but involve modification by a conglomeration of inflammatory and compensatory factors. Chronic vascular inflammation is a dynamic process of the arterial vessel wall where cycles of inflammatory and thrombotic activity play a critical role in the development of atherothrombosis, resulting in the acute coronary syndromes. Atherosclerotic lesions represent a cascade of cellular and molecular assaults on vascular endothelium, beginning early in life. Factors such as elevated levels of low-density lipoprotein cholesterol, cigarette smoking, elevated homocysteine levels, infectious agents and genetic predisposition inflict injury on the endothelium, triggering compensatory responses that alter normal endothelial function and environment. As a whole, the injurious process triggers a chronic and complex inflammatory process that involves migration of destructive substances, cycles of cellular proliferation and necrosis and remodeling of the lesion. Ultimately, the core of lipid and necrotic tissue becomes covered by a fibrous cap. Neurohormonal and inflammatory factors contribute to the destabilization and rupture of susceptible atherosclerotic plaques, leading to coronary thrombosis and acute coronary events. Unstable plaques, vulnerable to rupture, are usually not large and appear on coronary angiograms to obstruct less than 50% of the arterial lumen. The larger plaques tend to be stable, noninflamed and covered with a thick fibrous cap. The vulnerable plaque is generally smaller, often composed of unstable and inflammatory constituents and with a soft thin cap. Inciting factors within the plaque core act to undermine the plaque structure. The smaller, unstable plaque, because of its potential to rupture and initiate thrombosis, poses a greater clinical threat.

Traditional serum markers of myocardial injury in acute coronary events (creatine kinase of muscle band [CK-MB] isoform of CK, cardiac troponin [cTn] I and T, myoglobin) reflect only the sequelae of the inflammatory milieu and plaque rupture. The pathophysiological results of the inflammatory process...
include impairment of flow in the coronary artery, ischemic myocardial dysfunction and necrosis or death of myocardial tissue. In contrast to the physiologic injury markers, newly identified serum substances that result from or are the components of vascular inflammation and/or atherosclerotic plaque instability have drawn recent attention for their ability to portend acute clinical events and their outcomes. Because these new markers offer earlier warning before the actual onset of myocardial injury, their expanding role in acute coronary event management is assured.

QUESTIONS

1. Limitations inherent to the use of current serum markers for myocardial injury are which of the following?
   a. levels increase only in the presence of transient myocardial injury
   b. levels increase only in the presence of acute congestive heart failure
   c. levels increase immediately after onset of myocardial ischemia
   d. levels increase 3 to 4 hours after the onset of signs and symptoms

2. Serum markers that reflect early vascular plaque inflammation or neurohormonal activation include which of the following?
   a. CK-MB
   b. pregnancy-associated plasma protein A (PAPP-A)
   c. high sensitivity C-reactive protein (hs-CRP)
   d. plasma D-dimer
   e. B-type natriuretic peptide (BNP)
   f. interleukin-6 (IL-6)
   g. myeloperoxidase (MPO)
   h. cTn

3. The vascular inflammatory and cardiac-specific neurohormonal markers in acute coronary events are helpful in which of the following?
   a. as a guide to early therapy
   b. can aid in stratifying therapy in acute coronary events by the ability of markers to determine the risks of complications and clinical outcomes
   c. can help eliminate unnecessary intensive therapy in low-risk coronary events

ANSWERS

1. d. levels increase 3 to 4 hours after the onset of signs and symptoms

Outcomes in acute coronary syndromes are influenced by the speed and accuracy of diagnosis and the timeliness of appropriate therapy. Traditionally, the basis of chest pain evaluation in the ED has been a detailed history, physical examination, the electrocardiogram (ECG) and analysis of serial serum markers. Unfortunately, many injury markers are limited in their diagnostic value during the very early stages of acute coronary syndromes. Most markers of myocardial cell injury that reflect the structural consequence of coronary ischemia (serum cardiac enzymes, cTn) do not increase until 3 to 4 hours after the onset of pain. The clinical evaluation and ECG findings, when added to the limited diagnostic window of the traditional markers, provide only partial information in risk stratification. Examples include (a) the patient with UA and plaque rupture without evidence of myocyte necrosis (negative cTn or CK-MB) but with nonspecific ST-segment changes, who remain at risk of an acute MI; (b) the postinfarction patient at risk of impending cardiac failure; and (c) after percutaneous coronary intervention and stent insertion at risk of restenosis. Although high cTn levels in acute MI are consistent with an increased short-term risk of mortality, they are of no value in the long-term prognosis.

