

Review

Bench-to-bedside review: The value of cardiac biomarkers in the intensive care patient

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Abstract

The use of cardiac biomarkers in the intensive care setting is gaining increasing popularity. There are several reasons for this increase: there is now the facility for point-of-care biomarker measurement providing a rapid diagnosis; biomarkers can be used as prognostic tools; biomarkers can be used to guide therapy; and, compared with other methods such as echocardiography, the assays are easier and much more affordable. Two important characteristics of the ideal biomarker are disease specificity and a linear relationship between the serum concentration and disease severity. These characteristics are not present, however, in the majority of biomarkers for cardiac dysfunction currently available. Those clinically useful cardiac biomarkers, which naturally received the most attention, such as troponins and B-type natriuretic peptide, are not as specific as was originally thought. In the intensive care setting, it is important for the user to understand the degree of specificity of these biomarkers and that the interpretation of the results should always be guided by other clinical information. The present review summarizes the available biomarkers for different cardiac conditions. Potential biomarkers under evaluation are also briefly discussed.

Introduction

Nearly 30% of patients admitted to a general intensive care unit (ICU) have underlying cardiac diseases, and approximately one-half of these 30% are admitted to the ICU with cardiac problems as the primary cause [1,2]. The latter group is mainly comprised of patients with acute myocardial infarction, acute heart failure (HF) or cardiogenic shock. Pulmonary embolism, sepsis-related cardiac dysfunction and arrhythmias are also commonly found in the ICU.

The diagnosis of cardiac problem can be a difficult task in the ICU, partly due to the nonspecificity of clinical signs and symptoms. Prompt treatment can reduce mortality and improve patient outcome, and therefore the value of rapidly identifying the problem and assessment of the condition

cannot be understated. Although the introduction of intensive care echocardiography has made the diagnoses easier, diagnoses based on echocardiography alone are not always sufficient and the application requires ready availability of skilled operators [3]. For example, while an enlarged right ventricle denotes pressure or volume overloading, echocardiography sheds little light on the etiology. Proper diagnosis requires the incorporation of various clinical information including medical history, physical examination, electrocardiography, chest X-ray scans and, recently, biomarker levels.

Biomarkers offer certain advantages over other diagnostic tools. First, biomarkers can help clinicians efficiently formulate differential diagnoses. Second, as biomarker levels often correlate with the severity of the disease, they can be used to guide therapy. Third, some of the biomarkers can provide prognostic values. The earliest type of cardiac biomarkers was cardiac enzymes, the uses of which were restricted to the diagnosis of acute myocardial infarction (cardiac necrosis). The discovery of new cardiac biomarkers and the increased sensitivity of the assays have extended the boundary of applications, for example, to the detection of other cardiac pathophysiological processes such as pump failure and right ventricular pressure overload secondary to pulmonary emboli. The present review summarizes the findings of some cardiac biomarkers and examines their usefulness in the ICU.

Detection of cardiac dysfunction in the ICU

Traditionally, the intensivist has relied on medical history, physical examination and basic investigations such as the electrocardiogram and the chest X-ray scan to detect cardiac dysfunction. Occasionally, invasive measurements such as the pulmonary artery catheter will be employed. Although echocardiography can play a major role, the limited availability

BNP = B-type natriuretic peptide; CK-MB = creatine kinase-myocardial band; CRP = C-reactive protein; cTn = cardiac troponins; cTnI = cardiac troponin I; cTnT = cardiac troponin T; HF = heart failure; H-FABP = heart-type fatty acid binding protein; ICU = intensive care unit; IL = interleukin; SRMD = sepsis-related myocardial dysfunction; TNF = tumor necrosis factor.

in many ICUs prompts the need for a simpler method to detect cardiac dysfunction. Serum biomarkers seem able to fulfill this role, and some have been evaluated for uses in myocardial ischemia and necrosis, acute decompensating HF, reversible myocardial depression, valvular disease and pulmonary embolus.

Acute heart failure

Nearly 5 million people in the United States and at least 10 million people in Europe have HF. In the United States, HF accounted for at least 20% of all hospital admissions for patients over 65 years old [4]. From 1989 to 2003, approximately 14,000 patients were diagnosed with HF in New South Wales, Australia each year [5].

