Biomarkers of Atherosclerosis: Is the Evaluation Essential Preoperatively?

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Abstract

Atherosclerosis is a chronic inflammatory condition leading to various cardiovascular as well as cerebrovascular events and peripheral vascular disease (PVD). Presence of significant atherosclerosis leads to perioperative adverse events, morbidity and mortality in the high risk surgical population. The usual methods for evaluating the like hood of adverse cardiovascular or cerebrovascular events postoperatively in these set of patients depends primarily on scoring system and functional status of the cardiovascular system during preoperative assessment. The pre-existing disease activity and possible postoperative adverse cardiovascular event (CVE) can be estimated to some degree from the preoperative levels of biomarkers associated with atherosclerosis.

This mini-review summarizes the potential role of biomarkers related to the atherosclerosis process in the cardiovascular risk stratification of patients undergoing non cardiac surgery. A Med Line search of literature on atherosclerosis biomarkers in the perioperative period and adverse post-operative cardiovascular event was conducted; and thirty-three reports are added to this review.

Keywords: Atherosclerosis; Perioperative period; Biomarkers

Introduction

Atherosclerosis is a chronic inflammatory process in the blood vessels that results in the formation of atheromatous plaque over the endothelial lining of blood vessels leading to stiffness and loss of elasticity of the vessel, stenosis of the artery, aneurysm formation, plaque rupture and dysfunction of endothelial cell lining [1]. Pre-existing atherosclerosis may lead to acute unanticipated myocardial infarction during the perioperative period. Unanticipated arrhythmia, congestive cardiac failure, acute coronary syndrome and cerebrovascular accidents are some other perioperative adverse events which can cause major postoperative morbidity and mortality. Apart from the various non-biochemical tests available for risk stratification, measurement of biomarkers in the blood during perioperative period can provide a clue for postoperative CVE [2-4].

Biomarkers of Atherosclerosis that Provide a Clue for Postoperative Cardiovascular Event

Traditional biomarkers: Lipoproteins, Creatine kinase, Asparate aminotransferase, lactate dehydrogenase and troponins

Recent biomarkers

- Acute phase reactants

1. C-reactive protein
2. Serum amyloid A
3. Fibrinogen
4. Complement protein

- Cell adhesion molecule

1. Intracellular adhesion molecule-1 (ICAM-1)
2. Vascular cell adhesion molecule-1 (VCAM-1)
3. P-selectin

- Cytokines and chemokines

1. Interleukins
2. Tumor necrosis factor-α
3. Endothelins

- Miscellaneous

1. Brain natriuretic peptide
2. Cystatin C
3. Matrix metalloproteinase
4. Leptin

Traditional biomarkers

Lipoproteins: Low density lipoprotein and apolipoprotein (apo B) remains the main target of atherosclerosis therapy and measure the atherogenesis of plasma. Present studies primarily focused at the apo B: apo A-1 ratio. The consensus conference from American Diabetic Association, stress the effectiveness of apo B level as a predictor of perioperative CVE in patients in patients on statin therapy [5]. According to the guide lines the safe apo B targets are <90 mg/dL for individuals with the presence of diabetes or cardiovascular disease (CVD) risk factors and <80 mg/dL with known diabetes or CVD with an additional CVD risk factor [5].

Creatine kinase (CK): Creatine kinase is expressed in most of the body tissues and organs, and has three iso-enzymes. The CK-MB iso-enzyme is found in maximum concentrations in the myocardial tissue. In the patients presenting with acute myocardial infarction, the level of CK-MB begin to rise 4-6 h after the onset of chest pain, peak level

reaches at 12 to 24 h and return to base line by 48 to 72 h. The ratio of plasma CK-MB to total CK is a better indicator of myocardial cell damage rather than the level of CK-MB alone.

Troponins: Cardiac troponins (troponins T and I) are the regulatory proteins that control the calcium interaction between actin and myosin during heart muscle contraction. Troponins are needed to assess the prognosis of acute coronary syndrome (ACS), diagnosis of acute MI and prediction of CVE perioperatively. Among the three subunits of troponins, troponin-T (Tn-T) and I (Tn-I) are the tissue components of cardiac muscle and are exceedingly specific for myocardial tissue. The elevated plasma concentration are detected 3-12 h after myocardial damage and the concentration remain upraised for 5-9 days for Tn-I and up to 14 days for Tn-T.

