltd:* Nat Clin Pract Neurol. *2008;4:86-96, copyright 2008.*[31]

species including the high energy hydroxyl radical.[22] Reactive oxygen species, or oxygen free radicals, are extremely damaging to remaining cellular and subcellular structures and act principally by way of lipid peroxidation to destroy cells, as well as regions of tissue. Lele and associates[23] have shown that labile iron is measurable in the venous blood within minutes after the onset of ACS (Figure 5). The rise and fall of labile iron is believed to represent the periodicity in which oxidative stress is causing further myocyte damage above and beyond ischemic injury. Defenses against the propagation of oxidative injury, including glutathione, are only partially effective in containing the wavefront of damage. Even in the setting of mechanical reperfusion, there can be evidence of ongoing myocardial injury manifested by a sustained rise in Tn, CK-MB, incomplete ST-segment resolution, and persistent regional wall motion abnormalities. It is possible that indicators of oxidative damage (catalytic iron, lipid peroxidation markers, reduced glutathione, activity of superoxide dismutase) may become therapeutic targets in future patients with more extensive infarctions.[24,25]

B-Type Natriuretic Peptides

Cardiac ischemia and increased wall tension is an accepted mechanism to explain gene activation, production of messenger ribonucleic acid, and assembly of the precursor to natriuretic peptides (NPs).[26] The gene for B-type natriuretic peptide (BNP) is located on chromosome 1 and can be rapidly activated in response to signal transduction from the myocyte cell wall (Figure 6).[27] After protein synthesis BNP is cleaved from the precursor molecule, proBNP, by the enzyme corin into the active BNP hormone and the inactive N-terminal prohormone BNP (NT-proBNP) fragment. Biologically active BNP is released from cardiomyocytes in response to wall tension, which, according to the law of Laplace, is determined by the pressure within and the radius of the chamber. Because the left ventricle has the greatest mass by far of all the cardiac chambers, these NPs largely reflect the dynamic wall tension experienced by the left ventricle that occurs with ischemia and segmental myocardial wall dysfunction.[28] All assays for BNP and NT-proBNP recognize epitopes on the parent peptide proBNP; thus, in the setting of ACS it is possible that levels of these proteins reflect both immature and mature peptide products.[29] In addition, fragment peptides are known to be in the circulation of patients with heart failure (BNP3-32 and BNP6-32),

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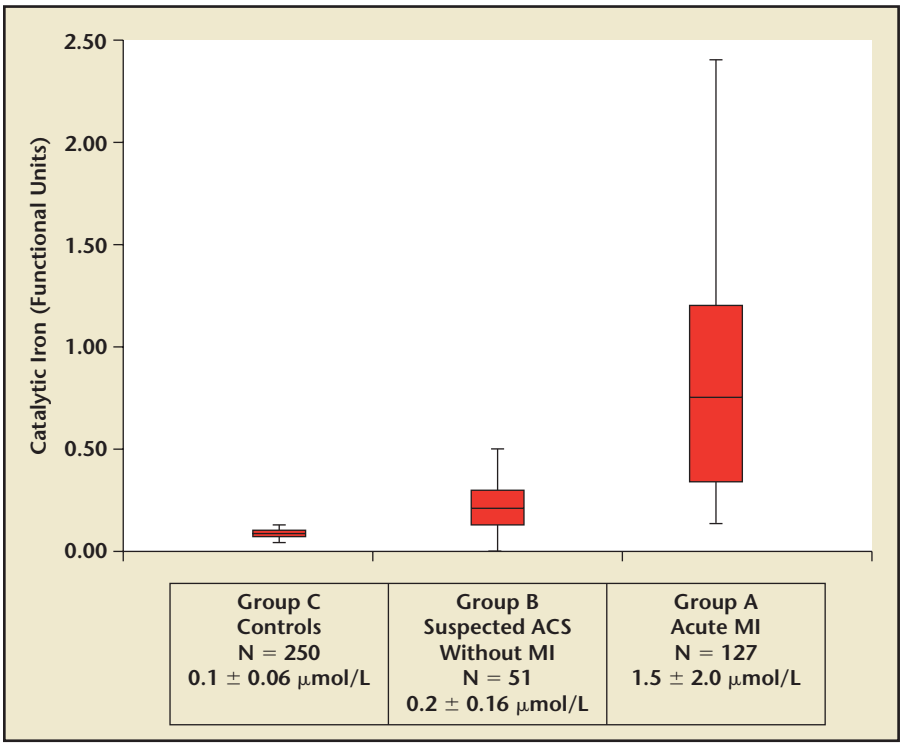

