Troponin compared with late enhancement in the assessment of myocardial injury

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Abstract

Cardiac troponins are regarded as the reference standard for detection of myocardial cell necrosis. Contrast-enhanced cardiac magnetic resonance imaging (CE-MRI) represents a modern technology that allows comprehensive evaluation of the heart after myocardial infarction. It enables assessment of global and regional myocardial function, confirmation and quantification of myocardial infarction, identification of viable myocardium suitable for revascularization procedures, and detection of specific complications including microvascular obstruction. Thus CE-MRI represents a useful complementary diagnostic tool after acute coronary syndromes. However, increased concentrations of troponin may also be encountered in symptomatic patients without acute coronary syndrome – ie, in patients with acute pulmonary embolism, myocarditis, cardiac ischemic amyloidosis, and dilated and hypertrophic cardiomyopathies. As increased concentrations of troponin are associated with adverse outcomes in most of these differential diagnoses, the reason for the myocardial damage must be actively pursued. Along with typical morphological and functional findings on cardiac MRI, different patterns of non ischemic late hyperenhancement have proved to be useful in discriminating ischemic from non ischemic myocardial damage, and to establish a correct differential diagnosis.

Keywords: Cardiac MRI, cardiac troponin, differential diagnoses, infarct size, late hyperenhancement, microvascular obstruction

Introduction

Prognosis after acute myocardial infarction is strongly determined by the extent of myocardial injury [1]. Assessment of left ventricular function after myocardial infarction is helpful for risk stratification and selection of patients requiring an implantable cardioverter defibrillator for prevention of sudden cardiac death [2], and the presence and extent of “late hyperenhancement” on contrast-enhanced cardiac magnetic resonance imaging (CE-MRI) has been shown to give information on the ability of the myocardium to resume contractility after revascularization procedures [3,4].

Echocardiography has emerged as the most convenient method for the quantification of left ventricular function, but this technique does not allow direct quantification of infarct size, and gives only limited information on the presence of viable myocardium and the potential for functional recovery after revascularization procedures. Currently, several imaging techniques, including thallium sestamibi and positron emission tomography, are used for quantification of infarct size [5]. Among the novel techniques,
CE-MRI is noninvasive and does not involve exposure of the patient to radiation or potentially toxic contrast material. It has been shown to provide a good approximation of histological infarct size as assessed by triphenyltetrazolium chloride staining [6]. This technique is therefore preferred by some, because it allows noninvasive assessment of myocardial function and viability in vivo. It has a high spatial resolution, and is superior to single-photon emission computed tomography (SPECT) for the identification of subendocardial myocardial infarction [6,7]. Furthermore, CE-MRI is highly sensitive and permits quantification of small areas of myocardial injury attributable to native coronary artery disease or percutaneous coronary interventions, or both [8,9]. However, the use of cardiac MRI for quantification of infarct size is limited by availability and high cost. A convenient alternative, therefore, is to estimate infarct size from concentrations or activities of cardiac proteins in peripheral blood – as has been practiced for some years [5]. Today, cardiac troponins are established as the preferred biochemical markers for the diagnosis of myocardial infarction [10]. Moreover, there is increasing evidence that measurement of cardiac troponins may also allow estimation of infarct size and detection of the presence of microvascular obstruction.

Cardiac troponin and MRI infarct size

The cardiac troponins C, T, and I (cTnC, cTnT, and cTnI) are structural proteins of the myofilament that are exclusively expressed in cardiomyocytes. Upon irreversible cardiac injury, serum concentrations of cTnT show a biphasic curve, with an early peak within 24 h, resulting from the release of a small cytoplasmic pool, and a ‘plateau phase’ 72–96 h after the onset of symptoms, resulting from continuous proteolytic degradation of the contractile apparatus [11,12].

