ABNORMAL LABORATORY RESULTS

New cardiac markers

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SYNOPSIS

The use of cardiac troponins in the diagnosis of acute myocardial infarction has changed our understanding of coronary artery disease. Cardiac troponins are slowly released from necrosing myocardium so they are detectable in blood for several days. This prolongs the opportunity for identifying an infarction. Cardiac troponins have therefore significantly reduced the diagnostic role of creatine kinase-MB isoenzyme. Although there is only one assay for cardiac troponin T, confusion can arise because there are different non-standardised laboratory assays for cardiac troponin I. However, the clinically important issue is the detection of troponin rather than its absolute concentration. Of other new markers high sensitivity C-reactive protein may have a role in potential risk stratification, but it is not currently recommended for routine clinical use. In the context of the future diagnosis of other cardiac conditions, the neuroendocrine hormone, B-type natriuretic peptide may have a role in the diagnosis and monitoring of cardiac failure.

Index words: cardiac troponin, creatine kinase-MB isoenzyme, high sensitivity C-reactive protein, B-type natriuretic peptide.

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Introduction

The cardiac troponins have provided an important new insight into the pathophysiology of the acute coronary syndrome and stimulated new approaches to the management of ischaemic heart disease. They have been so significant in defining myocardial injury, that there has been a proposal to redefine acute myocardial infarction, with the presence of measurable cardiac troponin as the central diagnostic feature.[1]

Other markers are also being studied. These include B-type natriuretic peptide, a potential cardiac marker for cardiac failure, and the possible application of high sensitivity C-reactive protein (hs-CRP) as a predictor of future ischaemic heart disease.

Creatine kinase-MB isoenzyme (CK-MB)

The current WHO definition of myocardial infarction requires any two of the following to establish the diagnosis:

- a history consistent with myocardial ischaemia
- characteristic ECG changes
- increased cardiac enzymes.

Creatine kinase (CK) and more particularly its isoenzyme CK-MB still have a formal place in defining myocardial infarction. However the current definition is not a particularly useful one because studies have shown that, as currently defined, patients with myocardial infarction and unstable angina have similar outcomes.[2,3]

Interpretation of CK-MB is problematic, with both false positives and false negatives occurring. While CK-MB is relatively cardiac-specific, even healthy people may have low concentrations of this isoenzyme in their blood. People with chronic myopathies may have high concentrations of CK-MB because it is produced by regenerating skeletal muscle. A high concentration of CK-MB may therefore be unrelated to cardiac disease (false positive).

The half-life of CK-MB in the circulation is relatively short (approximately 12 hours). Samples collected many hours after an infarction may have both a low absolute concentration of CK-MB and a low ratio of CK-MB to total CK (due to the longer half-life of the major isoenzyme, CK-MM). This can give a false negative result.

Some specialists believe that it is no longer appropriate to use CK-MB in the diagnosis of myocardial infarction. It may be more helpful for investigating possible reinfarction, where its short half-life may be useful compared to the longer time that cardiac troponins spend in the circulation.

Cardiac troponin I and cardiac troponin T

The troponins are part of the actomyosin contractile apparatus of muscle cells. Structurally unique forms of troponin T and troponin I are found in cardiac tissue, enabling the development of immunoassays, which recognise only the cardiac forms of these two proteins. In most clinical situations both cardiac troponin I (cTnI) and cardiac troponin T (cTnT) seem to offer similarly useful clinical information.

When a cardiac myocyte dies, CK-MB passes rapidly from the cytoplasm into the circulation and is cleared. In contrast, most of the troponin within the myocyte is found in the structural elements of the cell, so when necrosis occurs there is a steady leaching of troponin into the circulation. Consequently, troponin remains in the circulation for several days after a cardiac event.

Despite extended searching, there is currently no evidence that the cardiac troponins may be produced by tissues other than myocardium. However, the presence of cardiac troponin,

while indicating that cardiac injury has occurred, provides no information as to the mechanism of injury. Cardiac troponin concentrations may rise in conditions unrelated to ischaemic damage such as pericarditis, trauma and sepsis. Such rises provide no information about the likelihood of future ischaemic cardiac disease.

When associated with coronary artery ischaemia even low concentrations of cardiac troponin predict an adverse outcome. This is regardless of whether the other WHO criteria for the formal diagnosis of myocardial infarction are met. The pathophysiological mechanism for these acute coronary syndromes is the presence of an unstable coronary plaque, with release of micro-emboli causing focal myocardial necrosis with release of cardiac troponin. The increased mortality is a reflection of a large thrombus separating from the unstable plaque.[3] This improved understanding of the mechanism of the acute coronary syndrome, has led to a proposal to redefine myocardial infarction, using the presence of a cardiac biochemical marker, with some evidence of coronary artery ischaemia, as the central diagnostic criterion.[1]

Cardiac troponins in patients with renal failure

A small proportion of patients with renal failure undergoing dialysis have detectable concentrations of cTnT. This finding was originally thought to be a false positive test, but careful analysis has shown that these patients do have a worse cardiac prognosis. When one considers that approximately 20% of patients on dialysis die each year and that cardiac disease is the commonest cause of mortality[4], this result is not unexpected. Although there is some increase in cTnI in dialysis patients, this appears to be one area where cTnT is more informative.

