High-sensitivity troponin: does it predict the shape of the iceberg underneath the surface?

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This editorial refers to ‘High-sensitivity troponin I concentrations are a marker of an advanced hypertrophic response and adverse outcomes in patients with aortic stenosis’, by C.W.L. Chin et al. on page on page 2312 and ‘Direct comparison of high-sensitivity cardiac troponin I vs. T for the early diagnosis of acute myocardial infarction’, by M.R. Gimenez et al. on page on page 2303.

Cardiac troponins (cTn) are proteins bound to the actin components of the myofibrils of cardiac muscle, and different isoforms (cTnI and cTnT) exist with unique N-terminal sequences that distinguish them from the skeletal muscle isoforms. The clinical relevance of these markers was first documented in patients with chest pain suggestive of acute coronary syndrome, but it later became evident that a variety of pathologies, such as post-percutaneous coronary intervention (PCI) myonecrosis, myocarditis, pulmonary embolus, and sepsis can be associated with elevated cTn values.1–3

The modern day paradigm for the diagnosis of acute myocardial infarction (AMI) is based on the documentation of an elevated cTn value above the 99th percentile of a reference population (upper limit of normal; ULN) during the first 24 h of a clinical episode of coronary ischaemia with a rising and/or falling pattern.3 As most of the previous conventional cTn assays had detection limits close to the 99% ULN, previous cTn measurements could be analysed dichotomously into a positive or a negative test. Patients with a positive cTn value were at higher risk for future ischaemic events and benefited most from more aggressive strategies.4,5

These conventional assays are, however, hampered by an excessive analytical imprecision (often >20%) at the 99th percentile value, and this has forced manufacturers to develop more accurate assays, the so-called high-sensitivity (hs) assays.6 The hs-Tn assays are characterized not only by superior precision (<10% imprecision) but also by much lower detection levels. As a consequence, whereas with ‘conventional’ assays only a minority of the reference population has measurable cTn values, this percentage can be as high as >95% using hs assays.7

The burning issue is whether levels below the ULN may have some diagnostic or prognostic value in a patient population. As clinicians, we correlate an elevated cTn level with risk, but is the patient really safe if we do not see an elevated cTn level? Alternatively, using the metaphor of an iceberg, can ‘subnormal’ cTn levels indicate the shape of the iceberg underneath the surface (see Figure 1)?

Two novel studies using hs-Tn, one in the setting of chronic myocardial injury and the other in the setting of AMI, may provide some answers to this question.

High-sensitivity troponin in chronic myocardial injury

The study of Chin et al. correlated hs-cTnl with the long-term outcome of a cohort of 131 patients with asymptomatic moderate to severe aortic stenosis.8 The average cTnl concentration was 7.6 ng/L (5.7–13.2), and only 8% of patients had a plasma concentration above the ULN (i.e. 26 ng/L). The authors demonstrated that baseline hs-cTnl levels were associated with an increased risk (hazard ratio of ~ 2.0 per twofold increment in hs-cTnl concentration) of aortic valve replacement and cardiovascular death over a median follow-up of ~ 10 years. This hazard was present after correction for the severity of aortic stenosis. More than half of the patients in the highest tertile (>10.7 ng/L) had undergone an aortic valve replacement (AVR) or died from cardiovascular disease. Thus, subnormal values of cTnl are not as safe as could be thought and clearly predict the shape of the iceberg in this population of asymptomatic aortic valve disease. The authors also examined the possible mechanistic reasons for this prognostic value of cTnl by relating cTnl levels to different baseline clinical and cardiac imaging characteristics in a population with mild to severe aortic stenosis. Multivariate analysis revealed that only age, left ventricular (LV) mass index, and percentage fibrosis [as assessed on magnetic

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resonance imaging (MRI)] were independent determinants of cTnI levels, with the highest cTnI levels observed in patients with LV hypertrophy and, in particular, in those with concomitant myocardial fibrosis. These findings suggest that cTnI might be a valuable marker for the early detection of the transition from hypertrophy to heart failure as characterized by progressive cardiomyocyte death and replacement fibrosis. The authors have to be congratulated for this elegant study and for putting forward this new paradigm in the evaluation of patients with aortic stenosis. In this regard, recent studies in ambulatory elderly individuals have also shown that low (<99th percentile) chronic cTnI release is predictive of an increased risk of heart failure and mortality, indicating the importance of silent cardiac damage.9,10 There is still ongoing debate regarding whether the release of small quantities of cTn is related to ongoing irreversible myocardial necrosis or, alternatively, transient or chronic myocardial ischaemia. An interesting hypothesis, which could explain the difference between cTn release in ischaemia and necrosis, is the formation of membranous blebs that bud off from the plasma membranes of cardiac myocytes in response to hypoxia.11 Supply–demand mismatch, as is observed in LV hypertrophy, may be a reason for chronic low-grade hypoxia and the subsequent chronic release of low quantities of cTn.