B-type natriuretic peptide

B-type natriuretic peptide (BNP) is a 32-amino-acid peptide secreted mainly by the cardiac ventricles in response to pressure or volume overloading (ventricular stretch) [6]. BNP causes diuresis and natriuresis by decreasing tubular salt and water reuptake, increasing the glomerular filtration rate and inhibiting angiotensin action on the proximal tubule [7]. BNP also induces vasodilatation, thereby reducing afterload [8]. The peptide therefore plays an important role in the maintenance of circulatory homeostasis and serves to protect the cardiovascular system from volume overload. BNP has been used to differentiate cardiac causes of dyspnea from pulmonary causes in the emergency setting [9].

A number of clinical and epidemiology studies have demonstrated the relationship between HF and BNP or N-terminal-proBNP [10-12]. BNP is now commonly used to assist the diagnosis of HF, and has been endorsed as a useful diagnostic marker for HF [13,14]. In the Breathing Not Properly study, a plasma BNP level >100 pg/ml was demonstrated to predict congestive HF (sensitivity = 90%, specificity = 73%) [15]. BNP fails to correlate with the New York Heart Association class of dyspnea, however, and does not predict the severity of HF [16]. BNP is elevated in a number of conditions and is not specific to heart failure (Table 1). Considering the consistent high negative predictive values, BNP is most useful as a rule-out tool clinically.

In the ICU, plasma BNP concentrations are increased in patients with different types of cardiac dysfunction, including heart failure, left ventricular diastolic dysfunction, right ventricular pressure overload, and valvular stenosis. A BNP level >144 pg/ml predicts cardiac dysfunction with high sensitivity (92%) and high specificity (86%) [2]. As BNP is increased in a variety of cardiac conditions, it offers little help in differential diagnosis and has low specificity for detecting specific cardiac disease such as heart failure [2]. BNP levels are also found to be significantly confounded by age, gender and fluid loading [1,17,18]. Owing to its high negative predictive value, BNP is best used for ruling out cardiac dysfunction. Since BNP is increased in various cardiac

Table 1

Conditions or factors commonly associated with B-type natriuretic peptide or N-terminal-pro-B-type natriuretic peptide elevations

Age
Arrhythmias
Cardiomyopathy: hypertrophic, ischemic, or dilated
Congestive heart failure
Coronary artery disease
Gender
Hypertension
Left ventricular diastolic dysfunction
Pulmonary embolism
Renal failure
Right heart failure
Right ventricular overloading: fluid, or pressure overloading
Sepsis or septic shock
Sepsis-related myocardial dysfunction

conditions, the use of BNP as a specific diagnostic tool for HF cannot be recommended in the ICU.

Troponins

Although cardiac troponins (cTn) were initially used as serum markers for myocardial infarction, it is now known that cTn were also elevated in patients with HF even in the absence of overt ischemia [19,20]. The percentage of HF patients with elevated cTn could be as high as 45% [21]. The mechanism for this elevation is believed to be due to ongoing myocyte injury and the progressive loss of cardiac myocytes, hence releasing cTn into the circulation [22,23].

As a diagnostic tool for HF, however, cTn lack both sensitivity and specificity. cTn are more useful as a prognostic tool. Increased serum cTn, either cardiac troponin I (cTnI) or cardiac troponin T (cTnT), in patients with HF have been demonstrated to be associated with increased risks of cardiac events, rehospitalization and mortality [19,21,24,25].

Other potential heart failure markers

IL-18 is a member of the IL-1 family and possesses pro-inflammatory functions. IL-18 induces TNF α and IL-6. Circulating IL-18 is markedly increased in patient with congestive HF, and is decreased with inotropic treatment [26,27]. As plasma IL-18 levels decrease with improving clinical status, IL-18 can be used as a surrogate for guided therapy [27]. Noteworthy, however, is the fact that IL-18 is also elevated in ischemic heart disease [28].

Carbohydrate antigen 125 was originally used as a tumor marker but was later also found to be increased in patients

with HF [29,30]. Serum carbohydrate antigen 125 correlates with clinical status (New York Heart Association class), and correlates weakly with right atrial pressure, right ventricular systolic pressure and pulmonary artery wedge pressure [31,32]. Interestingly, carbohydrate antigen 125 does not seem to correlate with most of the echocardiographic left ventricular systolic and diastolic function parameters [31,32]. The fact that carbohydrate antigen 125 is also increased in isolated right heart failure, pericardial effusion and renal dysfunction precludes its use as a diagnostic tool for HF [33,34], although its significant reduction with aggressive treatment may render it a surrogate marker [31].

