INTRODUCTION

The homeostasis of healthy cells is disturbed when subjected to a supply-demand mismatch resulting in insufficient oxygen delivery, deprivation of nutrients, and decreased clearance of waste products. Although a cellular mismatch in supply vs. demand can be caused by a number of pathophysiological events, the root cause of most acute coronary syndromes (ACS), a continuum of cardiac ischemia from unstable angina through myocardial infarction (MI), is plaque instability, plaque rupture, and occlusive intracoronary thrombus formation. As such, thrombus formation and the resulting supply–demand mismatch are followed by a complicated cascade of events, the end point of which is myocardial ischemia and myocardial cell necrosis.

Biomarkers have provided information for the clinical assessment of patients with suspected acute cardiac disease since the early 1950s. Their utilization has, however, evolved substantially over the past 30–40 years1. Biomarkers were previously considered to be one of the three important variables, along with changes on the electrocardiogram and clinical signs and symptoms, necessary for the diagnosis of MI as defined by the World Health Organization (WHO) in 1979. Cardiac troponins are now designated as surrogates for necrosis and MI when elevated in the setting of acute cardiac ischemia, according to the consensus document of the European Society of Cardiology (ESC) and the American College of Cardiology (ACC)2. In addition, the use of natriuretic peptides (NP) has recently been introduced to improve the rule out of congestive heart failure (CHF) in symptomatic patients3. In the foreseeable future, a multi-marker strategy, employing a pathobiologically diverse set of biomarkers, could significantly help in the assessment of patients with cardiac disease.

Markers of plaque destabilization and/or markers of myocardial ischemia could be added to the existing markers of cardiac necrosis and function in this paradigm if shown to contribute additional independent information4.

BIOMARKERS OF CARDIAC NECROSIS

Following coronary artery occlusion, cellular changes commonly include disruption of the sodium-potassium pump, leakage of excess calcium into the cell, depletion of energy reserves, and conversion from aerobic to anaerobic cellular metabolism. If the occlusion is prolonged, cellular damage becomes irreversible, resulting in cell death and necrosis. Irreversible injury, i.e. necrosis, typically requires 30 min of ischemia. After 30 min cell death starts: 80% of cells at risk die within 3 hours, almost 100% by 6 hours of ischemia. Release of biomarkers in blood after necrosis occurs in different time frames which depend on:

- the intracellular location and whether molecules are bound or free;
- molecular weight (because heavier molecules diffuse at a slower rate);
- local blood and lymphatic flow;
- the rate of elimination from blood.

Theoretically, the ideal marker of necrosis should demonstrate the characteristics summarized in Table 1. It is now clear that, for their exquisite biological attributes, cardiac troponins come closest to the ideal and the following considerations try to give evidence for that.

The troponin complex has three protein subunits and is located on the thin filament of striated muscle. While troponin C has an identical amino acid sequence in both skeletal and cardiac tissues and, thus, has no potential as a cardiac-specific marker, troponin T (TnT) and troponin I (TnI) have different isoforms in cardiac and skeletal

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Persisting in circulation for days following necrosis
- Released in direct proportion to the extent of necrosis
- Estimate of infarct size
- Persisting in circulation for days following necrosis

Table 1
Characteristics of the ideal biomarker of necrosis
- Present only in cardiomyocytes → Absolute cardiospecificity
- Abundant in cardiac tissue → High sensitivity for the damage
- Released shortly after necrosis → Early diagnosis
- Released in direct proportion to the extent of necrosis
- Estimate of infarct size
- Persisting in circulation for days following necrosis → Late diagnosis

Cardiac troponins, when measured with highly sensitive last-generation immunoassays and interpreted using a lower cutoff to increase sensitivity in early hours after the onset of infarction, can reach the same performance of myoglobin in terms of negative predictive value, making the latter redundant if this approach is used.

Infarct size can also be estimated from troponin values obtained 72 hours after onset. The available data are stronger for this approach with cTnT than with cTnI, even if recent data have shown that, using 48-hour cTnI concentrations, the same information can be obtained. Finally, the increase in concentration of cardiac troponins after MI is prolonged compared with that of other biomarkers of necrosis. According to the slow continuous release of the myofibril-bound proteins, elevations of cardiac troponins persist for days to weeks after MI, even if this is dependent on the extent of myocardial damage.

