

Biomarkers of myocardial injury after cardiac arrest or myocardial ischemia

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1. ABSTRACT

Outcomes of victims of cardiac arrest or acute myocardial ischemic events have improved with advances in medical therapy. Heart failure, however, remains a leading cause of morbidity and mortality after these conditions have occurred. Clinical features may be useful for predicting patients who are at risk of developing such complications, but they lack of sensitivity and specificity. Biomarkers have been therefore suggested as means to provide relevant prognostic information. The more commonly used biomarkers after cardiovascular ischemic events, including cardiac arrest, are creatin kinases and troponins. In addition, natriuretic peptides and C-reactive protein have gained great interest and now sufficient data has been collected such to justify their clinical applicability. Finally, several other novel biomarkers, to be used after resuscitation from cardiac arrest or more generally after a myocardial ischemic event, have been anticipated. Nevertheless, the “perfect” biomarker, able to provide diagnosis and prognosis with high sensitivity and specificity does not exist. A multimarker strategy that categorizes patients based on the number of elevated biomarkers at presentation is therefore suggested.

2. INTRODUCTION

Cardiovascular disease is a leading cause of death in the Western world. In the United States, approximately one half of the 2 million deaths each year are due to cardiovascular disease. More specifically, as many as 400,000 Americans and 700,000 Europeans sustain cardiac arrest each year (1). Though the initial success of cardiopulmonary resuscitation is approximately 39%, a majority of victims die within 72 hours (2, 3). Severe heart contractile failure due to post-resuscitation myocardial dysfunction has been implicated as the most important mechanism accounting for these fatal outcomes (4, 5).

The prognosis of patients resuscitated from cardiac arrest can be estimated by information obtained from the clinical history, electrocardiogram (ECG) abnormalities, and, more recently, from biochemical indicators of myocardial injury and dysfunction, as well as markers of renal failure and inflammatory activity (6).

During the last two decades, biomarkers and laboratory parameters, commonly used in clinical cardiology, have gained increasing significance and play important roles as

Table 1. Biomarkers of cardiac ischemic events

During cardiopulmonary resuscitation	After an ischemic event or resuscitation from cardiac arrest
Coronary perfusion pressure ¹	Creatine Kinases ¹
End tidal CO ₂ ¹	Troponins ¹
VF Amplitude and Frequency ¹	B-type natriuretic peptide ²
Amplitude Spectrum Area ²	N-terminal pro-B-type natriuretic peptide ²
	Mid-regional pro-atrial natriuretic peptide ²
	C-reactive protein ²
	Pentraxin 3 ²
	Arginine vasopressin ²
	C-terminal provasopressin ²
	Adrenomedullin ²
	Endothelin-1 ²

¹Traditional biomarker, ²Novel biomarker

indicators of risk for coronary events, in primary and secondary prevention, in the diagnosis and management of acute myocardial necrosis and heart failure patients. The development of novel biochemical markers has also led to new insights in the pathophysiology of coronary artery disease, acute coronary syndromes, including cardiac arrest, and heart failure conditions (7).

The term “biomarker”, however, might be referred not only to a dosable humoral biochemical feature or facet but to every different “message” that can be assessed from the patient during treatment or the subsequent follow-up. Indeed, this anticipation is more evident under the specific setting of cardiac arrest. For this particular condition, we therefore need to discriminate among messages that provide feedback regarding the effects of treatment, cardiopulmonary resuscitation in this specific case, and messages that bring information on the progress of disease, and in particular on the post-resuscitation cardiac dysfunction and ultimately survival.

In this review, after an initial introduction to the pathophysiologic events associated with cardiac ischemic events, we will briefly describe the “bio-information” commonly used during cardiopulmonary resuscitation to guide the resuscitation maneuvers and predict outcome, to finally focus more attention on the cardiac “biomarkers” routinely and experimentally used to assess prognosis following resuscitation from cardiac arrest or reperfusion after episodes of local myocardial ischemic insults. All the biomarkers discussed are summarized in Table 1.

3. PATHOPHYSIOLOGY OF MYOCARDIAL INJURY FOLLOWING CARDIAC ARREST OR A MYOCARDIAL ISCHEMIC EVENT

3.1. Mechanisms accounting for post resuscitation/reperfusion myocardial dysfunction

Occlusion of the coronary arteries for as little as 5 minutes followed by reperfusion produces functional abnormalities for up to 48 hours (8). Those phenomena have been related to a condition called “myocardial stunning” due to release of reactive oxygen species, without evidence of inflammatory reaction. This condition is comparable to a situation of global ischemia and reperfusion following an episode of short duration of

cardiac arrest. Nevertheless, when the duration of ischemia is long enough to produce myocardial injuries and infarction, inflammatory responses might occur and might be also accelerated by reperfusion itself.

In the setting of cardiac arrest, the myocardium is a prime target for injury caused by the condition of ischemia (including the period of total “no flow”, during untreated cardiac arrest, and the period of “low-flow”, during chest compressions) and reperfusion. This leads to functional abnormalities, including ischemic contracture during cardiac arrest and cardiopulmonary resuscitation, arrhythmia during the reperfusion period, and ultimately post-resuscitation myocardial dysfunction and death. Post-resuscitation myocardial dysfunction, which encompasses both systolic and diastolic function, is the consequence of the global myocardial ischemia and reperfusion injury, plus additional adverse effects related to treatment, drugs and repetitive electrical defibrillations (9-13).

The mechanisms responsible for post-resuscitation myocardial dysfunction are therefore not well understood (14). However, several mechanisms have been anticipated, including apoptosis of myocytes following reperfusion. Global ischemia as a consequence of cardiac arrest, in fact, might lead to either primary necrosis or apoptosis (15-19). Oxygen deprivation provokes mitochondrial dysfunction with subsequent loss of membrane potential, cytochrome c release, and cell death of ventricular myocytes (20). In addition, the profound imbalance between ATP synthesis and utilization, a consequence of mitochondrial dysfunction, the impairment of ionic homeostasis and the formation of reactive oxygen species, represent other determinant processes through which mitochondria accelerate, or even determine, the evolution of cell injury toward necrosis or apoptosis (21). The cell death program is activated in cardiac myocytes by various stressors, including cytokines, increased oxidative stress and DNA damage (22). However, whether apoptosis is a mechanism accounting for post-resuscitation myocardial dysfunction remains controversial. Nevertheless, it has become increasingly recognized as one of the mechanisms of cell death during ischemia/reperfusion injuries (23). What the real mechanisms beyond myocyte death are, the cellular basis underlying the development of cardiac ischemic disease and dysfunction ultimately is the loss of functional cardiomyocytes and the inability of the remaining cells to adequately compensate (24). The endogenous regenerative capacity of cardiac progenitor cells, which may exist in adult myocardium, is inadequate to counterweigh the loss of cardiomyocytes that occurs after a cardiac ischemic event (25).