Cardiac injury and necrosis

Creatine kinase-myocardial band

Irreversible myocardial necrosis is the landmark of acute myocardial infarction. Myocardial injury leads to the release of specific cytosolic substances that can be used as a marker for injury. Creatine kinase-myocardial band (CK-MB) is an enzyme present primarily in cardiac muscles [35]. The enzyme is released rapidly (within 4 to 6 hours) into the circulation after the onset of infarction. It peaks at 24 hours, and returns to normal levels by 36 to 72 hours [36]. CK-MB is not cardiospecific, however, and skeletal muscle injury can increase its circulatory level [37]. Other uses of CK-MB include estimating the infarct time, the infarct size and expansion, and reinfarction [38].

Troponins

Troponin T and troponin I are part of the contractile apparatus of striated muscle, including the cardiac myocytes. cTnT and cTnI are the most specific and sensitive markers of myocardial injury, and there is no clinical difference between cTnT and cTnI for diagnosing cardiac necrosis [39]. The trigger for cTn release is necrosis, and cTn assays can detect as little as 1 g myocardial necrosis [40]. cTn begin to increase within 2 to 4 hours after onset of symptoms, and remain elevated for days. Early release is believed to be attributable to the cytosolic pool, and later release attributable to the structural pool. cTn are particularly useful in determining whether a given event is acute, chronic or reinfarction by observing if the level is increasing or re-elevating.

Not only are cTn elevated in patients with acute and chronic cardiovascular disease, but also in patients with non-cardiovascular disease. Studies in both symptomatic and asymptomatic patients have shown that renal failure is associated with chronic elevations of cTn [41]. Sepsis or pulmonary embolism can also independently increase cTn [42]. Other causes of cTn elevation include trauma, pericarditis, HF, hypertension, and inflammatory diseases (Table 2) [43]. Encountering patients with elevated cTn without apparent causes is also not infrequent. There are a number of reasons for this, including the high sensitivities of the new-generation assays, the use of low cutoff points and the imprecision of the assays. In view of this uncertainty,

Table 2

Conditions commonly associated with cardiac troponin elevations

Arrhythmias
Congestive heart failure
Coronary artery disease
Coronary vasospasm
Critically ill patient
Hypertension
Myocarditis
Pericarditis, acute
Pulmonary embolism
Pulmonary hypertension, severe
Renal failure
Sepsis/septic shock
Sepsis-related myocardial dysfunction
Systemic inflammatory diseases
Takotsubo cardiomyopathy
Trauma

serial testing has been recommended to improve specificity [44]. A single measurement of cTn, albeit elevated, does not reflect the mechanism of myocardial damage and should not be used alone to diagnose myocardial infarction. cTn, however, is still useful in predicting outcomes in patients with or without acute coronary syndromes [45,46].

Heart-type fatty acid binding protein

Heart-type fatty acid binding protein (H-FABP) is a small cytosolic protein found in cardiomyocytes responsible for fatty acid transportation [47]. H-FABP is rapidly released into the circulation following myocardial injury, and is detectable within 2 to 3 hours of the onset of clinical symptoms [48]. The diagnostic sensitivity of H-FABP for acute myocardial infarction in the superacute phase (within the first 3 hours) is 93.1%, which is higher than that for CK-MB and for cTn. The specificity, however, is lower than that of cTn (64.3%) [49].

In a study involving 108 patients with acute ischemic-type chest pain admitted to a mobile intensive care unit, H-FABP showed a better sensitivity to identify myocardial infarction than cTnI, myoglobin and CK-MB. In patients with normal prehospital cTnI levels and no ST-elevation ($n=63$), a positive H-FABP test had 83.3% sensitivity and 93.3% specificity for predicting evolving myocardial infarction [50]. H-FABP also offers better sensitivity than cTnT for detecting ongoing myocardial damage in congestive HF [51]. Elevated serum H-FABP is associated with an increased risk of death and major cardiac events in patients with acute coronary syndromes despite negative serum cTn and BNP [52].

Inflammatory markers of atherosclerotic plaque

Inflammation plays a key role in coronary artery disease [53]. All stages of plaque development and eventual rupture leading to acute coronary syndromes can be considered an inflammatory response [54]. The detection of key molecules involved in the atherosclerotic inflammatory cascade therefore offers an attractive approach for detecting cardiac ischemia and predicting outcomes [55].

C-reactive protein

C-reactive protein (CRP) is produced mainly in the liver and is believed to have a direct role in the pathophysiology of atherosclerosis. CRP enhances macrophage uptake of low-density lipoprotein and contributes to foam cell formation. The protein also causes plaque instability, induces adhesion molecule expression, and associates with endothelial dysfunction [56,57]. CRP was elevated in patients with unstable angina but not in those with variant angina caused by vasospasm, indicating that CRP is associated with inflammation in the coronary artery rather than in the ischemic myocardium [58]. CRP was also increased in other inflammatory conditions such as acute injury, infection, and chronic renal failure [59,60]. High levels of CRP in unstable angina are associated with worsening outcome [61].