A raised level of Tn-T and Tn-I has been found to be useful in the prediction of adverse CVE and therefore considered to be a useful preoperative screening test for high risk individuals. In one of the cohort study, using Tn-I value 0.02 ng/ml as a diagnostic cut-off point for the presence of coronary artery disease (>70% stenosis), elevated Tn-I classified sixty five percent of population as high risk. The authors concluded that Tn-I value to have a similar predictive accuracy to that of stress testing with imaging studies (70%) and better than ECG parameters during stress testing (53%) [6]. Different studies show increased troponins in various major surgery have a high sensitivity, specificity and negative predictive value when perioperative CVE is the question [7-10]. Cardiac troponin value however have certain limitations; i) the value does not necessarily equate to recent myocardial infarction or any other CVE, ii) it is difficult for the clinician to distinguish whether a raised level of troponins is the result of atherosclerotic plaque rupture or due to some other reason, iii) there is difficulties in determining the upper reference limit of the normal range for different tests.

Aspartate aminotransfrase (AST): AST has ubicubitus distributions, its concentration increased within 6-10 h after acute MI, peaking at 12-48 h and return to normal level within 3-4 days. Because of low specificity it is been hardly used to determine perioperative CVE.

Lactate dehydrogenase (LDH): Among the five isoenzymes of LDH, LDH-I is common in heart muscle. The plasma concentration of LDH-I start to rise 12-24 h after MI, reach a summit within 2-3 days and returns to base line by 14 days. The utility of this enzyme as a CVE marker in the perioperative setting is gradually declining.

Acute phase reactants

The role of various acute phase reactants (APRs) as a predictor of postoperative outcome has been investigated by several authors. Among these biomarkers the majority of work has been focused on C-reactive protein (CRP). However, there are other biomarkers which have a contribution towards the pathogenesis of atherosclerotic disease and postoperative CVE in patients suffering from atherosclerotic disease.

C-reactive protein (CRP): C-reactive protein is produced primarily by the hepatic cells in response to the release of interleukin-6 (IL-6) or tumour necrosis factor-α (TNF-α), the pro inflammatory cytokines. CRP is found within the atherosclerotic plaques in both coronary and peripheral vessels [11-13]. The median CRP level in a normal healthy individual is 0.8 mg/L with an inter percentile range 0.3-0.7 mg/L. During an acute phase reaction the plasma level reaches to a peak of 300 mg/L within 24-48 h and rapidly reverses within 19 h at the initiation of inflammatory stimulus. This time of decline is constant for all the cases. The high sensitivity assays (hs-CRP) measure the low CRP concentration which cannot be measured by the routine biochemistry laboratory. With this assay an accurate measurement of CRP concentrations up to 3 mg/L are now possible. According to American heart association and centre for disease control and prevention, a hs-CRP level of >3 mg/L should considered as risk factor for perioperative CVE in patients with asymptomatic atherosclerosis or stable ischemic heart disease and levels >10 mg/L have a greater prognostic value in those suffering from acute coronary syndrome [14].

Vidula et al., evaluated the prognostic significance of CRP in patients with peripheral vascular disease (PVD) [15]. In the authors study at four years of follow up, each 50% elevation in CRP level was associated with an increased risk of all causes of mortality (HR1.14,95% CI 1.05-1.24) and cardiovascular disease related mortality (HR 1.17,95% CI 1.05-1.30) A 2 year follow up suggesting that increased CRP level predicts an increased in cardiovascular risk. Few of the previous authors shown that a preoperative CRP level >2 mg/L was associated with post-operative complications in small group of patients undergoing cardiac surgery and an uneventful recovery occurred in all patients with a concentration of 2 mg/L [7,16]. Rossi E et al. found a CRP concentration >9 mg/L preoperatively as a predictor of adverse CVE in patients undergoing non cardiac surgery [17].