Before hs-cTn measurements become a standard risk marker in the evaluation of patients with asymptomatic severe stenosis, the following issues remain to be solved.

(i) How normal are normal reference values? ‘Healthy’ reference populations are primarily based upon persons without overt cardiac disease or without known risk factors. In most persons, however, no laboratory data or cardiac imaging data are available. Therefore, subclinical diseases such as LV hypertrophy or moderate coronary artery disease might be present and are associated with minor increases in cTn.12 Hence, the true normal population will fall in the lower ‘normal’ range, as was also documented by the present study of Chin et al: the true healthy people (n = 13) had an average hs-cTn concentration of 3.2 (1.3–11.0) which is below 50% of the ULN. More data on hs-cTn levels in truly healthy persons should be gathered to better distinguish (and avoid overlap) between true healthy populations and ‘subclinical’ patients. In the meantime, serial measurement of hs-cTn (e.g. every 6–12 months) with a focus on the change in hs-cTn levels might overcome the issue of overlap, as was also shown in a subgroup of the study population included by Chin et al.

(ii) The application of hs-cTn as a prognostic marker in the management of severe aortic stenosis is only clinically relevant if a troponin-based decision for (early) cardiac surgery will improve clinical outcome compared with a clinically driven decision for cardiac surgery. This will require large-scale prospective studies.

**High-sensitivity troponin in acute myocardial injury**

In the second study, Gimenez et al. investigated the value of both hs-cTnT and hs-cTnI for the early diagnosis of non-ST-segment elevation myocardial infarction in a large population of 2226 patients with symptoms suggestive of AMI.13 The diagnostic accuracy at presentation was high and similar for hs-cTnT and hs-cTnI, with an area under the receiver operating characteristics curve (AUC) of ~ 0.94. Previous research groups, among them also the research group in the present study, have shown that hs-cTn measurements on admission achieve higher accuracy than conventional cTn measurements.14,15 However, the observed sensitivity of 72% and negative predictive value of 94% (using the diagnostic cut-off value of the

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**Figure 1** The different shapes of the iceberg underneath the surface for chronic myocardial injury and for acute myocardial injury. The y-axis represent the level of high-sensitivity (hs) troponin with the upper limit of normal (ULN) at the intersection with the x-axis.
99th percentile normal reference) with this hs-cTn assay remain suboptimal and can therefore not been applied as the only parameter for excluding AMI. This lower sensitivity is related to the fact that some patients will show admission troponin values below the ULN and the proportion of patients with subnormal admission values will be higher (and the accuracy will be lower) among early presenters (<3 h), as was also nicely shown by the study of Gimenez et al. Therefore, also in AMI, the presence of subnormal values may predict the presence of an infarction, although, due to the rapid increase of hs-cTn values in the setting of acute coronary syndrome, the shape of the iceberg is much steeper than that in the chronic myocardial injury model, and many patients with AMI will already show elevated troponin levels on admission. Nevertheless, normal hs-cTn, particularly in the upper normal range, should alert the physician and, as recommended by the guidelines, a second troponin measurement 3 h after the first measurement should be taken in order to ‘rule in’ or to ‘rule out’ a myocardial infarction.3 In the study of Gimenez et al., this was clearly documented by the further increase of the AUC from 98–99% if the hs-cTn values after 3 h were also considered.

In conclusion, 100 years ago, the Titanic sank after a collision with the lower part of an iceberg. At that time, no sophisticated equipment was available to detect a protruding ice mass below the water surface. Now, with hs-cTn measurements on board, we no longer have the excuse to be surprised by the hazard. We should be alert (and react) if we encounter a troponin value in the upper range of normal not only in an acute chest pain patient but also in a chronically ill cardiac patient such as an asymptomatic patient with severe aortic stenosis.

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References