Interleukins

IL-6, a proinflammatory cytokine produced by macrophages in atherosclerotic plaque, induces hepatic synthesis of all the acute phase proteins, including CRP [54,62]. Elevated IL-6 was associated with a 3.5-fold increase in 1-year mortality in patients with acute coronary syndrome [63]. Healthy individuals with high IL-6 also had an increased risk for future myocardial infarction [64]. One should bear in mind, however, that IL-6 is unlikely to be helpful in differentiating diseases because it is an inflammatory cytokine that is elevated in many diseases, and in almost any inflammatory disease. As such, IL-6 is not specific enough to be used as a diagnostic tool.

IL-18 is also a proinflammatory cytokine that is highly expressed in atherosclerotic plaque (macrophages). Significantly higher levels of IL-18 mRNA were found in symptomatic (unstable) plaque than in asymptomatic (stable) plaque, suggesting IL-18 destabilizes atherosclerotic plaque leading to ischemic syndromes [65,66]. IL-18 was a strong predictor of death from cardiovascular causes in patients with coronary artery disease [67]. Owing to its high level in HF, IL-18 is not suitable for selectively diagnosing ischemic heart disease.

Sepsis-related myocardial dysfunction

Sepsis-related myocardial dysfunction (SRMD) refers to the transient depression in left ventricular function in patients with sepsis [68]. SRMD is a common complication, occurring in up to 50% of septic patients, and early recognition and aggressive supportive therapy are mandatory as the mortality in these patients is high [69].

B-type natriuretic peptide

Patients with severe sepsis or septic shock had elevated BNP levels [1,2,70]. BNP correlated with the cardiac index in patients with septic shock, and levels were higher in those with reduced left ventricular function [71,72]. Our recent study found that patients with severe sepsis or septic shock had higher BNP than normal levels regardless of cardiac function. Interestingly, differentiation of septic patients with or without SRMD with BNP alone was proved not practical as both populations demonstrated similar levels of BNP [73]. Given the number of confounding factors of BNP in this setting, the specific use of BNP in diagnosing SRMD is not recommended at this stage [2,74].

Cardiac troponins

cTn levels have been shown to be associated with SRMD [75,76]. Neither myocardial ischemia nor necrosis (irreversible damage) could fully explain the elevated cTn levels observed in SRMD [77]. It is postulated that a transient (reversible) increase in membrane permeability of the cardiomyocytes in SRMD, together with intracellular degradation of troponin I, was responsible for the increased cTn levels [78,79]. The use of cTn as a diagnostic tool for SRMD is again limited by its low specificity.

Pulmonary embolism

cTn and BNP were elevated in patients with pulmonary embolism, and could be the result of right ventricular overload or dysfunction secondary to pulmonary hypertension [80,81]. About 70% of patients with pulmonary embolism had elevated cTnI, and was significantly associated with right ventricular dysfunction [80]. BNP and N-terminal-proBNP were also found to be elevated in pulmonary embolism, but only in patients with concomitant right ventricular dysfunction [82]. BNP concentrations were found proportional to the severity of embolism, probably due to the increasing degree of right ventricular stress [83].

In a recent single-centered small study, it was observed that patients with elevated H-FABP on admission had a higher risk of developing major pulmonary embolism-related complications [84]. H-FABP was also found to have a better discriminatory ability for pulmonary embolism-related complications than cTnT and N-terminal-proBNP [84].

Other potential cardiac biomarkers

Ischemia-modified albumin

The ability of human serum albumin to bind cobalt is reduced in myocardial ischemia [85,86]. Using blood samples collected within 2 hours of arrival at the Emergency Department, ischemia-modified albumin (noncobalt-binding albumin) was found to be increased in patients with unstable angina (sensitivity = 91%) [87]. The sensitivities, however, were lower for detecting myocardial infarction. Muscle ischemia, low albumin levels and physical exercise have all been shown to affect ischemia-modified albumin levels [88-90].

Whole blood choline

Choline is released by cleavage of membrane phospholipids by phospholipase D. Whole blood choline and plasma choline concentrations increase rapidly after activation of phospholipase D in acute coronary syndromes [91]. Whole blood choline and plasma choline are significant and independent predictors of major cardiac events in admission cTnT-negative patients [92]. Both cholines are predictive for events related to tissue ischemia, and are independent of other known factors such as age, gender, prior myocardial infarction, coronary risk factors and the electrocardiogram [92].

