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*Commentary***Will High-Sensitive Troponin Immunoassays Lead to more Clarity or Confusion in Clinical Practice?**

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Abstract

Although an increase in cardiac specific troponin I (cTnI) and T (cTnT) always indicates myocardial damage, the test is not able to identify the mechanisms responsible for this damage, which may not be due to ischemia, but rather to other clinical conditions. In the present issue of Clinical Science, Filusch et al. assessed cTnI by a high-sensitivity assay in patients with pulmonary arterial hypertension. This study suggests that even in patients with extra-cardiac diseases, high-sensitive troponin assays could lead to better risk stratification of patients in whom conventional cTnI assays show values within the “normal range”. These data support the hypothesis that increased levels of cTnI and cTnT are an index of cardiac tissue damage even in patients with extra-cardiac diseases, thus enabling appropriate diagnosis and, when necessary and available, specific treatment.

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Commentary

At the dawn of the new century, the discovery of the cardio-specific biomarkers, troponin I (cTnI) and T (cTnT), leads to the new definition of acute myocardial infarction (AMI) (1,2). The application of these International Guidelines (1,2) in clinical practice greatly increased the diagnostic accuracy, leading a 25% up to 55% increment of diagnosed AMI in the first years of the new century (3). According to the new definition of AMI (1,2), an increase of troponin levels above the 99th percentile upper reference limit (99th URL) should be considered as clinically relevant. Furthermore, it is recommended that the cTnI and cTnT values corresponding to the 99th URL should be measured with an imprecision ≤ 10 CV% (1,2). Unfortunately, none of the immunoassay methods, commercially available at the time of guidelines publication, was able to fulfill these recommendations (4,5).

More recently, a new generation of the cTnI and cTnT assays has been set-up by manufacturers in order to improve the analytical performance in accordance with international guidelines (1,2) and quality specifications (4,5). The advent of novel troponin immunoassays with increased analytical sensitivity should actually increase the sensitivity, but also decrease specificity in the clinical diagnosis of AMI (4). Although an increase in cTnI or cTnT always indicates myocardial damage, the test is not able to identify the mechanism responsible for that damage, which may not be due to ischemia, but to other clinical conditions (Table 1) (4). Indeed, several recent studies reported troponin values above 99th URL in many patients without clinical evidence of AMI, as “false-positive” results with decreased assay specificity, especially in case of advanced age, heart failure, severe co-morbidities, or assuming potential cardio-toxic drugs, as reported in Table 1 (4). Hence, it may not be clear for most patients and physicians whether the new high-sensitivity cTnI and cTnT methods will lead to more clarity than confusion (4,6).

In an article published in this issue of Clinical Science, Filusch et al. (7) measured serum cTnT by a conventional assay and a novel high-sensitive assay (hsTnT) (lower detection limit 2 pg/mL) in 55 patients (idiopathic n=20, chronic thromboembolic n=30, and interstitial lung disease n=5) with pulmonary arterial hypertension (PAH) (7). The most important results obtained in this study are: 1. cTnT was detectable in 90.9% of patients using the hsTnT assay, but only in 30.9% using the conventional method; 2. cTnT values above the 99th URL were seen in 27.3% of patients using hsTnT assay, as compared to 10.9% using the conventional one; 3. There is a very close correlation between hsTnT and six minute walk distance ($r = -0.92$, $p = 0.0014$); 4. hsTnT predicted death at least as effective as heart-type fatty acid binding protein (hFABP) or terminal peptide precursor of B-type natriuretic hormone (NT-proBNP); 5. hsTnT predicted WHO class more than 2 better than NT-proBNP or hFABP (7). These data suggest that the novel hsTnT may be useful for risk stratification in patients with PAH. The most important limitation of this study is the relatively low number of patients studied; consequently, the results of this study, in particular those regarding the comparison/association with the other biomarkers (i.e., six minute walk distance, hFABP and NT-proBNP) should be confirmed by larger clinical studies.

PAH is a rare progressive disease, which leads to increasing pulmonary vascular resistance, severe right heart failure and premature death (8). In the USA, the median

survival without treatment for the idiopathic form of PAH is only 2.8 years (9). A recent meta-analysis has shown that only the treatment with intravenous prostacyclins has proven survival benefit in PAH patients, particularly in those with severe disease (9). However, treatment is not only expensive, but also associated with severe side effects in a relevant proportion of patients. Therefore non-invasive identification of high-risk subgroups may be helpful not only in risk assessment, but also in the selection of treatment modalities and care intensity. Moreover, reliable indicators of clinical worsening and disease severity may be useful to delineate the disease severity and prognosis as well as to monitor the clinical course and response to therapy (7). The results reported by Filusch et al. (7) indicate that hsTnT may soon become part of the standard work-up and follow-up of PAH patients.

Any improvement of analytical precision and clinical sensitivity of a laboratory test is always a good thing; this concept should be applied also to novel generation of high-sensitive cTnI and cTnT immunoassays (4). The high degree of analytical sensitivity (limit of detection less than 10 pg/mL) and the absolute cardio-specificity of the novel generation of troponin immunoassays allow the detection of very small areas of myocardial damage (probably only 10-50 mg of tissue) (4).

An increase in analytical and diagnostic sensitivity should allow more accurate and earlier diagnoses. In patients with acute coronary artery syndrome, recent studies have found that elevation of troponin values can be detected after 2 h (or even earlier) from onset of ischemic symptoms with the high-sensitive cTni and cTnT immunoassays, but only after 3-6 hours with conventional methods (4,6). This may lead to earlier triage to an invasive strategy, while a repeated normal level at an earlier time point than currently recommended may lead to earlier discharge from the emergency department and cost savings as well (4,6). Even in some patients with extra-cardiac diseases, as suggested by the results reported by Filusch et al. (7) for PAH, high-sensitive troponin assays should enable better risk stratification within the group of patients showing values below 99th URL with the conventional assays.

In conclusion, it is really important to stress the concept that increased values of cTnI and cTnT are anyway an index of cardiac tissue damage, even in patients with extra-cardiac diseases, such as PAH (or the other clinical conditions listed in Table 1), thus suggesting an appropriate diagnosis and, when necessary and available, a specific treatment.

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