Measurement of cardiac troponins to detect myocardial infarction using high-sensitivity assays: South African guidelines

With the use of specific cardiac markers with higher sensitivity, new perspectives have emerged on the nature of myocardial necrosis and injury, which are associated with acute coronary syndrome (ACS). The third universal definition of myocardial infarction now classifies myocardial infarction (MI), based on the relevant pathology, clinical presentation, prognosis and treatment strategy, as spontaneous MI (type 1), MI secondary to an ischaemic imbalance (type 2), cardiac death due to sudden fatal MI (type 3), and MI associated with revascularisation procedures (types 4 and 5). What has also become evident is the extent of necrosis and injury that is associated with pathologies of other organs and conditions.1-3

The clinical circumstances associated with elevated values of cardiac troponin (c-Tn) due to myocardial injury have been listed, and comprise conditions related to primary myocardial ischaemia, conditions related to supply/demand imbalance of myocardial ischaemia, conditions not related to myocardial ischaemia and conditions related to multi-factorial or indeterminate myocardial injury. A shift in focus is apparent, not only from valuing these highly sensitive cardiac biomarkers for their exceptional diagnostic sensitivity and negative predictive value for the diagnosis of MI, but also for their application in ACS risk stratification.4-6

Guidelines on the use of high-sensitivity cardiac troponin (hs-cT) markers have recently been set in the consensus statement of the Ethics and Guidelines Standing Committee of the South African Heart Association. This editorial aims to appraise these guidelines in the light of more recent research findings and newer guidelines.

The committee recommends that high-sensitivity troponin assays be widely adopted as the preferred biomarker for the diagnosis of myocardial infarction, based on evidence of earlier diagnosis of MI, more reliable ruling out of MI, and shortening of the chest pain triage (to four hours compared to former assays). All cardiac troponin measurements are to be reported in ng/l. The first sample is to be collected on first assessment, followed by a second sample after three hours, should the first value be lower than the 99th percentile (URL) of a normal reference population for the specific assay, or between the URL and the WHO-defined URL for MI. Serial measurements are to be reported as percentage change. A specific algorithm for both hs-cTropT and hs-cTropI is proposed for the diagnosis of MI.

The Expert Consensus document on the third universal definition of myocardial infarction states that sample repeat may be three to six hours later, followed by further sampling depending on uncertainty concerning timing of the initial symptoms and whether the injury was evolving or resolving.8,9

Rule-in for MI constitutes a rise and/or fall in values, with one value above the decision limit (99th percentile value), using an assay with an imprecision (coefficient of variation) ≤ 10% if accompanied by a strong pre-test likelihood, the diagnosis being based mainly on the latter.1 Repeat measurements display the dynamic pattern of troponin values and aid in differentiating between acute and chronic causes of troponin elevation in the circulation.

The guidelines defined for South Africa (SA) differ from those in the Consensus document. They state: ‘The percentage change (rise or fall) in hs-cT levels in two samples three hours apart is used to establish a diagnosis of MI when the troponin level is below the WHO cut-off. For troponin I a 50% change in an initial value is diagnostic of MI. In the case of troponin T, a 50% change in an initial value of < 53, or a 20% change in an initial value between 53 and 100 ng/l, is diagnostic of MI.’ They are similar to those set by the study group on biomarkers in cardiology of the ESC Working Group on Acute Cardiac Care, in that the 50% change rule is applied for the second sample, but they do not apply the WHO cut-off point and state as prerequisite for rule-in that the values at three hours (and optionally at six hours) be greater than the URL.

In the South African guidelines, the WHO cut-off values are also taken into consideration for decision making, in that values between the URL and the WHO cut-off values are subject to repeat measurement at three hours, the percentage change being dependent on the first assessment value being smaller than the WHO cut-off values. Of note is that use of change as a measure for rule-in may increase the specificity for MI, but at the cost of a decrease in sensitivity,1,4 and that, as stated by Thaygesen et al., ‘It should be clear that dynamic changes are not specific for MI but rather are indicative of active myocardial injury with necrosis’.

The validity of the use of the URL as well as repeated measurements at three hours for rule-in or rule-out of MI have been substantiated in several studies. The selection strategy for the reference population, however, markedly influences the 99th percentile reference values for troponin assays if it does not consider relevant demographic, biological and clinical variables and this affects the diagnostic performance of highly sensitive immunoassays, as suggested in the SA guidelines.

Furthermore, inter-assay differences concerning reference values for specific populations appear to impact on risk stratification. A higher cut-off point for the diagnosis on NSTEMI may be appropriate in patients with mildly elevated hs-TnI and without evidence for STEMI, and use of absolute change over serial measurements is suggested to perform better and decrease time to rule-in and rule-out of NSTEMI compared with relative change.
The 20% limit of defining a significant increase from the time of first assessment if baseline values are above the URL has been established within the National Academy of Clinical Biochemistry laboratory medicine practice guidelines and represents a significant (> 3) standard deviation variation on the basis of a 5–7% analytical imprecision (analytical CV), but is assay dependent, and remains a challenge that requires further clinical and prospective studies, as concluded by Lippi et al. and others. The 50% limit of defining a significant increase if baseline values are below the URL does not appear to be based on high-level evidence but purportedly optimises the overall accuracy of MI diagnosis.