Animal and human studies using thallium SPECT and MRI have demonstrated an excellent correlation between infarct size and cTn concentrations [13–17]. Using cardiac MRI, the pattern of late hyperenhancement is distinctive for myocardial infarction, with a compact area of subendocardial late hyperenhancement visible after the administration of gadolinium [18]. In patients with myocardial infarction, this area typically starts from the endocardial border of the myocardium, with a variable extent towards the epicardial border (Figure 1). The areas of late hyperenhancement correspond to the territory of the infarct-related coronary artery; the extent of late hyperenhancement is usually given as percent transmurality and is reported either semiquantitatively, or quantitatively as absolute or relative infarct size. The transmurality of hyperenhancement has been shown to correlate with the ability of myocardial contractility to recover after revascularization [3,4]. In contrast, several other nonischemic patterns of late hyperenhancement have been reported in patients with myocarditis, cardiomyopathies, cardiac amyloidosis, and other systemic diseases with cardiac involvement [18].

Regarding quantification of infarct size without the need to perform MRI, an increasing amount of evidence coming from CE-MRI studies shows that any single measurement of cTn concentration between 24 and 96 h after the onset of symptoms allows an excellent estimation of infarct size [13–17]. The relationship between cTnT and cTnI is excellent for large ST-segment elevation myocardial infarction (STEMI) and useful – albeit less impressive – for the heterogeneous group of non-STEMI episodes [19,20]. Although serial measurements are as effective as single-time-point protocols, the latter may be better accepted in clinical practice, because a simple algorithm is more convenient and more cost-effective than serial measurements [19,20].

The diagnosis of periprocedural myocardial infarction after percutaneous coronary intervention (PCI) is relatively straightforward, as myocardial ischemia is the mechanism underlying PCI-related myocardial necrosis. Johansen et al [21] were able to demonstrate consistently that the majority of increases in cTnT after PCI persisted for at least 96 h, indicating continuing release of cTnT from the contractile apparatus and reflecting irreversible myocardial injury. In cardiac CE-MRI, areas of myocardial infarction have been identified as the source of increased concentrations of minor serum markers [8,9]. Ricciardi et al [8] used CE-MRI and demonstrated that even mild increases in CK-MB concentrations after PCI were attributable to discrete microinfarction [8]. All patients with increased CK-MB concentrations had discrete hyperenhancement in the target-vessel perfusion territory.

Figure 1. Typical late enhancement (“bright is dead”) starting from the endocardial border after extensive anterior wall myocardial infarction.
Cardiac troponin for prediction of the presence and magnitude of microvascular obstruction

Microvascular obstruction (MVO) is believed to be related to peripheral embolization of platelet micro-aggregates, intimal edema, vasoconstriction, or leukocyte sticking [22,23]. The findings of experimental and clinical studies clearly demonstrated that, irrespective of cause, MVO is associated with a greater degree of myocardial damage, more severely depressed left ventricular function, and a higher mortality [24–27]. Therefore, identification of patients with MVO would be useful for risk stratification at minimum, and might be helpful also in eventually elucidating both its pathophysiology, and possible therapeutic approaches.

Sophisticated techniques such as contrast echocardiography, delayed radionuclide imaging, and CE-MRI have been shown to be capable of identifying this lack of small-vessel perfusion [28–31]. Data have also confirmed that the presence and maximal extent of MVO are best evaluated by early post-contrast MRI [32]. With CE-MRI, zones of hypoenhancement surrounded by areas of hyperenhancement are believed to represent areas of microvascular obstruction in patients after acute myocardial infarction (Figure 2). These areas correspond well to anatomically defined no-reflow zones determined by histological thioflavin S staining [33]. Several studies have clearly demonstrated that patients with MVO have suffered larger infarcts (as determined by CE-MRI, maximal creatine kinase, and cTnI) than those without MVO [24,34]. It is noteworthy that the extent of MVO also correlated positively ($r = 0.754$, $P < 0.0001$) with infarct size [24]. In agreement with this, Tarantini et al [30] reported a progressive increase in peak cTnI concentrations, with the lowest values in those patients without transmural necrosis or severe MVO, intermediate values in those with transmural necrosis without MVO, and highest values in patients with transmural necrosis and MVO. Our own (as yet unpublished) findings suggest that cTnT values between 24 and 96 h after AMI are significantly greater in the presence of MVO. The best single value for the prediction of MVO is a cTnT concentration greater than 2.52 µg/L at 24 h after the patient’s admission to hospital, and the ability of cTnT to predict MVO persists after adjustment for potential confounders such as duration of ischemia and success of epicardial reperfusion.