3.2. Markers of inflammatory cascade and innate immunity pathway activations following myocardial ischemia

Myocardial ischemia and reperfusion, whether as a consequence of a local event or cardiac arrest, is an insult that is also associated with inflammatory and innate immunity responses, which ultimately lead to myocardial healing and scar formation (26, 27). Several processes are

involved in a sequence of events that include interactions between pleiotropic mediators, starting with initial activation of complement pathways, production of reactive oxygen species, and activation of the cytokine cascade and chemokine upregulation (8, 28-32). Chemokines stimulate recruitment of inflammatory leukocytes into the infarct area, while cytokines promote adhesive interactions between leukocytes and endothelial cells, enhanced by the concurrent loss of endothelial-derived nitric oxide, another of the earliest manifestations of ischemia-reperfusion injury (33, 34). The cell-mediated inflammatory response is thereby initiated by the neutrophil migration and interaction with the damaged endothelium and subsequent infiltration in the reperfused myocardium, where proteolytic enzymes are released and local cytotoxic effects produced (35-38). Despite these potentially injurious effects, the post-reperfusion inflammatory response also enhances healing. Monocyte Chemoattractant Protein induced in the infarcted area, in fact, regulates mononuclear cell recruitment. Monocyte subsets play distinct roles in phagocytosis of dead cardiomyocytes and in granulation tissue formation through the release of growth factors and subsequent induction of angiogenesis and fibroblast accumulation. Clearance of dead cells and matrix debris may be essential for resolution of inflammation and transition into the reparative phase. In addition, expression of cytokines inhibiting the inflammatory response, such as IL-10 may suppress injury. Matrix metalloproteinases and their inhibitors regulate the extracellular matrix deposition and mediate ventricular remodeling. In this sense, changes in biomarkers of collagen synthesis and degradation suggest that extracellular matrix remodeling is an active process in patients with congestive heart failure and left ventricular systolic dysfunction after acute myocardial infarction. High type I collagen telopeptide serum level, for example, has been proposed as a new biomarker of myocardial injury associated with a high cardiovascular accident rate (39).

Several studies have focused on the role played by the acute myocardial inflammatory reaction as a mediator of the ischemia-reperfusion syndrome. Although it has been clearly demonstrated that neutrophils are the predominant leukocytes accumulating in the injured myocardium and the major source of the reactive oxygen metabolites produced at reperfusion, the role of other leukocyte subtypes, i.e. macrophages, remains to be clarified especially on the early phase of reperfusion. Macrophages, in fact, have been demonstrated to become the prevalent cells of the inflammatory infiltrate in the late reperfusion, thus contributing to the healing and remodeling mechanisms after acute myocardial infarction (40). Mononuclear cells, however, infiltrate the infarcted myocardium in the first few hours of reperfusion. The mechanisms responsible for monocyte recruitment have recently been elucidated and they have been wholly attributed to the dosable complement factor C5a, during the initial hour of reperfusion (41). Transforming growth factor-beta 1 also contributes significantly to the chemotactic activity during the second and third hours of reperfusion, while, after the third hour, monocyte chemotactic activity is largely dependent on monocyte chemoattractant protein-1 (42). Increased monocyte

recruitment may lead to more effective healing. After recruitment in the infarcted area, monocytes differentiate into macrophages and local upregulation of Macrophage Colony-Stimulating Factor may have an important role in this process (27). The exact role of the macrophages in the healing scar has not been fully investigated, however they may serve as an important source of cytokines and growth factors (43, 44). Recent evidence, however, suggests that activated macrophages may also be responsible, at least in part, for the pathogenetic changes that follow ischemia-reperfusion. In fact, plasma levels of macrophage activating factor-1 are elevated in patients with acute myocardial infarction, and neutralization of this cytokine is beneficial in preventing reperfusion injury (45, 46).

The innate immune system is clearly involved in the pathogenesis of cardiovascular disease and therefore represents a possible new target to be studied for diagnosis and treatment after myocardial ischemia (28). Specifically, Toll-like receptors (TLRs) have emerged as important mediators at a proximal step of innate immunity pathways (47). TLRs have been, in fact, recognized as main contributors to pathogen-induced inflammation and, more recently, injury-induced inflammation. Upon stimulation by exogenous and endogenous ligands, TLRs tend to cluster, recruit other extracellular and intracellular accessory proteins to the complex, and trigger signaling cascades that ultimately impact transcription of proinflammatory genes (48, 49). In the signaling pathways downstream of the Toll/interleukin (IL)-1 receptor (TIR) domain, a TIR domain-containing adaptor, myeloid differentiation factor 88, has been demonstrated to be essential for induction of inflammatory cytokines, such as tumor necrosis factor-alpha, IL-4, IL-12, and interferon (IFN)-gamma (50, 51). Expression of TLRs has been found in cardiomyocytes, adventitial fibroblasts, and dendritic cells (52-55). TLRs are therefore highly expressed in endothelium and heart, suggesting a functional importance of these receptors in the cardiovascular system (56). For instance, consistent with its role as a receptor for lipopolysaccharides (LPS), cardiac expression of TLR4 is essential for LPS-induced left ventricle (LV) dysfunction and myocardial expression of tumor necrosis factor-alpha, IL-1 beta, and inducible nitric oxide synthase (57, 58). When a condition of myocardial ischemia/reperfusion has been reproduced on 2 strains of TLR4-deficient mice and controls, TLR4-deficient mice sustained significantly smaller infarctions with fewer neutrophil infiltrations, lipid peroxides, and complement deposition, compared to control mice. Similarly, serum levels of IL-12, IFN-gamma, and endotoxin were not increased after ischemia-reperfusion in those mice (59).

The functional role of TLR2 in response to ischemia and ischemia/reperfusion-induced myocardial injury separate from microbial pathogens has also been demonstrated in experimental studies using TLR2 knockout mice (60). Significantly lesser myocardial fibrosis was observed in TLR2- knockout mice in contrast to wild-type control mice. Left ventricular dimensions at end-diastole and end-systole were smaller and a fractional shortening percentage higher in the TLR2-knockout mice, which ultimately survived longer in comparison to control mice

(61). As a consequence of the role of inflammation following myocardial ischemia, dosage of inflammation response markers are now emerging as future tools for diagnosis and prognosis following myocardial ischemic events.

