Clinica Chimica Acta 412 (2011) 1279–1296

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/clinchim

Invited critical review

Biochemical markers in acute coronary syndrome

I. Ramasamy

Worcester Royal Hospital, Worcester WR5 1DD, United Kingdom

ARTICLE INFO

Article history:
Received 2 April 2011
Accepted 3 April 2011
Available online 8 April 2011

Keywords:
Acute coronary syndrome
NSTEMI
STEMI
Cardiac biomarkers
Troponin
C-reactive protein
Ischemia modified albumin
B-type natriuretic peptide

ABSTRACT

Owing to their higher risk for cardiac death or ischemic complications, patients with acute coronary syndrome (ACS) must be identified from other causes of chest pain. Patients with acute coronary syndrome are divided into categories based on their electrocardiogram; those with new ST-segment elevation and those who present with ST-segment depression. The subgroups of patients with ST-segment elevation are candidates for immediate reperfusion, while fibrinolysis appears harmful for those with non-ST elevation myocardial infarction. There is increasing evidence to encourage appropriate risk stratification before deciding on a management strategy (invasive or conservative) for each patient. The TIMI, GRACE or PURSUIT risk models are recommended as useful for decisions regarding therapeutic options. Cardiac biomarkers are useful additions to these clinical tools to correctly risk stratify ACS patients. Cardiac troponin is the biomarker of choice to detect myocardial necrosis and is central to the universal definition of myocardial infarction. The introduction of troponin assays with a lower limit of detection will allow for earlier diagnosis of patients who present with chest pain. Analytical and clinical validations of these new assays are currently in progress. The question is whether the lower detection limit of the troponin assays will be able to indicate myocardial ischemia in the absence of myocardial necrosis. Previous to the development of ultrasensitive cardiac troponin assays free fatty acids unbound to albumin and ischemia modified albumin were proposed as biochemical markers of ischemia. Advances in our knowledge of the pathogenesis of acute coronary thrombosis have stimulated the development of new biomarkers. Markers of left ventricular performance (N-terminal pro-brain natriuretic peptide) and inflammation (e.g. C-reactive protein) are generally recognized as risk indicators. Studies suggest that using a number of biomarkers clinicians can risk stratify patients over a broad range of short and long term cardiac events. Nevertheless, it is still under debate as to which biomarker combination is best preferred for risk prediction. This review will focus on recent practice guidelines for the management of patients with ACS as well as current advances in cardiac biomarkers, their integration into clinical care and their diagnostic, prognostic and therapeutic utility.

Contents

E-mail address: indrar@ozemail.com.au.

0009-8981/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.cca.2011.04.003

1. Background

1.1. Causes of chest pain

The diagnosis of the cause of chest pain must take into account the type of chest pain, the associated symptoms and signs and patient characteristic. Patients who present with chest pain can either present with acute chest pain of recent onset which may be ongoing and persistent, episodic, recurrent chest pain or persistent chest pain which may continue for days or hours. A sudden total occlusion of a coronary artery by thrombosis or by embolisation causes an acute myocardial infarction (AMI). Pain may be recurrent and episodic as with angina from atherosclerosis. When the angina pain occurs at lower levels of stress, or even at rest, the episodes suggest unstable rather than stable angina. AMI may be asymptomatic in patients with impaired pain response or with preexisting collateral vessels. In patients with chronic total occlusion, angina may develop because circulation to the affected myocardium through collaterals is impaired during periods of stress. Aortic dissection commonly presents as severe pain of discrete onset. The pain of pericarditis may be of sudden acute onset, may be recurrent and episodic or may persist for hours or days as a dull ache. Various other causes of chest pain and their presentation are given in Table 1 [1].