CD154

The soluble CD40 ligand, now known as CD154, is found both on the cell surface and in soluble form. CD154 is a platelet-derived inflammatory cytokine and can be found on lymphocytes and the endothelial surface. Interaction with the CD40 receptor leads to B-cell activation and induction of other inflammatory markers, such as cell adhesion molecules, cytokines and chemokines [93]. In patients with HF, the abundance of CD154 on platelets is increased and correlates with New York Heart Association classification [94]. Elevated CD154 levels independently predict cardiovascular events and death [95].

Urocortin

Urocortin, like BNP, is a cardioprotective peptide and can be found in the brain and in the heart [96]. Urocortin increases myocardial contractility, induces vasodilatation, and possesses antiapoptotic and anti-inflammatory activities [97,98]. In patients with HF, urocortin is associated with left ventricular dysfunction [99]. Studies involving humans are limited, and more research is needed before urocortin can be used as a biomarker.

Myeloperoxidase

Myeloperoxidase, a proinflammatory enzyme involved in low-density lipoprotein oxidation, is significantly elevated in HF patients [100]. Elevated plasma myeloperoxidase levels in HF subjects were associated with worsening conditions [101]. In the emergency setting, myeloperoxidase predicts the risk of myocardial infarction in patients with chest pain even in the absence of cardiac necrosis [102].

Multimarker approach

The reliance on a single biomarker for diagnostic or prognostic purpose has in many cases proven unsatisfactory. A number of studies have demonstrated that the value of using biomarkers for diagnosis or prognosis could be more apparent if several biomarkers were used together. For example, when CRP was used in conjunction with BNP or cTn in the emergency and cardiology settings, the prognostic value was better than each biomarker used singly [103,104]. Similarly, the combination of cTnT, electrocardiogram and ischemia-modified albumin could identify 95% of patients whose chest pain was attributable to ischemic heart disease [87,105].

Intensive care unit

A number of cardiac biomarkers are now commonly used in the ICU; in particular, cTn, CRP, and CK-MB. cTn are known to be increased in intensive care patients, and are not confined to patients with cardiac injury or acute coronary syndromes [106-109]. Nonthrombotic cardiac conditions, as well as noncardiac conditions, are also associated with increased cTn levels (Table 2). The presence of elevated cTn *per se* is not sufficient to diagnose cardiac injury [110,111]. Based on the data provided by Lim and colleagues [111], the Bayesian probability that a critically ill patient with an increased troponin level will have cardiac injury (myocardial infarction) is between 0.5 and 0.6; that is, the chance of prediction is only slightly better than tossing a coin.

Although CRP has been used as a cardiac marker in the emergency or cardiology settings, it is not normally used as a cardiac biomarker in the ICU. CRP is instead used as an acute phase inflammatory marker to assist the diagnosis of infection [112,113]. In a heterogeneous ICU population, elevated concentrations of serum CRP on ICU admission were correlated with an increased risk of organ failure and death [114]. To date, we are not aware of any study demonstrating the usefulness of CRP as a cardiac biomarker in the intensive care setting.

