Acute Coronary Syndromes

Cardiac Troponin T at 96 Hours After Acute Myocardial Infarction Correlates With Infarct Size and Cardiac Function

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OBJECTIVES
In clinical practice, myocardial infarct size can be estimated non-invasively by nuclear imaging techniques or contrast-enhanced magnetic resonance imaging (CE-MRI). Due to limited availability and high costs, serologic tests are frequently used as an alternative.

BACKGROUND
We examined the ability of a single value of cardiac troponin T (cTnT) 96 h after onset of ST-/non–ST-segment elevation myocardial infarction (STEMI/NSTEMI) to estimate absolute infarct mass.

METHODS
Functional and CE-MRI were conducted on a 1.5-T whole-body system 4 days after STEMI/NSTEMI using gadolinium (0.2 mmol/kg/bw). Infarct sizes were measured employing a specified software (Philips Medical Systems, Best, the Netherlands) and correlated with TnT measurements 96 h after onset of STEMI/NSTEMI.

RESULTS
We enrolled 23 STEMI and 21 NSTEMI patients. Median time delay from onset of symptoms to balloon angioplasty was 6.25 and 9.9 h for STEMI/NSTEMI patients, respectively. Contrast-enhanced magnetic resonance imaging (median 4 days) revealed an absolute mean infarct size of 16.2 g (7.7 to 30.1 g) with a mean ejection fraction of 58% (53% to 63%) and mean stroke volume of 84 ml (75 to 107 ml). Absolute infarct sizes and median cTnT values were larger in STEMI than in NSTEMI (29.3 g [interquartile range (IQR) 16.0 to 53.0] and 1.88 μg/l [IQR 0.7 to 2.57] vs. 8.8 g [IQR 3.3 to 16.4] and 0.83 μg/l [IQR 0.4 to 1.3], both p < 0.02). Linear regression analysis was excellent for STEMI (r = 0.910) and moderate albeit still significant for NSTEMI (r = 0.575).

CONCLUSIONS
A single 96-h cTnT value provides an accurate estimate of absolute infarct mass in myocardial infarction. The ability to quantify and the potential to distinguish effects of novel drug regimens on infarct size make cTnT attractive for routine practice and as a clinical end point. (J Am Coll Cardiol 2006;48:2192–4) © 2006 by the American College of Cardiology Foundation

In routine clinical practice, infarct size is estimated non-invasively by electrocardiographic and imaging techniques including radionuclide imaging, technetium-99m sestamibi, or thallium scintigraphy (1). Due to the limited availability and high costs, serologic tests are frequently used as an alternative. The frequently used serum concentrations of cytoplasmatic enzymes such as creatine kinase (CK) or CK-MB and lactate (LDH) or hydroxybutyrate dehydrogenase (HBDH) for estimation of infarct size is hampered by the need for serial measurements to identify peak or cumulative serum concentrations. A second shortcoming is the lack of cardiospecificity. Cardiac enzymes and, to a lesser degree, CK-MB mass are also expressed in skeletal muscle cells. Thus, the origin of elevated markers cannot be unequivocally allocated in many cases (2). In contrast, cardiac troponin T (cTnT) is a structural protein of the myofilament, which is exclusively expressed in cardiomyocytes. Upon irreversible injury, cTnT serum concentrations show a biphasic curve with an early peak within 24 h resulting from the release of a small cytoplasmatic pool and a “plateau phase” 72 to 96 h after the onset of symptoms resulting from continuous proteolytic degradation of the contractile apparatus (3,4).

We hypothesized that a single cTnT measurement at 96 h could represent an ideal estimate for infarct size. To test this hypothesis, we quantified infarct size and left ventricular function by contrast-enhanced cardiac magnetic resonance imaging (CE-MRI).

METHODS
During July 2004 to March 2005, we enrolled 44 patients admitted to the chest pain unit of the University of Heidelberg with an acute myocardial infarction. Myocardial infarction was diagnosed in accordance with European Society of Cardiology/American Heart Association Guidelines. Acute myocardial infarction without ST-segment elevation was defined by an elevation of cTnT above 0.03 μg/l on at least 1 occasion within 24 h after the ischemic index event with a rise or fall during subsequent sampling.

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Manuscript received January 3, 2006; revised manuscript received July 19, 2006, accepted July 23, 2006.

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Acute ST-segment elevation myocardial infarction (STEMI) was defined by elevation of the ST-segment >0.1 mV in at least 2 contiguous leads or new onset of left bundle branch. In all patients, acute myocardial infarction was retrospectively confirmed by an elevation of cTnT above 0.03 µg/l. Blood samples were taken on admission and 96 h after onset of ischemic symptoms were centrifuged and stored at -20°C until assayed. The study protocol complies with the Declaration of Helsinki, was approved by the local institutional ethical committee, and patients gave written informed consent.

**Measurement of cTnT.** Blood samples were taken on admission and 96 h after onset of ischemic symptoms. Cardiac troponin T was measured quantitatively using electrochemiluminescence technology (3rd generation cTnT, Elecsys 2010, Roche, Mannheim, Germany). The lower detection limit of this assay is 0.01 µg/l with a recommended diagnostic threshold of 0.03 µg/l.