Problems related to the lack of definitive diagnostic standards for MI have often been underlined in the past. The advent of cardiac troponins, providing high sensitivity for small injury and virtually absolute specificity for myocardial damage, assign now to laboratory a key role in detection of this disease. Opposite to the traditional WHO definition (requiring presence of two out of three criteria, including biochemistry), today an acute MI can not be diagnosed without the biochemical evidence of myocardial necrosis: an accurate diagnostic standard

Table 2
Cardiac diseases other than acute myocardial infarction causing elevation of cardiac troponins in blood
- Acute rheumatic fever
- Amyloidosis
- Cardiac trauma (including contusion, ablation, pacing, firing, cardioversion, catheterization, cardiac surgery)
- Carbon monoxide poisoning
- Cardiotoxicity from cancer therapy
- Congestive heart failure
- Critically ill patients
- Diabetic ketoacidosis
- End-stage renal failure
- Glycogen storage disease type II (Pompe’s disease)
- Heart transplantation
- Hemoglobinopathy with transfusion hemosiderosis
- Hypertension, including gestational
- Hypotension, often with arrhythmias
- Hypothyroidism
- Idiopathic hypertrophic cardiomyopathy
- Myocarditis/Pericarditis
- Postoperative noncardiac surgery
- Pulmonary embolism
- Sepsis
- Subarachnoid hemorrhage
- Thiamine deficiency (beriberi)
has finally been established and this is represented by cardiac troponin.

**BIOMARKERS OF CARDIAC FUNCTION**

Biochemical tests have traditionally not played any role in the clinical assessment of cardiac function. With the recent clinical characterization of cardiac NP, the concept of a plasma marker for assessment of ventricular dysfunction has, however, been introduced and intensely pursued. In particular, it was demonstrated that the B-type NP have greater pathophysiological and clinical importance.

It is now clear that measurement of NP in plasma does not unequivocally diagnose a specific cardiac disease, but it should be used in a more general way in order to detect possible cardiac involvement and verify the need of further specific, but more expensive, cardiac investigations. While normal NP concentrations make heart failure unlikely with a very high negative predictive value, high concentrations of these biomarkers simply call for further investigations: imaging is therefore required to identify the underlying cardiac pathology, revealing the systolic and diastolic ventricular function and thus determining the appropriate treatment (9). This is instrumental to incorporate NP in the first step for the evaluation of symptomatic subjects suspected of having CHF3.

This definite clinical application has led to the development of several fully automated immunoassays for measuring B-type NP-related peptides, giving substantially comparable clinical performances (Figure 1). In clinical practice, it is, however, necessary to take into consideration the specific assay employed to obtain the results, as no result interchangeability exists. Assays differ in their reactivity with circulating peptides, so that commercial assays, nominally measuring the same analyte, may be differently affected by cross reactivity problems. For B-type NP measurements, no two assays are, therefore, analytically equivalent at present. Values are significantly dependent on the type of assay used as a result of the specificity of the employed antibodies against different B-type NP-related peptides. For this reason, it is not possible to recommend a single cutoff value to be universally adopted. As results are heavily method-dependent, it should clearly be stated that reference intervals and decision limits derived from clinical studies are only valid for the particular assay used and must not be extrapolated to other assays. With this important limitation in mind, a definitive use of NP for diagnostic and prognostic purposes is now warmly recommended (Table 3)10.

**BIOMARKERS OF CARDIAC ISCHEMIA AND PLAQUE RUPTURE**

As troponins reflect myocyte death, earlier markers of ischemia in the absence of necrosis are additionally needed to detect myocardial damage even before the irreversible injury is induced and, hopefully, to reliably rule out myocardial damage from the emergency room at patient presentation. A marker of cardiac ischemia could also be valuable in distinguishing acute MI from non-ischemic causes of myocardial necrosis that lead to increases in cardiac troponins. Recently, a number of candidate biomarkers of cardiac ischemia have been proposed and still remain the subject of ongoing research (Table 4). Before moving toward consideration of clinical implementation, each of these candidates must be evaluated critically with respect to key biochemical and clinical characteristics. Particularly, major pitfalls are represented by the lack of rapid, high-quality assays.

![Figure 1](image-url)  
*Commercially available assays for measuring BNP-related peptides*
and by biomarker elevations during ischemia in any vascular bed (lack of cardiospecificity).

New markers for coronary plaque instability and rupture are also arising, such as whole blood choline, released by activation of phospholipase D related to coronary plaque destabilization; pregnancy-associated plasma protein A, a potentially pro-atherosclerotic metalloproteinase; soluble CD40 ligand, a signaling protein reflecting platelet activation; and myeloperoxidase, a leukocyte enzyme secreted during neutrophil activation. Despite the emergence of multiple candidate biomarkers for plaque vulnerability, none of these has, however, sufficient evidence to recommend widespread adoption into clinical practice. Once again, adequate assays are not available, optimal cutoffs and timing of measurement should be defined, and the additive clinical value when compared with currently available tools (i.e. troponin) definitively demonstrated11.

Table 4

Proposed biomarkers of cardiac ischemia

- Ischemia-modified Albumin (IMA™)
- B-type Natriuretic Peptides
- Unbound Free Fatty Acids
- Serum Creatine
- Deoxyribonuclease I
- Sphingosine-1-phosphate
- Nourins

REFERENCES