Other complexities of measurement, as studied to by Thygesen, are the substantial differences between ‘high-sensitivity’ assays and the concern that the manufacturers’ claims for assay precision cannot be achieved in clinical laboratories. Relevant analytical issues alluded to in the SA guidelines are falsely high values because of heterophile antibodies and human auto-antibodies interfering with the assay, and falsely low levels with haemolysis. In addition, Lippi et al. reported interferences being observed, caused by rheumatoid factor, complement, presence of fibrin in serum or plasma after centrifugation of the sample, unsuitable samples (e.g. haemolysed, lipaemic, icteric), and analytical errors (e.g. instrument malfunctioning). Of interest is a report by Gould et al. on carry-over to subsequent samples with certain analysers, potentially leading to false-positive results.

Conclusion

The South African guidelines on the use of high-sensitivity cardiac troponins as biomarkers are timely and of great value, provided that clinicians take up the challenge of applying them clinically.

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References

1. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, writing group on behalf of the joint ESC/ACCF/AHA/WHF task force for the universal definition of myocardial infarction. Third universal definition of myocardial infarction. J Am Coll Cardiol 2012; 60(16): 1581–1598.
2. Jaffe AS. Troponin – past, present, and future. Curr Probl Cardiol 2012; 37(6): 209–228.
3. Daubert MA, Jeremias A. The utility of troponin measurement to detect myocardial infarction: review of the current findings. Vasc Health Risk Manag 2010; 6: 691–699.
4. Lippi G, Montagnana M, Aloe R, Cervellini G. Highly sensitive troponin immunoassays: navigating between the scylla and charybdis. Adv Clin Chem 2012; 58: 1–29.
5. Ziebig R, Lun A, Hocher B, et al. Renal elimination of troponin T and troponin I. Clin Chem 2003; 49: 1191–1193.
6. Apple FS, Jesse RL, Newby LK, Wu AH, Christenson RH. NACB and IFCC Committee for Standardization of Markers of Cardiac Damage Laboratory Medicine Practice Guidelines: analytical issues for biochemical markers of acute coronary syndromes, Circulation 2007; 115: e352–e355.
7. Consensus statement of the Ethics and Guidelines Standing Committee of the SA Heart Association, SHeart 2010; 9: 210–215.
8. MacRae AR, Kavaskal PA, Lustig V, et al. Assessing the requirement for the six-hour interval between specimens in the American Heart Association classification of myocardial infarction in epidemiology and clinical research studies. Clin Chem 2006; 52: 812–818.
9. Thygesen K, Mair J, Giannitsis E, et al.; the study group on biomarkers in cardiology of the ESC Working Group on Acute Cardiac Care. How to use high-sensitivity cardiac troponins in acute cardiac care. Eur Heart J 2012; 33(18): 2252–2257.
10. Keller T, Zeller T, Poetz D, Tikas S, et al. Sensitive troponin I assay in early diagnosis of acute myocardial infarction. N Engl J Med 2009; 361: 868–877.
11. Reichlin T, Irfan A, Twerenbold R, et al. Utility of absolute and relative changes in cardiac troponin concentrations in the early diagnosis of acute myocardial infarction. Circulation 2011; 124: 136–145.
12. Thygesen K, Alpert JS, White HD. Joint ESC/ACCF/AHA/WHF task force for the redefinition of myocardial infarction. Universal definition of myocardial infarction. Eur Heart J 2007; 28: 2525–2538.
13. Mueller M, Celik S, Biener M, et al. Diagnostic and prognostic performance of a novel high-sensitivity cardiac troponin T assay compared to a contemporary sensitive cardiac troponin I assay in patients with acute coronary syndrome. Clin Res Cardiol 2012; 101(10): 837–845.
14. Keller T, Zeller T, Peetz D, et al. Sensitive troponin I assay in early diagnosis of acute myocardial infarction. N Engl J Med 2009; 361: 868–877.
15. Reichlin T, Hochholzer W, Bassetti S, et al. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. N Engl J Med 2009; 361: 858–867.
16. Keller T, Zeller T, Ojeda F, et al. Serial changes in highly sensitive troponin I assay and early diagnosis of myocardial infarction. J Am Med Assoc 2011; 306(24): 2684–2693.
17. Giannitsis E, Becker M, Kurz K, Hess G, Zdunek D, Katus HA. High-sensitivity cardiac troponin T for early prediction of evolving non-ST-segment elevation myocardial infarction in patients with suspected acute coronary syndrome and negative troponin results on admission. Clin Chem 2010; 56: 642–650.
18. Weber M, Bazzino O, Estrada JN, Miguel R, Salzberg S, Fuselli JJ, et al. Improved diagnostic and prognostic performance of a new high-sensitive troponin T assay in patients with acute coronary syndrome. Am Heart J 2011; 162: 81–88.
19. Keller T, Ojeda F, Zeller T, et al. Defining a reference population to determine the 99th percentile of a contemporary sensitive cardiac troponin I assay. Int J Cardiol 2012 May 4. [Epub ahead of print].
20. Collinson PO, Heung YM, Gaze D, Boa F, Senior R, Christenson R, Apple FS. Influence of population selection on the 99th percentile reference value for cardiac troponin assays. Clin Chem 2012; 58(1): 219–225.
21. Cardinaels EP, Mingels AM, Jacobs LH, Meex SJ, Bekers O, van Dijen-Visser MP. A comprehensive review of upper reference limits reported for (high-) sensitivity cardiac troponin assays: the challenges that lie ahead. Clin Chem Lab Med 2012; 50(5): 791–806.
22. Mills NL, Lee KK, McAllister DA, et al. Implications of lowering threshold of plasma troponin concentration in diagnosis of myocardial infarction: cohort study. Br Med J 2012; 344: e1533.
23. Apple FS, Ler R, Murakami MM. Determination of 19 cardiac troponin I and T assay 99th percentile values from a common presumably healthy population. Clin Chem 2012; 58(3): 625–630.
24. Weber M, Bazzino O, Estrada JN, Miguel R, Salzberg S, Fuselli JJ, et al. Improved diagnostic and prognostic performance of a new high-sensitive troponin T assay in patients with acute coronary syndrome. Am Heart J 2011; 162: 81–88.
25. Keller T, Ojeda F, Zeller T, et al. Defining a reference population to determine the 99th percentile of a contemporary sensitive cardiac troponin I assay. Int J Cardiol 2012 May 4. [Epub ahead of print].
26. Collinson PO, Heung YM, Gaze D, Boa F, Senior R, Christenson R, Apple FS. Influence of population selection on the 99th percentile reference value for cardiac troponin assays. Clin Chem 2012; 58(1): 219–225.
27. Cardinaels EP, Mingels AM, Jacobs LH, Meex SJ, Bekers O, van Dijen-Visser MP. A comprehensive review of upper reference limits reported for (high-) sensitivity cardiac troponin assays: the challenges that lie ahead. Clin Chem Lab Med 2012; 50(5): 791–806.
28. Mills NL, Lee KK, McAllister DA, et al. Implications of lowering threshold of plasma troponin concentration in diagnosis of myocardial infarction: cohort study. Br Med J 2012; 344: e1533.
29. Apple FS, Ler R, Murakami MM. Determination of 19 cardiac troponin I and T assay 99th percentile values from a common presumably healthy population. Clin Chem 2012; 58(3): 625–630.
centres, since many lives are saved using pacemakers as therapy in post-surgical, paroxysmal or permanent complete atrioventricular blocks.