Specifically, cardiac arrest involves a whole-body ischemia and reperfusion syndrome that triggers a systemic inflammatory response. The post-resuscitation period seems to be characterized by high levels of circulating cytokines and adhesion molecules, the presence of plasma endotoxin, and dysregulated leukocyte production of cytokines. This is a profile considered similar to that seen in severe sepsis (62). Coagulation abnormalities occur consistently after successful resuscitation, and their severity is associated with mortality. During and after cardiopulmonary resuscitation, activation of blood coagulation, platelet activation with formation of thromboxane A, and alteration of soluble E-selectin and P-selectin have been described (63-69). In addition, plasma protein C and S activities after successful resuscitation are lower in non-survivors than in survivors. Low baseline cortisol levels may be associated with an increased risk of fatal early refractory shock after cardiac arrest, suggesting adrenal dysfunction in these patients. These post-resuscitation abnormalities after cardiac arrest again mimic the immunologic and coagulation disorders observed in severe sepsis (70). When plasma cytokine, endotoxin, and *ex vivo* cytokine production in whole-blood assays were assessed in patients resuscitated from cardiac arrest, high levels of IL-6, IL-8, IL-10, and soluble TNF- α receptor type II were able to discriminate among survivors and nonsurvivors. Moreover, among nonsurvivors, the initial need for vasopressor agents was associated with higher levels of IL-1 receptor antagonist, IL-10, and IL-6 (71). TNF- α , in particular, was detectable in 54% of patients and related to mortality. In a recent investigation, pro-inflammatory markers, anti-inflammatory cytokines, such as IL-10, have also proved capability to predict risk of recurrence of acute coronary events (72).

A short-term and self-limited expression of this pro-inflammatory cascade usually provides the heart with a rapid adaptive response to the ischemic insult injury as part of an early warning system (73). However, under the condition of sustained and excessive activation of the above described processes, i.e. during chronic heart failure, detrimental effects may contravene the beneficial ones (74, 75). Timely resolution and spatial containment of the inflammatory response are therefore essential for optimal infarct healing (76). Therefore inflammatory cytokines are important biomarkers that may be assessed in patients resuscitated from cardiac arrest. Although they do not represent specific cardiac markers, their serial dosage provides important information on the status of the patient and ultimately on outcome.

4. MARKERS AND INDICATORS FOR SUCCESSFUL RESUSCITATION MANEUVERS DURING CARDIAC ARREST

The highest priority after "sudden death" is to start external cardiac compression to maintain at least minimal coronary and cerebral perfusion. The rationale for

instituting chest compression prior to attempted defibrillation is best explained by the high energy cost of ventricular fibrillation (VF). During cardiac arrest, coronary blood flow ceases, accounting for a progressive and severe energy imbalance. Intramyocardial hypercarbic acidosis is associated with depletion of high energy phosphates and correspondingly severe global myocardial ischemia resulting in myocardial contractile dysfunction (77, 78). After prolonged, untreated VF, the right ventricle becomes distended and fails to expel its stroke volumes. The ischemic left ventricle becomes contracted (79). Progressive reductions in left ventricular diastolic and stroke volumes have been well documented together with increases in left ventricular free-wall thickness ushering in the stone heart (80, 81). After onset of contracture, the probability of successful defibrillation is remote. Early cardiopulmonary resuscitation, which contributes to the restoration of coronary perfusion pressure and myocardial blood flow, delays onset of ischemic myocardial injury and facilitates defibrillation (82).

Chen *et al.* described three time-sensitive electrophysiological phases, including 1) the electrical phase of 0-4 minutes, 2) the circulatory phase of 4-10 minutes and 3) the metabolic phase of > 10 minutes (83). During the electrical phase, immediate defibrillation is likely to be successful. As ischemia progresses, the success of attempted defibrillation diminishes without cardiopulmonary resuscitation. This phase is characterized by transition to slow VF wavelets during accumulation of ischemic metabolites in the myocardium. Type II VF often fails defibrillation attempts because of re-entry and recurrence of VF. In the metabolic phase, there is no likelihood of successful restoration of a perfusing rhythm.

Existing and established predictors of good quality cardiopulmonary resuscitation and thereby successful resuscitation include coronary perfusion pressure (CPP), and end-tidal CO₂ (EtCO₂) (82, 84-87).

Blood flows generated by chest compressions are dependent on the pressure gradient between the aortic and the venous pressures. CPP, defined as the difference between simultaneously measured minimal aortic pressure and right atrial pressure during compression diastole, is highly correlated with coronary blood flow during cardiac resuscitation and is currently recognized as the best single indicator of the likelihood of successful defibrillation (88). Based on both experimental and clinical observations, return of spontaneous circulation (ROSC) can be predicted when CPP is maintained above 15 mmHg during chest compressions (85).

Under conditions of cardiac arrest and cardiopulmonary resuscitation, cardiac output is usually less than one-third of normal and therefore pulmonary flow and EtCO₂ is dramatically reduced. EtCO₂ is therefore an indirect measurement of pulmonary blood flow and cardiac output produced by chest compressions (86, 87). EtCO₂ is highly correlated with CPP during cardiopulmonary resuscitation, and may thereby serve as a non-invasive surrogate for CPP and therefore has emerged as another

valuable tool for monitoring the effectiveness of chest compressions during cardiopulmonary resuscitation (89). When EtCO₂ exceeds the threshold level of approximately 10 to 15 mmHg during cardiopulmonary resuscitation, greater likelihood of successful ROSC has been reported (90, 91).

With the intent to identify a better predictor of ROSC, there has been focus on the analyses of the electrocardiographic features of ventricular fibrillation (VF) waveform. To this date, the electrocardiogram represents the best “cardiac biomarker” for use during cardiopulmonary resuscitation. The initial approaches to ECG analysis included measurements of VF amplitude, and then frequency (92, 93). Weaver *et al.* observed that patients in which the VF amplitude was greater than 0.2 mV had a significantly greater likelihood of resuscitation (92). Median frequency of VF also served as another predictor of the success of electrical defibrillation (93). In a porcine model of VF and cardiopulmonary resuscitation, a median frequency of more than 9.14 Hz had 100% sensitivity and 92 % specificity in predicting the success of defibrillation. “Amplitude spectrum area” (AMSA) now represents a more accurate predictor for successful defibrillation. It is calculated from the resulting amplitude frequency spectrum according to the following equation: $AMSA = \sum A_i \times F_i$, where A_i is the amplitude at the i th frequency F_i . This method has the potential advantage that it is not invalidated by artifacts produced by chest compression and ventilation and thereby can be utilized during cardiopulmonary resuscitation without the detrimental effects of interruptions. Experimentally, consistent evidence of the validity of AMSA has been proved in both animal and human victims of cardiac arrest (94-98). Specifically, AMSA values of more than 12-13 mV-Hz predict successful defibrillation in human victims of cardiac arrest (97, 98). Accordingly, AMSA has now emerged as a clinically applicable method, derived from the electrocardiographic tracing, which may provide a real-time indicator for effectiveness of chest compressions and prediction of the success of defibrillation.