1.2. Pathophysiology of myocardial ischemia

The pathogenesis of coronary atherosclerosis is multifactorial. Briefly, endothelial injury results in the adhesion and transmigration of leukocytes from the circulation into the arterial intima and the migration of smooth muscle cells from the media into the intima. Macrophages recruited into the artery wall become lipid laden foam cells by engulfing modified lipoproteins. As the lesion progresses, inflammatory mediators cause the expression of procoagulant factors and matrix degrading proteinases that can weaken the fibrous cap of the plaque. If the fibrous cap ruptures coagulant factors in the blood can access the thrombogenic lipid core, causing thrombosis on a previously nonocclusive atherosclerotic plaque. This process diminishes coronary artery perfusion through stenosis or by distal embolisation of the thrombus [2]. An ACS develops when a vulnerable or high-risk plaque undergoes disruption, which is a stimulus for thrombosis. Two types of thrombi can form, a platelet rich clot (referred to as a white clot) that forms in areas of high shear stress and only partially occludes the artery, or a fibrin-rich clot (referred to as a red clot) that is the result of an activated coagulation cascade and decreased flow in the artery. Red clots are frequently superimposed on white clots and this characteristic causes total occlusion. The severity of findings on coronary angiography frequently parallels the clinical severity of ACS. Mostly white clots are found in patients with non-ST elevation (NSTEMI) and red clots form in patients with ST segment elevation (STEMI) ACS. The differences in the pathophysiology of NSTEMI and STEMI are the bases for different therapeutic goals and approaches [3].

Myocardial ischemia, which is a perfusion imbalance between supply and demand, can occur with normal coronary arteries. Nonatherosclerotic causes of coronary stenosis can be found in patients with congenital anomalies of coronary arteries, collagen vascular disease, valvular aortic stenosis or hypertrophic cardiomyopathy. Ischemia secondary to increased oxygen demand is found in fever, hyperthyroidism and sustained tachyarrythmias. Reduced coronary blood flow as in hypotension and reduced myocardial oxygen delivery such as anemia or hypoxemia can precipitate unstable angina. The chest pain syndrome of myocardial ischemia is similar regardless of whether the cause is intrinsic coronary atherosclerosis or other coronary and noncoronary causes of myocardial ischemia [1].

Table 1
Some non-cardiac causes of chest pain and their presentation.

Cause of chest pain	Type of chest pain
Pulmonary	Pulmonary embolism may be associated with severe pain at time of onset and if it leads to pulmonary infarction it may be associated with recurrent episodic pain, especially at the time of breathing. Pulmonary hypertension is more commonly associated with chest pain following exertion. Pneumonia or pleuritis may present with pain of acute onset and may become recurrent at times of movement or breathing
Gastrointestinal	Can be acute or recurrent and episodic. Most gastrointestinal causes are related to eating, vomiting or other gastrointestinal signs and symptoms e.g. cholecystitis, peptic ulcer disease
Musculoskeletal	Can be acute (associated with injuries) or recurrent and episodic associated with movements. Many musculoskeletal associated chest pain are not related to physical activity and this lack of relationship can be a way of distinguishing it from angina and coronary artery disease.

1.3. Electrocardiogram (ECG) changes in acute coronary syndromes

The ECG findings depend on the nature of the process (reversible i.e. ischemia vs irreversible ie infarction), duration (acute vs chronic), extent (transmural vs subendocardial) and localization (anterior vs inferoposterior), as well as the presence of other underlying abnormalities (ventricular hypertrophy, conduction defects). With transmural ischemia the overlying ECG leads will record ST elevation, with subendocardial ischemia the overlying leads will record ST depression. ST segment elevations are typically followed within hours to days by evolving T wave inversions and often by Q waves. The division of acute myocardial infarction into STEMI and NSTEMI types is useful as acute reperfusion therapy (mechanical or pharmacologic) is the preferred strategy in the former group. In NSTEMI the goal of antithrombotic therapy is to prevent further thrombosis and allow endogenous fibrinolysis to dissolve the thrombus and reduce the degree of coronary stenosis, revascularization is frequently used to increase blood flow and prevent reocclusion or recurrent ischemia. In contrast, in STEMI, the infarct-related artery is usually totally occluded and immediate pharmacological or catheter-based reperfusion is the initial approach with the goal of obtaining normal coronary flow [3].

Previously abnormal Q waves were considered to be markers of transmural myocardial infarction, while subendocardial infarcts were thought not to produce Q waves. However, later studies showed that transmural infarcts may occur without Q waves and that subendocardial infarcts may be associated with Q waves. Therefore infarcts are classified as 'Q-wave' and 'non-Q-wave' infarcts. ECG changes due to ischemia may occur spontaneously or may be provoked by various exercise protocols. In patients without prior infarction transient ST segment elevation during an episode of chest pain or exercise is a reliable sign of transmural ischemia and downward sloping or transient ST depressions are more likely to be subendocardial ischemia. The spectrum of clinical presentations ranging from unstable angina, through NSTEMI and STEMI is referred to as ACS. Over 90% of patients with prolonged ischemic episodes and ST-segment elevation have myocardial infarction [4].