As a general limitation, the rates of MVO reported in studies vary widely. This variation may be explained by the use of different MRI techniques for determination of the obstruction. The two most commonly used methods for assessing no-reflow include first-pass perfusion techniques [35–37] and late-enhancement imaging [24,34,36]. The first-pass perfusion technique has the shortcoming that a perfusion mismatch might be interpreted as an area of no-reflow [38].

Cardiac troponin and nonischemic patterns of late enhancement

Myocarditis

Several cardiac MRI studies have demonstrated that hyperenhancement can be found in at least 85% of patients with acute myocarditis evolving within the first 2 weeks after the onset of symptoms [39]. The two relevant CE-MRI approaches described so far depend on the measurement of myocardial global (early) relative enhancement [39] or the visualization of late gadolinium enhancement. Early enhancement probably reflects myocardial hyperemia and increased capillary permeability as features of present inflammation, whereas late enhancement mostly indicates irreversible myocardial injury (Figure 3). More recently, T2-weighted imaging was found to be useful in a combined imaging approach [40]. The incidence of late hyperenhancement in myocarditis is a controversial issue. Reported incidences vary between 44% and 55% using antimyosin scintigraphy [41,42], and the 88% incidence reported by Mahrholdt et al [43]. The reason for such discrepancies may be related to differences in patient populations or study designs.

Cardiomyopathies

Dilated cardiomyopathy

Increased concentration of cTnT have been reported in dilated cardiomyopathy in the absence of coronary stenoses, and were related to an adverse prognosis [44]. There are substantial differences between
concentrations of biomarkers in patients who present with acute decompensated chronic heart failure, depending on the underlying etiology of the heart failure syndrome [45]. Hyperenhancement in ischemic cardiomyopathy characteristically spreads from the subendocardium up to the epicardium, and is confined to the perfusion territories of the coronary arteries [46]. In contrast, several patterns of infarct-atypical, nonischemic late hyperenhancement have been reported in dilated cardiomyopathy, including a pattern in the midventricular rim of hyperenhancement that predominantly involves the septum and is found in 9–28% of patients (Figure 4). This hyperenhancement is presumed to reflect patchy areas of replacement fibrosis [47]. The presence of this particular pattern of hyperenhancement has been shown to be an independent predictor of all-cause mortality and the onset of potentially life-threatening ventricular arrhythmias.

**Hypertrophic cardiomyopathy**

Increased concentrations of cTn may be encountered in hypertrophic cardiomyopathy, may be prognostically important, and correlate with worsening of left ventricular function [48]. The exact reason for this is unclear, but it may include relative myocardial ischemia resulting from an imbalance between inappropriate hypertrophy of the myocardium and insufficient coronary arterial supply, and myocyte abnormalities determined by gene mutations causing myocyte injury [48].

Myocardial scarring is a common finding in patients with hypertrophic cardiomyopathy; it occurs mostly in hypertrophied regions and is usually patchy with several foci, predominantly affecting the midventricular wall, the junctions of the interventricular septum, and the right ventricular walls (Figure 5) [49–51]. The extent of hyperenhancement measured by CE-MRI correlates with conventional risk markers, and has also been related to the occurrence of ventricular arrhythmias and an increased number of clinical risk factors for sudden death [51–53]. However, the prognostic value of the presence and extent of hyperenhancement in patients with hypertrophic cardiomyopathy remains unknown, and the results of current studies are awaited [51].

**Amyloidosis**

Cardiac involvement is common in systemic amyloidosis. Usually, it is either diagnosed by a positive heart biopsy, or suspected from left ventricular hypertrophy (interventricular septal thickness 12 mm or more) in
REFERENCES


Heart Metab. 2009; 43:13–18