5. BIOMARKERS OF CARDIAC INJURY FOLLOWING RESUSCITATION FROM CARDIAC ARREST OR REPERFUSION AFTER AN ISCHEMIC EVENT

The more commonly used biomarkers after cardiovascular ischemic events, including cardiac arrest, are creatine kinases (CK) and troponins. In addition, natriuretic peptides (NPs) and C-reactive protein (CRP) have gained great interest and now sufficient data have been collected to justify its clinical applicability. Finally, several other novel biomarkers, to be used after resuscitation from cardiac arrest or more generally after a myocardial ischemic event, have been anticipated. Experimental as well as initial clinical results on the use of novel biomarkers are promising and will be discussed in section 5.2. Nevertheless, further investigations are necessary prior to the routine assessment of these novel biomarkers following cardiac arrest or myocardial ischemia.

5.1. Traditional biomarkers

As little as 10 years ago, a discussion on cardiac biomarkers was limited to CKs, aspartate aminotransferase, and lactate dehydrogenase. These enzymes are released in the setting of myocardial necrosis and thus were used as tools for the diagnosis of myocardial infarction. In the intervening years, however, several new cardiac biomarkers, namely CK-MB and troponins I and T, were discovered and became routine for understanding the pathophysiology and to estimate the prognosis following myocardial ischemic insults.

5.1.1. Troponins

Troponin I, C, and T form a complex that regulates the calcium-modulated interaction of actin and myosin in striated muscle. Among the cardiac markers, troponins I and T are sensitive and specific markers of myocardial injury and are used routinely for the diagnosis of acute coronary syndromes. They provide prognostic information and are of great value for risk stratification of patients (99-103). Elevated troponin blood levels have been reported in several cohorts of patients with heart failure, and the magnitude of elevation has been correlated with the severity of the disease and with adverse outcomes (104-106). Because of their high cardiac specificity, elevated blood troponins may suggest ongoing myocardial damage and may serve as a marker for the progression of disease during the post reperfusion recovery. Currently, for every patient who has suffered a myocardial ischemic event or who has been resuscitated from cardiac arrest, cardiac troponin T or I are considered the first-line test and two samples are recommended for collection, one at admission and the other 12-24 hours later (107).

Cardiac troponin T has been investigated extensively and has been found to be a sensitive marker of myocardial necrosis (108-110). The presence of elevated levels of troponin T in the general population has a prevalence of less than 1% and this condition is commonly associated with an underlying cardiovascular disease or high-risk phenotypes for cardiac accidents, especially in persons with chronic heart failure. Currently, new highly sensitive assays for determination of troponins are available and have shown that troponin T retains a prognostic value at previously undetectable concentrations. When troponin T levels were investigated in more than 4000 patients with a left ventricular ejection fraction of <40% using both the standard assay, with a detection limit of less than 0.01 ng/mL, and the high sensitivity assay, with a detection limit of less than 0.01 ng/mL, troponin T detection increased from approximately 10% of the population to more than 90%. The circulating concentration of this highly sensitive troponin T showed even greater prognostic accuracy in association with increases in another biomarker, namely type-B natriuretic peptide (BNP). In 658 patients who presented with BNP above the median and troponin T below, mortality was 14%. However, in an additional 632 patients with BNP below the median and troponin T above, mortality was 20%. Finally, in the 1331 patients with both markers above their respective median concentrations, mortality increased to 32% (111). A continuous, slow release of troponins from the myocardium might reflect an

ongoing cardiac myocyte cell death. This condition has been associated with the condition of ventricular dysfunction following myocardial ischemia in both animal models and humans patients suffering with chronic heart failure (112, 113). If ongoing cardiac damage at a very low rate is the determinant of these circulating troponins, other mechanisms may, however, account for this phenomenon, such as stretching of cardiac myocytes with transient loss of cell membrane integrity. Apoptosis contribution to troponin T elevation might also be another cause (114, 115).

The issue of specificity of cardiac troponins is critical to the proper use and interpretation of the data. Troponin specificity has not been fully defined. If specificity for the myocardium is high, events can be attributed with a high degree of certainty to cardiac injury. However, if specificity is less robust, increases may occur because of release from skeletal muscle rather than the myocardium and thus may be a marker of acute illness rather than cardiac injury (116). This would be of particular concern for patients with more diverse underlying clinical problems. Cardiac troponins are expressed in fetal and neonatal skeletal muscle in humans and experimental animals, but are suppressed in healthy adult skeletal muscle (117). Nevertheless, they are re-expressed in response to skeletal muscle injury in rats (118).

Elevation of troponin I is highly specific for myocardial injury and may facilitate distinguishing among other clinical conditions associated with elevation of other markers. Troponin I from cardiac muscle and slow- and fast-twitch skeletal muscle, in fact, are products of different genes. Thus, developed monoclonal antibodies to cardiac troponin I have no cross-reactivity with the skeletal muscle forms (119). Specificity of troponin I has been therefore investigated in patients suffering from various clinical conditions associated with elevation of cardiac biomarkers (120). Elevations of total creatine kinases are common, and more specifically CK-MB is high in 59% of patients with acute muscle injury, in 78% of patients with chronic muscle disease and marathon runners, and in 3.8% of patients with chronic renal failure. However, troponin I is elevated only in patients who have been diagnosed with myocardial infarction and myocardial contusion. There is also an important association between these elevations of troponin I and the presence of echocardiographic wall motion abnormalities. This further suggests that measurement of troponin I provides information comparable to echocardiography in clarifying the presence or absence of cardiac injury when elevations of CK-MB occur.

5.1.2. Creatin kinases

Measurement of CKs in the serum was extensively used in the 1970s as a useful tool in the diagnosis of acute myocardial infarction. In a large number of patients, however, an elevated CK value added little information because of the presence of concomitant skeletal muscle damage. This problem has recently been advanced by the development of techniques able to separate CK into its three isoenzymes, i.e. MM, MB, and BB. Separation and quantification of CK-MB isoenzyme, in

particular, provided a more specific indicator of acute myocardial ischemic injury compared to levels of total CK (121).