Conclusion

In undeveloped countries characterised by natural selection of patients with complete atrioventricular block, mortality is high. Lack of infrastructure, early detection and financial limitations are the main problems faced in the follow up of these patients. Re-organisation of the public health system, new programmes of prevention of cardiovascular diseases, and government subsidisation are needed in our milieu.

References

1. Elpek EE, Aghaji MA, Edaigbini SA, Onwuta CN. Cardiac pacemaker treatment of heart block in Enugu a 5-year review. Niger J Med 2008; 17(1): 7–12.
2. Ector H, Vardas P, on behalf of the European Heart Rhythm Association, European Society of Cardiology. Current use of pacemakers, implantable cardioverter defibrillators, and resynchronization devices: data from the registry of the European Heart Rhythm Association. Eur Heart J 2007; Supplement I: 144–149

3. Yayeh K, Ganou K, Tchamndja T, et al. Management of high-grade atrioventricular block in Lomé, Togo. Med Trop 2011; 71(6): 637–638.
4. Thomas MO, Oke DA, Ogumeyee EO, et al. Bradypacing: indications and management challenges in Nigeria. Pacing Clin Electrophysiol 2007; 30(6): 761–763.
5. Millar RN. Cardiac Arrhythmia Society of South Africa 1998 survey of cardiac pacing in South Africa. Report of the working group on registries of the cardiac arrhythmia society of South Africa (CASSA). Afr Med J 2001; 91(10): 873–876.
6. Zion MM, Marchand PE, Obel IW. Long-term prognosis after cardiac pacing in atrioventricular block. Br Heart J 1973; 35: 359–364.
7. Linde CL, Bocray A, Jonsson H, et al. Re-used pacemakers – as safe as new? A retrospective case–control study. Eur Heart J 1998; 19(1): 154–157.
8. Mitka M. Death not necessarily the end for heart devices. J Am Med Assoc 2007; 297(2): 144–145.
9. Mohindra R, Panu HS, Mohan B, Kumar N, et al. Syncope in rheumatic fever. Indian Heart J 2004; 56: 668–669.