Research Highlights

Highlights from the latest articles in biomarkers

Short- and long-term biological variation of cardiac troponin I

Evaluation of: Wu AHB, Lu QA, Todd J, Moecks J, Wilans F: Short- and long-term biological variation in cardiac troponin I measured with a high-sensitivity assay. Implications for clinical practice. *Clin. Chem.* 55, 52–58 (2009).

A study of 12 healthy volunteers donating blood every hour for 4 h and 17 healthy volunteers donating blood every other week for 8 weeks, aimed to evaluate the biological variation of cardiac troponin (cTn) I. Until recently, dogma was that circulating cTnI was in effect, zero; or with hindsight, below the detection limit of current commercial immunoassays. A value exceeding the 99th centile of a reference population forms the basis of the diagnosis of acute myocardial infarction. The assessment of biological variation was previously unavailable owing to the limited lower detection limits of routine assays. Using flow-based microparticle immunoassay with single-molecule counting technology, recent studies have challenged

this view, demonstrating a distribution of cTnI concentrations in apparently healthy people free from symptomatic cardiac disease. The present study determined a low index of individuality of cTnI for both short-term (<4 h) and long-term (8 weeks) changes. This is an unsurprising finding given that short-term physiological cardiac changes are not likely to occur. The recent findings do not cause concern in interpretation in patients with overtly positive cTnI values. Those patients who demonstrate very small amounts of cTnI positivity with fluctuations on serial sampling are often difficult to explain clinically. These patients are not likely to suffer an acute cardiac event, such as angina or acute myocardial infarction, but rather the cTnI represents secondary or nonischemic concomitant cardiac cell damage, such as in myocarditis, chronic kidney disease or cardiac failure. Knowing that the biological variation of cTnI is intrinsically low, small deviations of cTnI in serial sampling could aid in the diagnosis, treatment and prognosis of patients with secondary cardiac pathological conditions.

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Clinical significance of cardiac troponin I below the 99th centile

Evaluation of: Eggers K, Jaffe AS, Lind L, Venge P, Lindahl B: Value of cardiac troponin I cut off concentrations below the 99th percentile for clinical decision making. *Clin. Chem.* 55, 85–92 (2009).

The impact of immunoassay sensitivity is nowhere more important than with respect to cardiac troponin (cTn) assays.

Using a refined AccuTnI™ assay from Beckman Coulter (Fullerton, CA, USA), the 99th percentile of 1005 70-year-old subjects participating in the Prospective Investigation of the Vasculature in Uppsala Seniors (PRIVUS) was 0.044 µg/l. In 520 of these subjects (48% male) without cardiovascular disease, left ventricular hypertrophy, echocardiographic abnormalities and a normal age-related NTpro-b-type natriuretic peptide

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concentration, the 99th centile was lower at 0.028 $\mu\text{g/l}$. There was no significant difference between males and females. Using the Fragmin and Fast Revascularization during Instability in Coronary Artery Disease (FRISC II) study population, the use of the lower 99th centile identified more patients (7.9%) with a positive cTnI compared with only 4.4% when using the 0.044 $\mu\text{g/l}$ 99th centile. Gender-specific 99th centiles, but not the 90th percentile, had the ability to lower the cTnI positivity rate at 6 months. Overall, 75th and 90th percentiles provided the greatest prognostic power for predicting 5-year mortality. There are two main points that emerge from these data. First, the selection of 'normals' to define a cardiac troponin reference population impacts the 99th centile generated. Stricter exclusion criteria, including echocardiographic evidence of cardiac dysfunction and the use of

natriuretic peptides to exclude cardiac failure, resulted in a lower 99th centile, even in a relatively aged population. A reference population should be representative of the 'diseased' population who would benefit from testing. Using a very young, healthy population may even lower the 99th percentile further than that obtained within this study. Second, the use of a clinical-trial population does not represent 'real life' situations. The strict selection and exclusion criteria for trial entry results in elimination of patients with potentially confounding clinical conditions as well as raising the probability of pre-existing cardiac disease, often to 100%, thus the clinical efficiency of an assay is superior than in routine use. As sensitive cTn assays become a matter of routine, the diagnostic and predictive value in those patients without a final diagnosis of acute coronary syndrome requires further investigation.

Ultra-sensitive cardiac troponin assays detect more cardiac damage in subjects undergoing arduous physical exercise

Evaluation of: Mingles A, Jacobs L, Michielsen E, Swaanenburg J, Wodzig W, van Dieijen-Visser M: Reference population and marathon runner sera assessed by highly sensitive cardiac troponin T and commercial cardiac troponin T and I assays. *Clin. Chem.* 55, 101–108 (2009).

Cardiac troponin (cTn)T, unlike cTnI, is only manufactured by one supplier owing to patent ownership. Recently, a highly sensitive immunoassay for cTnT has been developed by Roche Diagnostics (Indianapolis, IN, USA), which is still performed by electrochemiluminescent

immunoassay on the Elecsys family of analyzers. Although exercise is advocated for healthy living, it has been demonstrated widely that endurance exercise causes a rapid release of cTnT into the circulation. This returns to normal quickly, in approximately 24–48 h; unlike an acute coronary syndrome where patients can remain positive for up to 2 weeks postevent. The biological and physiological role of circulating cTn following arduous exercise is still not fully understood. The release is heterogeneous, with some athletes demonstrating positivity whilst others do not demonstrate any rise in cTn. Approximately 45–50% of individuals demonstrate postexercise cTnT. Subjects

who run demonstrate greater postexercise positivity compared with those who cycle. Using the sensitive cTnT method, the postexercise positivity rate is much higher at 86% and associated with training experience and age. It is a shame that kinetic release during the event was not studied and serial sampling further than 24 h postevent were not taken. Overall, what is the clinical impact of this? To date, only pathological conditions have demonstrated a prognostic role for cTnT. In exercise, this remains to be proven. Maybe sensitive cTn assays along with routine physiological parameters could be used to monitor exercise tolerance and training regimen effectiveness.