More recently, CK-MB has been considered as the most sensitive and specific indicator available for the diagnosis of an acute myocardial infarction. The advantage of this biomarker is the degree and duration of its elevation in serum that approximates the extent of the acute myocardial infarction. However, a variety of factors may affect the reliability of this measurement, i.e. differences in the fractionation and assay methods, as well as the presence of CK-MB in tissues other than the myocardium and the release of CK-MB under conditions other than during an acute myocardial infarction (122). At present, measurement of CK-MB is an alternative to troponin measurement, but is only recommended, if troponin measurement is not available. When CK-MB is assessed during the evaluation and treatment of victims of myocardial ischemic events or cardiac arrest, it is critical to be sure that blood samples are obtained at least 6 to 9 hours after the onset of symptoms. The sampling frequency should consider an initial test at admission, a second 2 to 4 hours later, followed by a third one at 6 to 9 hours, with an extra optional 12 to 24 hour sample (123).

The sensitivity of CK-MB determination has been reported to vary from 50-60%, at the time of admission, to 92%-97% three hours later. The immunochemical tests demonstrate specificities ranging from 83.0% to 96.4% after three hours from the acute insult. This is important in the rapid management and treatment of patients during the initial period following resuscitation from cardiac arrest or the occurrence of an ischemic event. Nearly 50% of patients with acute myocardial infarction, in fact, initially have non-diagnostic ECGs. In fact, when serial serum samples, at the admission and three hours after presentation, for analyses of CK-MB, were obtained in more than 180 patients presenting with chest pain into the emergency room, but in the absence of diagnostic ECG, acute myocardial infarction was confirmed in 17% of patients (124).

In different settings, sensitivity and specificity of CK-MB values assessed at admission and 2 hours later, were investigated for detection of acute myocardial infarction. In that investigation cardiac troponin I was used as the sole marker to confirm myocardial necrosis in 975 chest pain patients with a baseline troponin level of 1.0 ng/mL and an initial ECG non-diagnostic for injury. Acute myocardial infarction was diagnosed in less than 5% of the patients. More specifically, the ROC curve area of the delta CK-MB level allowed for an early identification of acute myocardial infarction. A cutoff value for the 2-hour delta CK-MB level of 0.7 ng/mL had a sensitivity of 93% and a specificity of 94% in the early identification and exclusion of acute myocardial infarction in those specific patients presenting with non-ST-segment elevation chest pain (125). Those results were confirmed in a subsequent study, which included more than 400 patients with chest pain and non-diagnostic ECG. However, the best diagnostic value of CK-MB for diagnosis of myocardial ischemia was the one

obtained after six hours following the hospital admission (126).

In a recent study, the best cardiac biomarker was assessed to predict infarct size, left ventricular ejection fraction, and clinical outcome in patients undergoing primary percutaneous coronary intervention (PCI) for ST-segment elevation myocardial infarction, which is a frequent condition associated with cardiac arrest. Specifically, CK, CK-MB, and troponins T and I were determined in 378 patients before PCI and serially up to 72 hours. All CK, CK-MB, and troponins T and I after PCI significantly correlated with infarct size and ejection fraction. However, 72-hour troponin I, in particular, emerged as the only effective method to estimate infarct size, myocardial function, and risk stratification. It, in fact, correlated strongly with 5-day and 30-day infarct size. When a value of more than 55 ng/mL was measured, it was associated with a sensitivity of 90% and specificity of 70% with the presence of a large myocardial infarct and a left ventricle ejection fraction of less than 40% (127).

In a recent study of 26 victims of sudden cardiac arrest, Dr. Wang and colleagues investigated changes in CK-MB and troponin I, elevations of ST in electrocardiograms, and the result of coronary arteriography, in order to identify myocardial damage and acute myocardial infarction during cardiopulmonary resuscitation (128). All patients manifested myocardial damage after resuscitation. CK-MB and troponin I concentrations increased gradually, but without specificity for earlier identification of myocardial damage and ST elevation myocardial infarction. Elevation of the ST segment in the electrocardiogram, instead, showed a more predictive value. Decrease of the ST segment elevation in the electrocardiogram 2 hours after ROSC, or the peak of contents of CK-MB and troponin I, 12 or 16 hours after CPR, indicated myocardial damage. However, when elevation of ST segment did not descend within 2 hours following ROSC, or the levels of CK-MB and troponin I remained elevated 20 hours after resuscitation, ST elevation myocardial infarction had to be suspected, and interventional therapy or thrombolysis considered. In patients without coronary artery block, CK-MB level began to elevate 4 hours after ROSC, and peaked at the 12th hour. Troponin I also began to rise 4 hours after ROSC, peaked after 16 hours, and then decreased gradually. ST elevation was seen at the beginning of ROSC, then lowered quickly within 2 hours. In patients with coronary artery block, CK-MB and troponin I also began to increase 4 hours after CPR. However, they remained elevated after 20 hours. In these patients, the ST segment was elevated at the beginning of ROSC, and remained elevated after 2 hours following resuscitation (128).

5.2. New biomarkers for cardiac arrest and myocardial ischemia patients

5.2.1. Natriuretic peptides: BNP, N-terminal pro-B-type natriuretic peptide (NTproBNP) and Midregional pro-atrial natriuretic peptide (MR-proANP)

B-type natriuretic peptide (NP) and its more stable counterpart, N-terminal pro-B-type natriuretic peptide (NTproBNP), have shown great promise, covering a wide range of acute coronary syndromes (129).

Natriuretic peptide levels are now widely used in clinical practice and cardiovascular research and have been incorporated into most national and international cardiovascular guidelines for heart failure. NPs have numerous advantages compared to other biomarkers. NP levels allow for accurate diagnosis of heart failure and may be helpful to screen for asymptomatic left ventricular dysfunction in high-risk patients. NP levels are also important tools for risk stratification of patients with regard to the need for hospital admission or discharge. More specifically, NP levels at the time of admission are powerful predictors of re-hospitalization and death, and in combination with symptoms and signs, in the assessment of clinical decompensation (130).

In 450 patients suffering from an acute myocardial ischemic event, measurements of troponin I and BNP and CRP were performed. Elevations in troponins and BNP were independent predictors of death, myocardial infarction or congestive heart failure. When patients were categorized on the basis of the number of elevated biomarkers at presentation, there was a near doubling of the mortality risk for each additional biomarker that was elevated. Similar relationships persisted at both 30 days and through 10 months of observation. A subsequent validation cohort of more than 1600 patients confirmed the number of elevated biomarkers as significant predictors. Patients with one, two, and three elevated biomarkers had a 2.1, 3.1, and 3.7 fold increase in the risk of death, myocardial infarction or chronic heart failure within 6 months from the initial observation (131).