Fibrinogen: This acute phase protein is a key molecule in the process involved in the genesis of atherosclerosis. An elevated concentration of fibrinogen has been found to be an independent predictor of fatal cardiovascular complications in high risk patients with PVD [18].

Complement proteins: The complements proteins primarily synthesized in liver. It is also produced by macrophages and monocytes. The activation of complement system occurs during the initiation of biochemical cascade involved in inflammation. An elevated level of C5a found in plasma and atheromatous plaque can predict an increased cardiovascular risk [19].

Serum amyloid A: Serum amyloid A (SAA) protein is synthesized in liver, involved in acute phase reaction and maintains the reverse cholesterol transport system. Several studies have shown its' association in atherogenesis process and it is present in atherosclerotic lesions. The womens' ischemic syndrome (WISE) study evaluated women referred for coronary angiography for suspected myocardial ischemia and showed that SAA levels are independently associated with CAD and highly predictive of one year adverse CVE [20].

Cytokines

Interleukins (ILs): IL-6 is mainly important among all pro inflammatory ILs. It has been shown that base line IL-6 is predictive of peripheral arthrosclerosis disease progression within five years of its detection [12].

Tumor Necrosis Factor–α: This multifunctional pro inflammatory cytokine is associated with increased and recurrent coronary events according to CARE trial [21].

Endothelins: These powerful vasoconstrictors are expressed by endothelial cells. The plasma concentration of endothelin is raised in patients having atherosclerotic risk factors and those with atherosclerosis. The level increases with the severity of atherosclerosis or onset of coronary artery disease or any other CVE [22]. Endothelins also behaves as chemo attractants for the monocytes and macrophages and thought to have a role in neovascularization. The angiogenesis role

of ET has been proved from the presence of ET receptors on the neo vessels within the atherosclerotic plaque [22] Van Beneden et al. has shown that ET-1 concentration in plasma is a prognostic indicator in patients with atherosclerosis and congestive cardiac failure. However, in the authors view plasma brain natriuretic peptide (BNP) is a better prognostic indicator than ET-1 during perioperative period.

Cell adhesion molecules (CAM)

P-Selectin: This adhesion molecule is produced primarily by platelets that mediate monocytes rolling before they adhere to the endothelium in the initial stage of atherosclerotic plaque formation. The critical role of P-selectin in both leukocyte recruitment and atherosclerosis progression has been confirmed in various animal models. Blann AD and colleague demonstrated that a deficiency of P-selectin have a protective effect against atherosclerosis and an increase level is associated with progression of atherosclerosis, CAD and atrial fibrillation [23].

Vascular adhesion molecule-1 (VAM-1): VAM-1 is a strong predictor of atherosclerotic risk; however its role in adverse CVE is not proven [24].

Intercellular adhesion molecule-1 (ICAM-1): The ICAM-1 contributes to the adhesion of leukocytes to the activated endothelium and mediates the adhesion of monocytes, lymphocytes and neutrophils to the endothelial cells. There is evidence of expression of ICAM-1 on smooth muscle cells in human aorta and coronary vessels [25] Elevated levels of ICAM-1 have been found in patients with atherosclerosis. Witte DR and colleague demonstrated that ICAM-1 is related to advanced atherosclerotic lesions and estimated risk of CAD in otherwise healthy individual. Heim and colleague demonstrated that an increased baseline plasma concentration of ICAM-1 was associated with a greater incidence of future cardiovascular events in patients with known CAD [26].

Miscellaneous

Brain natriuretic peptide (BNP): Plasma brain natriuretic peptide (p-BNP) and N-terminal pro BNP (P-NT-BNP) released in response to myocardial stress An increased level of this peptide has also been demonstrated in patients with atherosclerosis and it correlates well with the severity of disease [27] The role of BNP and N-terminal pro BNP (NT-pro BNP) has been well proved to have an association with increased short and long term mortality in 2656 randomly selected individuals from a cohort among whom only 5% had a prior stroke or MI [28] After a median follow up of 4.5 years, the investigators found an increase in log-pro BNP to be a major predictor of composite end point of non-fatal MI or non-fatal stroke and major cardiovascular death.