2. b. PAPP-A
c. hs-CRP
d. plasma D-dimer
e. BNP
g. IL-6
h. MPO

Recently, the American College of Cardiology and the American Heart Association guidelines have recommended that risk stratification is one of the most important initial steps in the evaluation and treatment of acute coronary events. Novel inflammatory markers have improved our ability to identify patients at high risk for acute coronary events. Recently, new plasma markers that reflect neurohormonal activation and impending plaque rupture (independent of myocyte necrosis) have been linked to increased risk in acute coronary syndromes. Markers of plaque inflammation and neurohormonal activation make early diagnosis of acute coronary syndromes possible and, as a consequence, help determine the need for and type of aggressive therapeutic interventions. The following are examples of recent markers of neurohormonal activation, plaque inflammation, and plaque stability.
PAPP-A

PAPP-A is a high molecular weight metalloproteinase originally identified in the serum of pregnant women before delivery. PAPP-A was initially measured to help determine term date because levels increase to about 100 mIU/L at term. Metalloproteinase is a family of protein hydrolase-analyzing endopeptidases that contain zinc ions. The PAPP-A antigen is also measured in the fetal diagnosis of Down’s syndrome. The role of PAPP-A in tissue other than placenta has only recently been explored. PAPP-A, found equally in men and women, is abundant histologically in eroded and ruptured plaques but is not expressed in stable plaques. Serum PAPP-A levels are significantly elevated in patients with both UA and acute MI, but levels are not influenced by sex, age, risk factors, or medications. Activated macrophage foam cells, located within unstable plaques, produce and release metalloproteinase enzymes into the extracellular matrix. These enzymes cause degradation of the matrix structure, leaving the fibrous plaque cap soft and vulnerable to rupture. PAPP-A is a possible culprit in extracellular matrix degradation. This also activates insulin-like growth factor (IGF-I), a mediator of atherosclerosis. PAPP-A levels are determined by means of an enzyme immunoassay. A threshold of 10 mIU/L has been considered a positive marker of patients with impending acute coronary syndromes.

In a recent study, the control group and patients with stable angina (SA) had low PAPP-A levels (3.8-10.4 mIU/L) compared with patients with UA, who had elevated levels to 22.5 mIU/L. Patients with acute MI had levels increased to 46.6 mIU/L. Elevated PAPP-A levels identify patients with UA even in the absence of elevation in cTn or hs-CRP levels. PAPP-A as a marker can detect plaque rupture before markers that indicate onset of MI and myocardial necrosis. The capability for early determination of event risk makes PAPP-A a promising stratification tool in classifying patients presenting with acute coronary syndromes.

hs-CRP

CRPs are acute-phase proteins produced by the liver and are elevated when there is tissue injury, infection, or inflammation. CRPs are prothrombotic and promote tissue factor production, macrophage uptake of low-density lipoprotein, vascular cell adhesion molecule expression and induce monocyte chemoattractant protein 1. Elevated levels of hs-CRP are associated with an increased risk of recurrent events in all of the acute coronary syndromes.

Plasma D-Dimer

D-Dimer, a peptide, is the end product of fibrin breakdown and reflects the ongoing process of thrombus formation and dissolution that occurs at the site of active plaques in acute coronary syndromes. D-Dimer has been used conventionally in the diagnosis of deep vein thrombosis and pulmonary embolism; recent studies demonstrate an association between increased circulating levels of D-dimer and thrombotic complications in patients with MI. Levels of D-dimer can predict acute MI, recurrent coronary events, and peripheral atherothrombosis. Because of its role early in ischemic pathophysiology, D-dimer levels increase in acute coronary events before the elevation in levels of cardiac injury markers (including myoglobin).