It has been previously shown that BNP and NTproBNP were related to long-term prognosis in patients with predominantly ST-segment elevation acute myocardial infarction (132, 133). When, in fact, NTproBNP have been assessed during the subacute phase in 204 patients with ST-elevation myocardial infarction, in 220 with non-ST segment elevation MI and in 185 with unstable angina, median NRproBNP levels were significantly lower in long-term survivor than in non-survivor patients, namely 442 vs 1306 pmol/L (132). The prognostic information introduced by this novel marker has been shown to be superior to echocardiographically assessed left ventricular ejection fraction. Plasma BNP and NTproBNP measured 2 to 4 days after myocardial infarction, independently predicted left ventricular function and 2-year survival. Specifically, the early post-myocardial infarction level of NTproBNP was a powerful independent predictor of death or heart failure over the 2 years after myocardial infarction. In a recent study, NTproBNP levels were shown to be also predictive of short-term survival, after adjustment for conventional contemporary risk markers, such as troponin I (134). Therefore, natriuretic peptides have now emerged as powerful indicators for short-term, medium-term and long-term prognosis across the spectrum of acute coronary syndromes.

In patients who suffered from an acute coronary syndrome and had no evidence of clinical heart failure, NTproBNP provided prognostic information above and beyond conventional risk markers. It has been therefore

anticipated that BNP and NTproBNP releases, even in the absence of myocardial necrosis, are augmented by transient or permanent ventricular dysfunction induced by myocardial ischemia and more specifically the magnitude of the increase in NTproBNP may reflect the extent of the ischemic territory. These two peptides are considered as true "ventricular" hormones and their release is mediated by ventricular wall stress, and their synthesis is increased with cardiac injury and especially in the peri-infarct zone (133). However, in addition to the high sensitivity, NTproBNP and BNP elevations are associated with several other risk factors for adverse outcomes, including advanced patient age, renal impairment, cardiac arrhythmias, and preexisting systolic or diastolic dysfunction. Consequently, those biomarkers may ultimately reflect the result of different pathological conditions (132).

Mid-regional pro-atrial natriuretic peptide (MR-proANP) is a newly introduced stable fragment of N-terminal pro-atrial natriuretic peptide. Its prognostic value has been recently compared to that of NT-proBNP in patients with acute myocardial infarction. MR-proANP has emerged as another powerful predictor of adverse outcome, especially when it has been associated with concurrent elevated NT-proBNP (135). Mid-regional pro-atrial natriuretic peptide therefore may represent a clinically useful marker of prognosis after a myocardial ischemic event as part of a multi-marker strategy targeting the natriuretic neurohormonal pathways. In a retrospective analysis of 251 consecutive patients presenting to the emergency department with dyspnea, MR-proANP plasma concentrations were measured (135). A discriminative MR-proANP cutoff level of 169 pmol/L recognized dyspnea attributable to acute destabilized heart failure. The diagnostic value of MR-proANP therefore appeared to be comparable to that of BNP and NT-proBNP in discriminating heart failure patients.

5.2.2. Pentraxins: C-reactive protein and pentraxin 3 (PTX3)

Pentraxins are a super family of proteins characterized by a multimeric structure (137-139). The classic short pentraxin, C-reactive protein, is a prototypic acute-phase protein produced in the liver in response to inflammatory signals, which serves as a marker of inflammation and infection (140).

Recently, better understanding of the role of inflammation in atherosclerosis and myocardial ischemia has prompted measurements of inflammatory biomarkers to identify patients with increased risk for myocardial ischemic events. Elevated C-reactive protein levels, specifically, have been observed in patients with acute coronary syndromes and have been associated with increased coronary risk in healthy subjects. CRP is now recognized as a sensitive marker of inflammation that provides an independent prediction of cardiovascular disease (141-143). CRP has been found in endothelial atherosclerotic lesions, and evidence suggests that it may play a role in atherogenesis. Thus, CRP may not only reflect the degree of underlying inflammation predisposing to atherosclerosis, but may also play a direct role in promoting plaque rupture and

thrombosis (144, 145). Among middle-aged and elderly subjects with no apparent heart disease except for frequent ventricular premature complexes, CRP values have proved the validity for risk stratification. A CRP value of more than 2.5 µg/mL is, in fact, associated with a significantly higher risk of death and acute myocardial infarction. Those subjects deserve primary prevention measures and further follow up for structural heart disease. In acute myocardial infarction patients, the admission levels of plasma C-reactive protein, are elevated and associated with short and long term outcome (146).

Of all candidate serum markers that might add information to clinical risk assessment, high-sensitivity C-reactive protein measurement, therefore, appears to have the most potential for clinical use for multiple reasons. It is associated with a two-fold to a three-fold increase in the prevalence of myocardial infarction, stroke, and peripheral vascular disease, and it predicts incidence of cardiovascular events in those patients with and without pre-existing pathological conditions. In addition, it can predict increased risk largely independent of other established risk factors and the assays utilized are standardized. Various risk-reducing interventions also reduce CRP, and research is underway to assess whether specifically targeting CRP may reduce cardiovascular risk (147). Finally, C-reactive protein has been shown to serve as a powerful predictor of future cardiovascular events following acute coronary syndromes, even when troponins were not yet positive (148).

The prototypic long pentraxin, PTX3, shares similarities with the classic short pentraxins, but it has an unrelated long N-terminal domain coupled to the C-terminal pentraxin domain and differs in gene organization, cellular source, and ligands recognized. PTX3 is rapidly produced and released by several cell types, including mononuclear phagocytes, dendritic cells, fibroblasts, and endothelial cells, in response to primary inflammatory signals, i.e. Toll-like receptor engagement, tumor necrosis factor- α , and interleukin IL-1 beta (149). Recently, the measurement of pentraxin levels has been performed under conditions of ischemic heart disorders and it has been shown that PTX3 may exert a dual role and contrasting effects on complement activation (150-152). It supports clearance of microbes, facilitating recognition by phagocytes (), while it may also protect against unwanted complement activation in the fluid phase (153, 154). In a model of acute myocardial infarction following coronary artery ligation and reperfusion, tissue mRNA expression and circulating levels of PTX3 increased. PTX3-deficient mice, however, showed significantly greater heart damage together with higher circulating levels of IL-6 and increased C3 deposition in lesional tissue in contrast to PTX3-wild type animals (155).