Cystatin C: Cystatin C is primarily a novel biomarker for renal dysfunction has more importance than serum creatinine when perioperative renal failure is concern. An increase level of cystatin is also found to be associated with adverse CVE by several authors [29,30] An increase level of cystatin C was related to atherosclerosis risk and increase incidence of coronary artery calcium deposition in one of the study [30].

Matrix metalloproteinases (MMPs): MMPs are zinc dependent proteases produced by several cell types. They are classified into different subgroups based upon their structure and substrate specificity. MMPs are responsible for degradation of collagen and other extracellular matrix (ECM) components. MMPs particularly MMP-2 is involved in all stages of atherosclerosis process. They promote the migration of smooth muscle cell and early plaque development. In the subsequent stage of atherosclerosis, there is breakdown of ECM by MMP, which leads to rupture of atherosclerotic plaque and erosion of endothelium. MMPs also influence intraplaque angiogenesis through interaction between integreins and protenases. The aneurysm formation during atherosclerosis process is also due to the arterial remodelling and increased ECM breakdown by MMPs.

Studies also shown that there is an increase concentration of MMPs in patients with unstable angina or acute MI when compared with healthy controls [31]. The role of these proteins in post-operative CVE in patients with atherosclerosis is again unknown.

Leptin: Leptin, a 167 amino acid peptide produced mainly by adipose tissue, although the leptin receptors are expressed in several tissues of the body. Recent studies suggested that leptin is involved in various process of atherogenesis including endothelial dysfunction, platelet aggregation, oxidative stress, hypertrophy and proliferation of vascular smooth muscle cells. Several epidemiological studies have demonstrated that increase leptin level can predict acute CVE, restenosis of coronary vessels after angioplasty even after correction of body weight, plasma glucose, CRP and lipid levels [32].

What is the Role for Plasma Biomarkers in Patient with Known Atherosclerosis? Present Senario

In spite of a battery of available preoperative tests for stress induced myocardial ischemia; it is difficult to identify who are really the patients at risk for perioperative CVE. It might be due to the fact that vulnerable plaques cannot be identified by the available tests and thereby it is not possible to identify the population at risk of plaque rupture to give rise symptoms.

Among all the biomarkers, CRP appears to be the most promising biomarker for prediction of CVE during perioperative period. Though CRP does not correlate with the entire atherosclerotic burden, it may indicate other atherogenesis event eg. Vascular cell activation, expression of inflammatory mediators, grade of plaque destabilization, ongoing thrombosis or plaque rupture.

One should not forget that CRP act as an protective adverse event protein and maintain some balance between ongoing inflammatory process and stability of atherosclerotic disease. This can be used for interpretation of unstable atherosclerotic plaque only in patients who does not have any other coexisting inflammatory conditions. On the other hand, most of the patients who undergo a major surgical procedure have a greater incidence of CVE. Therefore CRP level estimation should be done in majority of such patients.

Use of multiple biomarkers simultaneously to predict the cardiovascular risk has been tried by few authors. The main conclusion of these studies is that use of multi biomarker score can reclassify the risk in 30% of the individuals and predict CVE in future [33].

Atherosclerotic Biomarkers, How Important are they in Perioperative Setting?

To be clinically useful biomarkers must change the management and thus improves the outcome. Targeting the therapy for a reduction of biomarker level in plasma those thought to be a risk factor or direct contributor towards atherosclerosis should reduce the risk of CVE.

However, the reports on the role of atherosclerotic biomarkers in perioperative CVE prediction is limited, with no existing researches supporting the fact that, " treatment plans can be changed according to the atherosclerosis biomarker level or a reduction of perioperative CVE can be done with targeting the therapy to decrease the biomarker level".

Summary and Conclusion

There is growing interest in biomarkers of inflammation and atherosclerosis rather than myocardial cell death. Some biomarkers seem to be risk factors (eg. elevated LDL levels) for atherogenesis, whereas others are inconclusive (eg. leptin). Few of the recent studies elaborated the association of several atherosclerotic biomarkers with increased cardiovascular risk. However till date there are no randomized trials exists to demonstrate that intensifying or modifying the treatment in response to elevated biomarker levels leads to reduction of CVE. This limits the clinical utility of atherosclerotic biomarkers in perioperative setting.

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