Figure 5. *First evidence of catalytic iron in the blood of patients suffering acute coronary syndromes (ACS). MI, myocardial infarction. Reprinted with permission from Lele S et al.[23] Copyright © 2009 Massachusetts Medical Society. All rights reserved.*

and glycosylation of both BNP and NT-proBNP can occur (as with many proteins) to a variable degree depending on levels of glycemia and circulatory durations of the peptides.[30] Both BNP and NT-proBNP rise quickly in the setting of decompensation and have sustained elevation provided increased wall tension and neurohumoral activation remain present. Elsewhere in this supplement, articles summarize the compelling evidence that, in addition to the clinical evaluation, traditional biomarkers, and cardiac imaging, both BNP and NT-proBNP yield additive information concerning pathophysiologic correlates (eg, left ventricular function), risk of heart failure, and probability of death.

Conclusions

ACS are common and important clinical events that remain a central focus in cardiovascular medicine. The pathogenesis of atherosclerosis, plaque rupture, thrombosis, and myocardial injury remains an accepted temporal sequence to which both diagnostic and therapeutic targets apply. Although it may be possible to capture some of the proximal events in the pathophysiological processes leading to ACS with biomarkers, the heterogeneity and complexity of these pathways present major challenges. In contrast, later events, including myocardial injury and the counterregulatory responses of the heart to injury, are well captured with existing biomarkers. For example, NPs yield valuable and unique information concerning myocardial tissue response to ischemia and its neuromechanical consequences. In the fu-

Main Points

- Blood biomarkers have played a pivotal role in the diagnosis, prognosis, and management of patients with suspected acute coronary syndromes (ACS). In addition to conventional panels of biomarkers, there are novel entities that may be able to signal different stages of an acute event, including plaque disruption, atherothrombosis, ischemic damage, tissue hypoxia, and oxidative stress.
- The natriuretic peptides are normal myocyte products that reflect myocardial tissue response to neurohormonal and mechanical forces that rapidly change during an ACS event.
- Natriuretic peptides yield valuable and unique information concerning myocardial tissue response to ischemia and its neuromechanical consequences.
- Because there are likely differential degrees to which occlusion, embolization, and myocardial demand contribute to ischemia and infarction, it is unlikely that any single marker will elucidate the pathophysiology occurring within an individual; thus, a panel of blood tests offers the best opportunity to better understand the mechanisms at work in any given case of ACS.
- The secondary wave of oxidative stress and cellular damage is apt to become a focus for the development of clinical laboratory testing and potentially adjunctive pharmacotherapy in the future.