There is also evidence linking PTX3 to ischemic heart disorders in human patients. PTX3 is induced in vascular smooth muscle cells by atherogenic modified low-density lipoprotein and is present in human atherosclerotic lesions (156, 157). In addition, PTX3 levels increase rapidly after acute myocardial infarction, reaching a peak within 7 hours after the onset of the event (158). Patients

with unstable angina and those undergoing stenting also exhibited high concentrations of plasma PTX3 (159, 160). In a series of more than 700 patients with ST-elevation myocardial infarction, PTX3 dosage emerged as an independent predictor of mortality (151). Thus, PTX3 might be a new prognostic marker for use during ischemic heart disorders. The evidence for a regulatory role in the pathogenesis therefore prompts further investigation of the clinical relevance of PTX3 assessment during various conditions of heart disease (151, 158-160).

5.2.3. Arginine vasopressin (AVP) and C-terminal provasopressin (copeptin)

Arginine vasopressin (AVP) or antidiuretic hormone is a nonapeptide produced in the hypothalamus. AVP is released from the neurohypophysis to promote renal water conservation, which contributes to osmoregulation and cardiovascular homeostasis, and plays an important role in cardiopulmonary resuscitation (161). The vasopressin system is activated after acute myocardial infarction. AVP is derived from a larger precursor peptide, preprovasopressin along with 2 other peptides, neurophysin II and copeptin (162, 163). There are concerns about the validity of measurement of AVP in plasma, because it is known to be unstable and rapidly cleared (164). Thus, measurement of AVP has not been widely adopted. Copeptin, however, is stable for days after blood withdrawal and can be quickly and easily measured, being secreted in equimolar amounts to vasopressin (165). In a recent prospective study, including approximately 1000 post-acute myocardial infarction patients, the plasma copeptin level was high on admission and reached a plateau between the 5th and the 7th day after the event. The biomarker was elevated in patients who died or were readmitted with heart failure compared with survivors. Copeptin, as pair than NTproBNP, was an independent predictor of death or heart failure at 60 days. Copeptin was able to predict adverse outcome, especially in those patients with an elevated NTproBNP. In this group of patients, levels of copeptin above 7 pmol/L were predictive of poor outcome, thus defining a high-risk group. The complementary information provided by copeptin to NTproBNP suggested that the stimuli to the secretion of both markers are different, and plasma levels are likely to reflect different aspects of cardiovascular homeostasis. Another advantage of copeptin is that it peaks during the first day from the ischemic event compared with the NTproBNP that peaks by the second day. In addition, no gender difference in copeptin levels have been reported, in contrast to NTproBNP (166). Prognostic value of this novel biomarker has been compared with BNP and NT-proBNP, on death or a composite cardiovascular endpoint in patients who developed heart failure after an acute myocardial infarction. Although higher levels of copeptin, BNP, and NT-proBNP were all significantly related to both mortality and cardiovascular events, copeptin was a stronger predictor of mortality compared with both BNP and NT-proBNP. More specifically, changes of copeptin levels after the first month from the initial event, added significant prognostic information (167).

The benefit of measuring both prohormones over their bioactive peptides includes the lack of receptor binding or protein interactions and longer half-lives, which

result in higher plasma levels. The prohormones are also more stable in blood *ex vivo*, and this makes them generally more applicable in clinical practice (165).

5.2.4. Adrenomedullin (ADM)

ADM is a newly discovered 52-amino acid peptide with structural homology with calcitonin gene-related peptide (168). Originally isolated from human pheochromocytoma cells, immunoreactive ADM has been detected in other tissues, including adrenal medulla, heart, brain, lung, kidney, and gastrointestinal organs (168, 169). The limited data available concerning the biologic activity of ADM suggest that it has powerful direct vasodilator effects and is able to increase cardiac output and induce diuresis and natriuresis (170-173). Plasma ADM levels are typically in the lower picomolar range in normal humans but are reported to be increased in hypertension, congestive heart failure, and chronic renal failure in proportion to the severity of disease (174, 175). In heart failure, plasma ADM has been shown to be inversely related to left ventricular ejection fraction and positively associated with left ventricular end diastolic pressure. Current findings indicate that ADM, especially in association with plasma catecholamines, is an indicator of both early and late myocardial functions after infarction. Nevertheless, the power of prediction of myocardial outcome of ADM remains inferior compared to the more sensitive and specific NTproBNP. Plasma ADM levels in heart failure presumably reflect a systemic or peripheral response to cardiac impairment and may be mediated by a variety of mechanisms, including induction of endothelial production of ADM, elevated levels of endothelin, or other humoral and neural mechanisms (176).

Adrenomedullin is derived from a larger precursor peptide proADM (185 amino acids), by post translational processing. In 264 healthy individuals, pro-ADM was investigated and it has been observed that it followed a gaussian distribution with a mean of 0.33 nmol/L, and had the advantage of no gender differences. Moreover, it significantly increased in patients with cardiovascular disease, to a mean value of 0.56 nmol/L (177). In a recent study, the prognostic impact of another part of the ADM precursor, midregional pro-adrenomedullin (MR-proADM), was investigated in approximately 1000 patients after acute myocardial infarction. MR-proADM has the advantage of being more stable in circulation and *ex vivo*. Plasma MR-proADM and NTproBNP were assessed from 3 to 5 days after onset of chest pain. MR-proADM increased in patients who died or developed heart failure in contrast to those who survived, i.e. 1.19 nmol/L vs 0.71 nmol/L. In a multivariate binary logistic model, log MR-proADM was a significant independent predictor of worse outcome. MR-proADM also provided further risk stratification in patients who had NTproBNP levels above the median. MR-proADM therefore emerged as a clinically powerful predictor of adverse outcome, to be used in the prognosis after acute myocardial infarction (178).