D-Dimer levels may be affected by other conditions that cause or are caused by thrombosis (eg, pulmonary embolism), or may involve other vascular pathologies (cerebrovascular disease, peripheral vascular disease, renal/hepatic insufficiency). The normal range for plasma concentrations of D-dimer is 150-400 µg/L via commercially available enzyme-linked immunosorbent assay (ELISA) kits, with a threshold higher than 500 µg/L.

BNP

In cardiac decompensation, hormones are released from both cardiac and extracardiac origins. Where norepinephrine and endothelin reflect the peripheral responses to cardiac impairment, natriuretic peptides are neurohumoral hormones produced by the heart. Atrial natriuretic peptides (ANP) are mainly expressed in response to atrial myocardial distension, and minute elevations in response to ventricular dysfunction. BNP are natriuretic peptides released by ventricular myocardium, stored mainly in the ventricular myocardium, released into the circulation in response to ventricular dilatation and pressure overload. BNP levels reflect neurohormonal activity and increase with disease progression: They are used currently as prognostic workers in acute coronary syndromes and congestive heart failure. Elevation of BNP levels in acute MI and UA is predictive of a greater risk of death, postinfarction heart failure, or reinfarction. Postinfarction studies demonstrate that elevated plasma BNP levels are associated with larger infarct size, increased probability of ventricular remodeling, lower ejection fraction, higher risk of heart failure, and increased mortality. This cardiac marker is a potent predictor of mortality in patients with all forms of congestive heart failure. BNP measurements serve as an index of severity of the ischemic injury, as well as the degree of impairment in
left ventricular function. Transient myocardial ischemia, causing an increase in left ventricular wall stress, leads to increased production and release of BNP, even in the absence of necrosis or preexisting left ventricular dysfunction. In homeostatic states, BNP influences natriuresis, inhibits the renin-angiotensin-aldosterone system and the sympathetic nervous system activity and facilitates vasodilatation. The release of BNP is thought to be a backup mechanism to ANP when ANP effects fail to generate adequate cardiac compensation. BNP levels, as a measure of an adverse prognosis, are valid even in the presence of neurohumoral blocking therapy. Levels of BNP during the first days following an acute coronary event can predict long-term mortality risk and help identify patients’ risk for adverse outcomes. BNP measurements also help determine the need for aggressive pharmacological and interventional therapies. In acute MI, BNP levels increase rapidly during the first 24 hours and then plateau. Elevated levels of BNP in acute coronary events increase the risk of death and when measured 1 to 4 days after MI, provide important prognostic information. In UA with no evidence of necrosis, an increase in BNP levels predicts a worse prognosis. Serial BNP levels provide more prognostic information than do those of a single measurement. In heart failure of any etiology, the BNP measurement is the most powerful neurohormonal predictor of left ventricular dysfunction and prognosis and can help in differentiating heart failure from other causes of dyspnea. The BNP threshold of 80 pg/mL, indicative of neurohormonal activation in heart failure, is similar to that in acute coronary syndromes. The routine use of angiotensin-converting enzyme (ACE) inhibitors does not alter the levels of BNP or norepinephrine.

IL-6

IL-6 is a cytokine, a nonantibody protein and intercellular mediator. Cytokine IL-6 is the primary driver of hepatic CRP synthesis. This marker is produced by a variety of cells in the body; plasma concentrations reflect the intensity of plaque vulnerability to rupture and restenosis following percutaneous coronary intervention. Cytokine IL-6 is involved in the pathogenesis of the acute coronary syndrome and has the following effects: stimulates the linear production of fibrinogen and CRP, stimulates the macrophage to produce tissue factor and matrix metalloproteinases, platelet aggregation, adhesion molecules, tumor necrosis factor, and vascular smooth muscle cell proliferation. Elevation of circulating IL-6 is a strong and independent marker of increased mortality in acute coronary events.1,10 Cytokine IL-6 predicts future MIs in healthy men as well as total mortality in the elderly.11