**Cardiac MRI.** Cardiac MRI was performed in a 1.5-T whole-body MRI scanner (Philips Medical Systems, Best, the Netherlands). Assessment of resting left ventricular function was determined by cine images using a steady-state free precession sequence in continuous short-axis planes covering the whole left ventricle from base to apex as well as 2- and 4-chamber views. Ten minutes after gadolinium contrast injection (Gd = 0.2 mmol/kg body weight of gadopentetate dimeglumine [Schering, Berlin, Germany]), 3 volume stacks of delayed contrast-enhanced images covering the whole left ventricle were planned on previous short-, 2-, and 4-chamber axis.

End-diastolic and -systolic volumes with resulting ejection fraction were generated manually using short-axis volumetry. Infarct size was visually defined as area of delayed hyperenhancement on short-axis views and determined manually by delineation of hyperenhanced versus normally saturated dark myocardium.

Magnetic resonance imaging analysis included quantification of absolute infarct size (grams) and left ventricular function in all patients.

**Statistics.** Plasma concentrations of cTnT are described as median values with the corresponding interquartile range (IQR). The baseline characteristics of patients with STEMI and non–ST-segment elevation myocardial infarction (NSTEMI) were compared using the Student t test or chi-square test. For all analyses, a value of p < 0.05 was regarded as statistically significant.

**RESULTS**

We included 44 patients with a mean age of 58 ± 12 years. A total of 28% of patients were women; mean body mass index was 28 ± 4 kg/m² (arterial hypertension = 57%, current smoking = 50%, elevated cholesterol levels = 57%, diabetes = 16%). Twenty-three patients had STEMI and 21 had NSTEMI. Another 5 patients had received glycoprotein inhibitors before angiography. Pre-interventional Thrombolysis In Myocardial Infarction (TIMI) flow grade 3 was present in 12 of 23 patients (52.2%) with STEMI and 8 of 21 patients (38.1%) with NSTEMI. Primary percutaneous coronary intervention was successfully attempted in 22 of 23 patients with STEMI, and early percutaneous coronary intervention was attempted in 20 of 21 patients with NSTEMI. For STEMI, the median time delay from onset of symptoms to balloon angioplasty was 6.25 h and 9.9 h for NSTEMI.

Magnetic resonance imaging was performed after a median of 4 days. Mean infarct size was 16.2 g (7.7 to 30.1 g). The left ventricular performance revealed a mean ejection fraction of 58% (53% to 63%) with a mean stroke volume of 84 ml (75 to 107 ml).

Absolute infarct sizes were larger in STEMI than in NSTEMI (29.3 g [IQR 16.0 to 53.0] vs. 8.8 g [IQR 3.3 to 16.4], p < 0.0002). Correspondingly, median cTnT values were higher in STEMI than in NSTEMI (1.88 µg/l [IQR 0.7 to 2.57] vs. 0.83 µg/l [IQR 0.4 to 1.3], p = 0.015).

Linear regression analysis showed a strong significant correlation between cTnT and infarct size (Figs. 1A and 1B). Correlation between cTnT and infarct size was excellent for STEMI (Fig. 1A) and moderate, albeit still significant, for NSTEMI (Fig. 1B).

**DISCUSSION**

In the present study, we tested the hypothesis whether a single cTnT sample obtained 96 h after the onset of symptoms correlates with infarct size as determined by CE-MRI. Our study provides 2 novel findings. First, a single cTnT at 96 h correlates strongly with absolute MRI infarct size. This relationship is highly significant in STEMI, and less impressive, albeit significant, in NSTEMI. Second, sampling at 96 h may not be the optimal time point for single measurement due to heterogenous time release curves of cTnT in NSTEMI.

Infarct size is a valuable surrogate outcome measure for clinical trials in patients with acute coronary syndromes and can either be measured non-invasively by employing electrocardiographic criteria or by using more advanced, but less available, radionuclide techniques (1). As an alternative and due to limited availability and high costs of imaging techniques, serologic tests are frequently utilized measuring...
cardiac non-structural cytoplasmatic enzymes such as CK or CK-MB, LDH, or HBDH. Unfortunately, there are 2 major shortcomings with these markers. First, the lack of cardiосpecificity sometimes allows more sources to be responsible for the rise of these markers (2). Second, measurement of infarct size by cardiac enzymes is hampered by the need to collect blood repeatedly so as not to miss the peak of marker release. In contrast, cTnT is an exclusively cardiac and predominantly structural protein of the myofilament.

Cardiac MRI has become the gold standard for quantification of ventricular function and determination of infarct size (1). Contrast-enhanced MRI has been shown to allow quantification of spontaneous or post-procedural MI of <1 g of infarcted myocardium per image (5) and has a better sensitivity for detection of small myocardial infarcts than single photon emission tomography (6). These and other advantages including the ability to detect infarct-related complications such as microvascular obstruction, papillary muscle necrosis, or extension of infarct to the right ventricle outweigh the potential shortcoming of overestimating infarct size by approximately 10% during the acute phase (7).

Generally, infarct sizes for NSTEMI patients were significantly smaller and could, in some cases, be below the MRI detection threshold for myocardial infarcts. Moreover, due to relatively low image resolution of CE-MRI images, small infarct areas could also be missed due to partial volume effect. Furthermore, in our approach, we performed scar imaging 10 min after administration of gadolinium. This could be either too early for clear visualization of small infarcts, or small infarcts potentially have different contrast agent wash-in and wash-out kinetics when compared with larger infarcts with edema and more pronounced microvascular obstruction.

However, it is tempting to speculate that patients with small infarcts have different cTnT release time curves than patients with large myocardial infarction. Therefore, it cannot be excluded that, in patients with NSTEMI, an earlier cTnT sampling time point would have resulted in a better correlation with infarct size or left ventricular function.

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