5.2.5. Endothelin-1 (ET-1)

Raised circulating concentrations of the endothelium-derived 21-amino-acid vasoconstrictor peptide endothelin have been reported during the initial hours following an acute myocardial ischemic event. ET-1 is

delivered mainly from the vascular endothelial cells and acts in an autocrine/or paracrine manner, mediating vasoconstriction predominantly by binding to its Eta receptors on the underlying smooth muscle cells (179, 180). In addition, although sustained elevation of circulating endothelin is observed in patients with complicated myocardial infarction, plasma levels decline rapidly in uncomplicated cases. Furthermore, in chronic heart failure and in myocardial infarction with heart failure, plasma endothelin concentrations and pulmonary capillary wedge pressure correlated closely (181-183). The plasma profile of endothelin in the acute phase of myocardial infarction has previously been investigated in several small-scale studies that demonstrated a rapid increase in plasma endothelin levels after admission, with a peak occurring approximately 6 hours after onset of symptoms, followed by a gradual decline toward normal values in uncomplicated myocardial infarction. In contrast, in patients with either persistent hypotension, pulmonary edema, postinfarction ischemia, or early reinfarction, sustained elevation of plasma endothelin concentrations were observed 72 hours after onset of the symptoms. The main stimulus for and site of endothelin production during and after acute myocardial infarction remains to be established. However, a high myocardial content of endothelin has been observed as long as 48 hours after reperfusion (184). Interestingly, simultaneous sampling of blood from different vascular beds in patients with chronic heart failure revealed no significant differences in plasma endothelin levels, compatible with a generalized systemic activation of endothelin production in chronic heart failure. It is therefore possible that acute ischemia may function as a trigger for cardiac endothelin production in the early phase of myocardial infarction, whereas peripheral hypoperfusion secondary to reduced cardiac output may represent a stimulus for subsequent persistent systemic endothelin production. Experimental work also indicated that catecholamines, angiotensin II, and arginine vasopressin may stimulate endothelin production (185-187). Since endothelin possesses potentially harmful pathophysiological properties and in addition may function as a marker of the degree of left ventricular dysfunction and subsequent elevation of filling pressure, persistent high plasma levels might be associated with a poor prognosis after an acute myocardial ischemic event.

Recently, plasma endothelin concentrations have been proved to provide prognostic information independently of clinical and biochemical variables previously associated with a poor prognosis following myocardial infarction. Specifically, plasma endothelin levels during the subacute phase of myocardial infarction were related to 1 year mortality in 142 patients. Plasma endothelin concentrations averaged approximately 5.6 pg/mL in patients with myocardial infarction, in comparison, to levels in patients admitted to hospital with acute chest pain without evidence of myocardial necrosis, which averaged 3.7 pg/mL. Patients who developed clinical heart failure during the hospitalization phase had significantly higher plasma endothelin levels than those who did not present with the pathological condition, namely 7.2 vs 4.9 pg/mL. In addition, plasma endothelin

concentrations levels measured on the 3rd day following acute myocardial infarction appeared significantly related to mortality. In patients who died, the mean value of ET-1 was, in fact, 9.2 pg/mL, whereas in those who survived, ET-1 did not increase over 5.1 pg/mL. Finally, patient age, previous treatment for systemic hypertension, presence of clinical heart failure, and plasma atrial natriuretic factor levels were all related to mortality in univariate analysis but provided no additional prognostic information to that obtained from endothelin determination in a multivariate model (188).

Due to its short plasma half life, the intermediate clearance due to receptor binding during pulmonary passage, and its cleavage by endopeptidases, ET-1 dosage might not be accurate (189). ET-1 is derived from a larger precursor peptide, pre-proET-1, of 212 amino acids. Peptides derived *in vivo* from the ET-1 precursors are more stable than ET-1 and might not be subjected to rapid turnover. Recently, C-terminal Endothelin-1 precursor fragment plasma was shown to follow a gaussian distribution in healthy individuals, without differences in men and women and to significantly increase during heart failure. CT-proET-1 may therefore be a rapid and easy method for indirectly assessing the release of ET-1 in critically ill patients (190). In a prospective study which included 30 patients suffering from acute ST elevation myocardial infarction or non-ST elevation myocardial infarction, measurements of CT-pro-endothelin-1 (CT-proET-1) were performed at admission, and 2 or 3 days and 4 months after acute myocardial infarction. CT-proET-1 was able to differentiate patients with subsequent long-term clinical events from those without. Specifically after 3 days from the acute event, patients with CT-proET-1 levels of more than 57 pmol/L were 6 times more likely to suffer from a recurrent myocardial clinical event. Elevated CT-proET-1 during the acute phase of myocardial infarction may therefore be another novel marker to predict an adverse long-term clinical event after an acute coronary syndrome (191).

6. CONCLUSIONS

Outcomes of patients after cardiac arrest or an acute myocardial ischemic event or infarction have improved with advances in medical therapy, but heart failure remains a leading cause of morbidity and mortality after these conditions have occurred. Clinical features may be useful for predicting patients who are at risk of developing such complications, but they lack sensitivity and specificity. Biomarkers are therefore emerging as useful tools for predicting prognosis in such patients. Elevated levels of troponin I, high-sensitivity C-reactive protein, and B-type natriuretic peptide are associated with higher rates of death and recurrent ischemic events (192-194). These 3 biomarkers assess different pathophysiological mechanisms in myocardial ischemia: elevations in troponin indicate myocardial necrosis and even minor elevations convey prognostic information beyond that obtained from measuring CK-MB; CRP is a marker of inflammation, that is now recognized as a central

determinant for ischemic complications; and BNP is elevated in response to left ventricular overload (195-197).

A variety of new biomarkers, i.e. NTproBNP, MTregBNP, AVP, ADM, and ET-1, as well as others, such as pro- (soluble CD40 ligand, placental growth factor, interleukin-1 and 6, TNF-alpha, myeloperoxidase, monocyte chemoattractant protein-1) and anti-inflammatory markers (interleukin-10, activin A) have been suggested to provide relevant prognostic information in patients with acute coronary syndrome. However, the clinical utility of these novel markers has not been established to date (198).

Accordingly, it is apparent that each biomarker yields important information, but the "perfect" biomarker, able to provide diagnosis and prognosis with high sensitivity and specificity does not exist. A multi-marker strategy that categorizes patients based on the number of elevated biomarkers at presentation, therefore allows risk stratification over a broad range of short- and long-term major cardiac events (131).

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Abbreviations: ADM: adrenomedullin, AMSA: amplitude spectrum area, AVP: arginine vasopressin, BNP: B-type natriuretic peptide, CK: creatin kinases, CPP: coronary perfusion pressure, CRP: C-reactive protein, ECG: electrocardiogram, ET-1: endothelin-1, ETCO2: end tidal CO2, IFN: interferon, IL: Interleukin, LPS: lypopolysaccharides, MR-proANP: midregional pro-atrial natriuretic peptide, NP: natriuretic peptide, NTproBNP: N-terminal pro-B-type natriuretic peptide, PTX3: pentraxin 3, ROSC: return of spontaneous circulation, TIR: Toll/interleukin-1 receptor, TLR: Toll like receptor, VF: ventricular fibrillation,

Key words Biomarkers, heart, myocardial ischemia, reperfusion, cardiac arrest, cardiopulmonary resuscitation

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