MPO

MPO is a leukocyte enzyme that promotes oxidation of lipid substances within an atheromatous plaque. In a small study, MPO was shown to be critical in the development of atherosclerosis and thus in the future measurement of MPO may serve as a marker of inflammation. Currently, MPO assays are not clinically available.4,12

cTn

The troponin proteins are not inflammatory markers; however, because of their importance as a marker of severity and prognosis, the troponin complexes deserve attention. Located on the thin filament of the contractile apparatus in both striated and skeletal muscle tissue. The contractile protein, troponin, is composed of 3 isoforms: 2 found in both cardiac and skeletal muscle (cTnT, cTnC) and 1 specific to myocardial fibers (cTnI). This protein complex regulates the force and velocity of muscle contraction by modulating the interaction of actin and myosin. The troponin complex is not found in smooth muscle. Cardiac contractile proteins are the most abundant proteins in cardiomyocytes and are useful markers of myocardial damage. After injury or damage of cardiac cells, proteins of the contractile apparatus (troponins) are released into the circulation. The increase in serum concentration of the troponins that follows myocardial injury makes the measurement of this marker highly sensitive in acute MI. Troponin levels remain elevated 4 times longer than CK levels.

The cTnI marker facilitates both early and late diagnoses of MI even in the setting of concomitant skeletal muscle disease and especially after noncardiac surgery. Increases in cTnI are not restricted to acute MI; cTnI has also been detected in serial sampling of patients with UA at rest. Initial elevations of cTnI, which permit an early diagnosis, occur as a result of the release of this enzyme from a stored pool. Persistent elevations are considered to be due to a slow release of cTnI from the contractile apparatus. Prolonged elevations of cTnI permit evaluation for cardiac damage days after cardiac injury.13 Cardiac troponins are not inflammatory markers of the arterial plaque: Troponin levels indicate the sequelae of the inflammatory process in the plaque.
The foundation of care in acute atherosclerotic heart disease involves multipharmacological therapy, that is, aspirin, ACE inhibitors, β-blockers, antithrombotic agents, and statins. Measuring levels of inflammatory markers provides additional therapeutic guidelines in acute coronary syndromes. HMG-coenzyme A reductase inhibitors (statins) are anti-inflammatory and are critical in reducing plaque inflammation and stabilizing impending plaque rupture. Statins reduce plaque lipid content, lipid oxidation and matrix metalloproteinase 2 reactivity and cellular apoptosis. In addition, statins increase levels of metalloproteinase inhibitor substances and collagen content of plaques. Statins alter hs-CRP levels; however, the change is only modest. Aspirin is effective in reducing primary and secondary coronary events, but has only a modest reducing effect on elevated hs-CRP levels.

Elevated BNP levels suggest activation of the cardiac neurohormonal system. Therapeutic implications of this marker may determine the need and timing of aggressive antiplatelet, antithrombotic therapy, neurohormonal antagonists (ie, β-blockade, ACE inhibitors) and revascularization. Normal BNP levels in acute coronary events are low long-term risks of heart failure and mortality; thus measurements of BNP can be critical in determining therapy.

SUMMARY

Most patients (about 85%) seen in the ED to rule out an acute coronary event do not have acute coronary disease. In addition, the presenting ECG findings have been nondiagnostic in 50% of patients with acute MI. Our current knowledge of atherosclerosis as being a chronic low-grade inflammatory process triggered the search for reliable serum markers that have improved the diagnostic accuracy management and prognosis of this prevalent disease. Newer and potential inflammatory markers currently under investigation deserve watching in future reports. These among others include those markers produced by the arterial wall itself, that is, cell adhesion molecules (CAM), intercellular adhesion molecules (ICAM), and vascular adhesion molecules (VCAM). The expression of CAM is a marker of dysfunctional endothelial cells. It is likely that more cardiac markers will be reported in the future. Time will tell.

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Laurie G. Futterman and Louis Lemberg

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