Problems with assays for cardiac troponin I

Cardiac troponin I is prone to modification in the circulation. It may be phosphorylated and oxidised and can exist as a complex with either cTnT or cardiac troponin C. This has some clinical relevance, because the different antibodies used in commercial assays may recognise these different molecular forms to varying extents. A major problem with cTnI assays is that the different assays are calibrated with different standards. The same blood sample may give quite different apparent concentrations in different assays. If it is accepted that the presence of **any** cardiac troponin in the presence of coronary artery ischaemia indicates a worse prognosis, then the absolute concentration is less important.

B-type natriuretic peptide

The cardiac natriuretic peptide family of neuro-endocrine hormones has a complex physiological role in modulating blood volume and pressure. This involves natriuresis and diuresis as well as antagonism to the angiotensin-renin system. These peptides are also antimitotic and may modulate cardiac hypertrophy.[5] In the presence of left ventricular dysfunction, with worsening cardiac failure, the concentration of plasma B-type natriuretic peptide (BNP) increases in proportion to the New York Heart Association's (NYHA) classification of severity. However, there are a number of other pathophysiological states in which BNP may be elevated, such as hypertension and cardiac hypertrophy, pulmonary hypertension and renal disease. The most appropriate use of this marker remains to be defined.

As with cTnI, several different assays for BNP or its associated peptides (e.g. NT-proBNP) have been used in the published studies. As these assays are not yet standardised, numerical values from one assay cannot be compared quantitatively with those from another.

C-reactive protein

C-reactive protein (CRP) is an acute phase reactant produced by the liver in response to cytokine release during inflammation. It has long been used in clinical practice to follow systemic inflammation, especially bacterial infection. More recently, epidemiological evidence has shown that basal levels of CRP, in the absence of apparent inflammatory disease (so-called hs-CRP) may be informative in predicting future myocardial or cerebrovascular events.[6]

The value of hs-CRP appears to relate to activity in the atherosclerotic plaque. Amongst the cellular elements of the atherosclerotic plaque are inflammatory cells, which, by releasing interleukin-6, cause secretion of CRP into the circulation. In the Physicians' Health Study, when people in the highest quartile of CRP values were compared to people with the lowest quartile of CRP values, they had a relative risk of future myocardial infarction of 1.9. In the Women's Health Study the relative risk was 4.4.

There are a number of problems in using CRP measurements to predict the likelihood of future cardiovascular events. These are both biological and analytical.

Biological variability in basal CRP concentration is considerable. Even mild, subclinical infections can cause significant increases in CRP concentration that are unrelated to cardiovascular disease. For this reason, no measurements should be made within two weeks of any infection. Even with this precaution, CRP concentrations may vary markedly. Several studies have investigated the variability of the CRP concentration in blood collected repeatedly from individuals over periods of weeks to months. The standard deviation for each individual varies from 30% to 63% of the mean value.[7] Thus it might be highly misleading to contemplate using a single measurement to guide possible therapy. It has been proposed that two separate measurements should be made on each individual, while they are quite well, and at intervals of

Key points

In patients with coronary artery disease:

- the presence of any cardiac troponin indicates a worse prognosis
- CK-MB is no longer the preferred marker in the diagnosis of myocardial infarction
- high sensitivity C-reactive protein and B-type natriuretic peptide are not currently recommended for routine clinical use

more than a week apart. The lowest value is then used to determine which quartile the person is in. Even this approach may be insufficient to correct for the variability.

There are outstanding laboratory problems with use of hs-CRP. Not all assays produce identical results. No laboratory has the resources to determine its own reference ranges, so transportability of results between assays is obviously of great importance in defining the concentrations that relate to the different quartiles of basal CRP concentration. At the present time it appears undesirable to attempt to use hs-CRP in individual risk stratification.

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FURTHER READING

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 95)

5. Ectopic production of cardiac troponins reduces their usefulness in assessing acute coronary syndromes.
6. Measuring high sensitivity C-reactive protein provides an accurate prediction of an individual's risk of cardiovascular disease.

National Prescribing Service Ltd (NPS) information hotlines

NPS operates two hotlines providing health professionals and the community with information about medicines.

Therapeutic Advice and Information Service (TAIS): 1300 138 677

For general practitioners, pharmacists and other community-based health professionals

The *Therapeutic Advice and Information Service* (TAIS) has been in operation for three years and to date has received more than 15 000 enquiries. The majority of callers were community pharmacists (48%) and general practitioners (35%). The most commonly asked questions were about drug interactions, adverse reactions and therapeutic options.

Information is provided by expert drug information specialists. The service operates Australia-wide, Monday to Friday 9am to 7pm (EST) for the cost of a local call.

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For consumers

TAIS is complemented by *Medicines Line,* a medicines information hotline for consumers. *Medicines Line* was launched in September 2002 and receives approximately 1000 calls every month.

Statistics show that most callers are females aged 24–64; 25% of callers ask for information on behalf of a child, partner or parent. Questions often reflect what is being reported in the media at the time and are focused on adverse reactions, interactions, and to a lesser extent the mechanisms of action of medicines. Questions are most commonly related to antidepressants, antihypertensives and complementary medicines.

Information is provided by expert drug information specialists. The service operates Australia-wide, Monday to Friday 9am to 6pm (EST) for the cost of a local call.