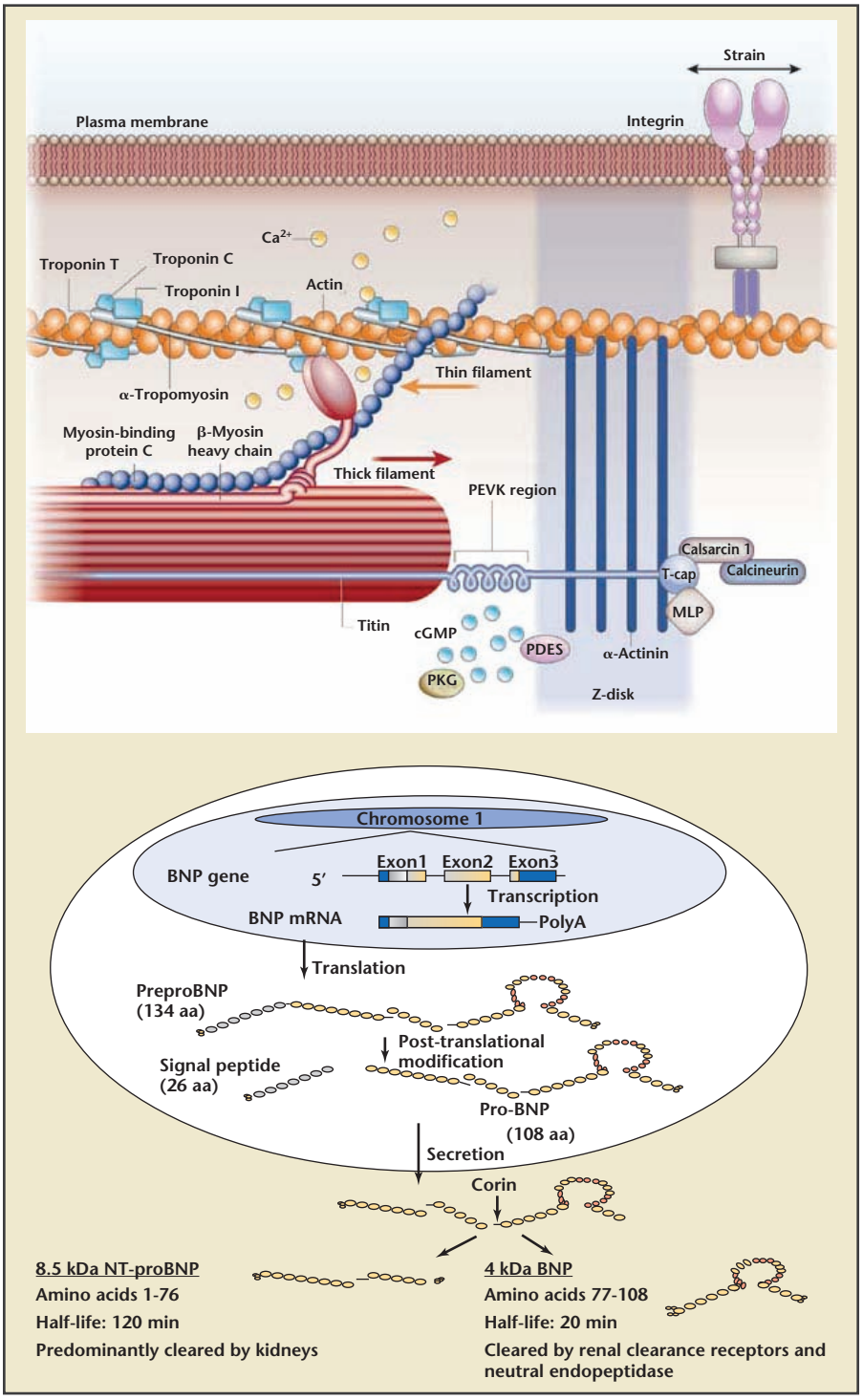

Figure 6. *In response to wall strain or tension that can be triggered by hemodynamic, neurohormonal, or ischemic stimuli, signal transduction occurs that signals the cell nucleus to upregulate expression of the B-type natriuretic peptide (BNP) gene on chromosome 1 and produce messenger ribonucleic acid coding for the pre-proBNP peptide. This product then undergoes several post-translational steps to result in the active 32 amino acid peptide (BNP-32).*

ture, the secondary wave of oxidative stress and cellular damage will become a focus for the development of clinical laboratory testing and potentially adjunctive pharmacotherapy. In this supplement of *Reviews in Cardiovascular Medicine*, a series of articles explore the integrative roles of multiple cardiac biomarkers, cardiac imaging, and the measurement of NP hormones in the diagnosis, prognosis, and management of ACS patients. ■

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