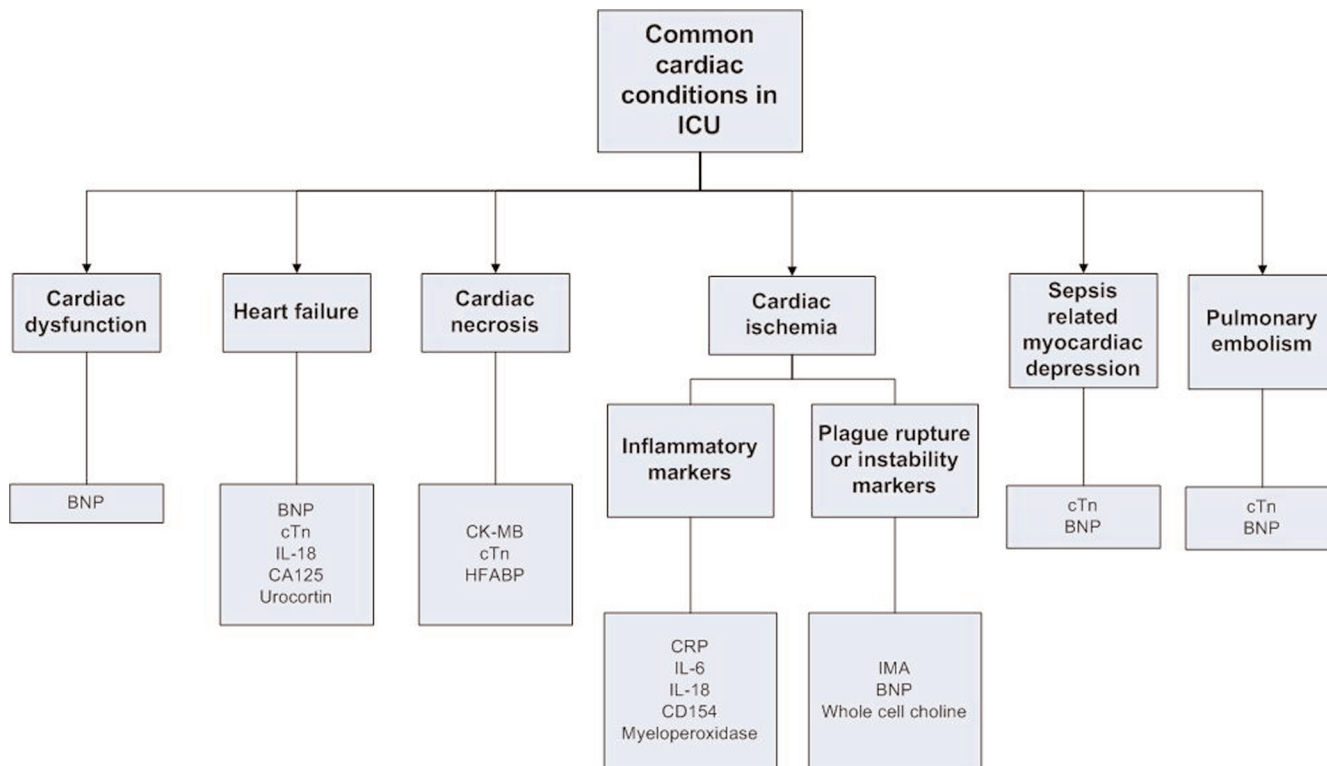
BNP is also a promising biomarker for use in the ICU, but its application is confined mainly to screening purposes. Applications in the area of differential diagnosis, guiding treatment as well as prognosis are still developing.

Given the comorbidities, aggressive treatments and the lack of specificity and sensitivity of a single cardiac marker, it is probable that the intensive care setting will benefit from the multimarker approach. The development of a multimarker approach for ICU use, however, should be distinctive; the question of which biomarkers are the best to use will require further research.

Conclusion

There is no doubt that cardiac biomarkers play an important role in providing additional information for differential diagnosis in the ICU. This additional information, depending on the biomarker(s) used, may include the presence or absence of cardiac disease, cardiac injury, atherosclerotic plaque, or pulmonary embolism (Fig. 1). While most information could be obtained from detailed clinical investigations, such as echocardiography, angiography and other hemodynamic assessments, the biomarker approach provides quick information and adds value to the diagnostic process. The helpfulness of the biomarker information will depend on the way in which it is used (for example, sampling time, the cutoff points chosen), the clinician's belief and approach, as well as the clinical context. The main attractions of using biomarkers are the close link between the

Figure 1



Common cardiac conditions encountered in the intensive care unit and the related biomarkers. Note the lack of specificity of some biomarkers. BNP, B-type natriuretic peptide; CA125, carbohydrate antigen 125; CD154, soluble CD40 ligand; CK-MB, creatine kinase-myocardial band; CRP, C-reactive protein; cTn, cardiac troponins; ICU, intensive care unit; IL, interleukin; IMA, ischemia-modified albumin; HFABP, heart-type fatty acid binding protein.

pathophysiology and the biomarkers, the rapid appearance of the biomarkers, the correlation between the biomarkers and the severity of the disease, the provision of prognosis, and the ease of performing the test.

The use of cardiac biomarkers in the ICU continues to evolve with new findings. Ideally, the biomarkers should be specific for cardiac diseases, but this is both theoretically and practically impossible due to the sharing of common biochemical or immunological pathways of the pathophysiological processes. Despite most of the biomarkers lacking sensitivity and specificity, this should not prevent biomarkers being used in a clinically useful way. Clinicians need to be aware of the biomarkers' limitations, and should interpret them within the clinical context. A multimarker approach may prove a valuable approach in the future for the ICU.

Competing interests

The authors declare that they have no competing interests.

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