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Diagnosing myocardial injury in the high-sensitivity troponin era

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Acute myocardial infarction (AMI) is the leading cause of disability and mortality worldwide.[1] The diagnostic and therapeutic approach to this very frequent and life-threatening disease has considerably evolved during the past decades, perhaps more impressively than any other human disorder.[2] This notable evolution has been paralleled by a constant and timetabled release of diagnostic guidelines, which have evolved from the celebrated *first*, through the *second* and *third*,[3] up to the recently released *fourth* Universal Definition of myocardial infarction.[4] Throughout such a relatively short history (*i.e.*, the first Universal Definition was only published in 2000),[5] the major breakthroughs have concerned the identification of cardiac troponins (either I or T) as the reference (and virtually only) biomarkers of myocardial injury, and the subsequent development of the so-called *high-sensitivity* cardiac troponin immunoassays, which have enabled to increase analytical sensitivity, precision and reproducibility of these measurements far beyond the limits of the former techniques. Albeit we may be indeed persuaded to conclude that cardiac troponins are as yet *the best there is*, it may be rather hazardous to put forward the concept that these biomarkers will be regarded *the best there ever will be*. This is simply due to the fact that not all the leading characteristics of an *ideal* cardiac biomarker, as shown in Table 1, are thoughtfully met by cardiac troponins.

If on one hand the gradual refinement of both analytical techniques and diagnostic criteria has allowed achieving a faster and more efficient diagnosis of AMI, the downside of these innovations has been represented by an increasing uncertainty around both clinical use and result interpretation of high-sensitivity immunoassays.[6] The most disrupting factor is indeed represented by the possibility to measure *physiological* cardiac troponin values in the vast majority (*i.e.*, between 95-99%) of healthy subjects, which has hence represented an essential paradigm shift in the way results of cardiac troponin testing have been interpreted for long. To put it simply, the traditional *black & white* scenario (*i.e.*, positive or negative), has turned into a grayscale, according to which cardiac troponin values exceeding the upper reference limit (URL) calculated in an ostensibly healthy population are no longer synonyms of myocardial infarction (nor of myocardial injury), and that measurable concentrations of cardiac troponins above the limit of detection (or the functional sensitivity) of a high-sensitivity immunoassay are not as safe as they have for long been considered. In this puzzling landscape, we believe that there may be – at least – six major paradigms that should always be considered when using cardiac troponins for diagnosing myocardial infarction in the emergency room (Table 2).

First and foremost, cardiac troponins are generic biomarkers of myocardial injury.[4] This concept is not ancillary, wherein many physicians and laboratory professional are still relying on the axiom that *increased cardiac troponins = AMI*. Albeit a thoughtful description of non-ischemic and non-cardiac causes of cardiac troponin elevation must be omitted due to space constraints, it may be worthwhile to mention here that whatever disease either directly (*i.e.*, myocarditis, myocardial contusion or stunning, high-frequency atrial fibrillation and so forth) or indirectly (*i.e.*, cancer, pulmonary embolism, *etc.*) triggers myocardial injury, this will be then mirrored by a variable elevation of measurable cardiac troponin in blood.[7] In fact, the Fourth Universal Definition of Myocardial Infarction underlines, for the first time, the clear-cut separation between *myocardial injury* and *myocardial infarction*, providing clinical and biochemical criteria for distinction.[4]

The second important issue concerns the biochemical and biological heterogeneity of cardiac troponins. Cardiac troponin I and T are encoded by two different genes, have a completely different biochemical structure and their metabolism (from intracellular release to catabolism) is not overlapping.[8] As such, the values of these two biomarkers, although displaying some notably comparable features, are not interchangeable. Quite predictably, therefore, different immunoassays will generate different results, and this problem cannot be completely overcome even assaying the same molecule. More specifically, the currently licensed high-sensitivity techniques entail one immunoassay for measuring cardiac troponin T and as many as 4 different immunoassays for measuring cardiac troponin I. The standardization of these latter methods remains dramatically poor, since no reference material has been identified so far, nor standardized epitopes of cardiac troponin I against which monoclonal antibodies should be produced have been definitely validated.[9] This aspects is of paramount importance for healthcare facilities operating within a (vast) network, in which patients may be diagnosed with one cardiac troponin I immunoassay in one center, but will then be managed with another method in another center, *e.g.*, where a cardiac cath lab is available.

The time elapsed between symptoms onset and blood collection is another major determinant of diagnostic performance. Regardless of the pathogenesis (AMI currently recognizes at least 5 different underlying pathogenetic mechanisms), irreversible myocardial necrosis typically occurs 20-40 min after myocardial

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ischemia, and cardiac troponins become measurable only afterwards.[10] This particular pathway is hence mirrored by the kinetics of cardiac troponins in blood, which is conventionally referred to as the *diagnostic window*. Although substantially elevated values of cardiac troponins may persist in blood for such a long time (*i.e.*, between 7 to 10 days, depending on type, size and revascularization of the infarct area) that late presentation is not an issue (unlike myoglobin, for example, whose concentration return to normal values after 1-3 days after the acute ischemic event), a diagnosis may be missed in early presenters when blood sampling time is too narrow. This notion especially concerns the recent publication of studies entailing the use of so-called short-track protocols, encompassing serial sampling at presentation and 30 minutes or 1 hour afterward. Beside the inherent risk of missing *early presenters*, who may hence test negative also at second blood sampling,[11] this approach has many other drawbacks. These typically include the fact that *very fast protocols*, especially those entailing second sampling after 30 min from the first blood collection, will carry the risk that cardiac troponin increases due to an ischemic event may still be comprised within the biological variability (*i.e.*, the reference change value) of the biomarker itself, which is approximately 50% for cardiac troponin I and approximately 20% for cardiac troponin T, respectively.[12] Along this line, Boeddinghaus *et al*. recently showed that 0-1 hour algorithms have an optimal diagnostic performance in younger subjects (*i.e.*, 91% of patients aged 40 years or younger can be safely ruled-out), whilst the proportion of elderly patients (*i.e.*, aged 70 years or older) who could be safely ruled-out with 0-1 hour blood sampling will dramatically decrease, far below 40%.[13] Even more importantly, the change of cardiac troponin values which can be appreciated after such a short time may also be comprised within the analytical imprecision of the immunoassay, and this will inevitably mislead the clinical interpretation.[14] Last but not least, there is an obvious risk that the laboratory will receive the second blood sample before the first has been processed and, likewise, that emergency physicians may also be confused by receiving two consecutive laboratory reports in such a short timeframe. Needless to say, the current turnaround time for cardiac troponin testing has been fixed at 1 hour, so that very fast protocols would be hardly manageable according to the large volumes and the increasing workflows characterizing modern clinical laboratories. Taken together, these factors would lead us to conclude that using diagnostic algorithms based on second blood sampling after ≥2 hours would be a more precautionary strategy for both ruling-out and ruling-in AMI.

The diagnostic threshold for considering as to whether a cardiac troponin value is diagnostic or not of cardiac injury has been for long based on the 99th percentile URL.[3] Several lines of evidence now attest that this strategy carries many drawbacks, whilst the use of lower cut-offs, perhaps coincident with limit of detection or functional sensitivity (*i.e.*, the value with ≤10% analytical imprecision) of the immunoassay may enable earlier and more efficient rule-out.[15] Interestingly, values comprised between the URL and the function sensitivity still retain clinical significance, wherein the higher the value within this range, the larger the risk of all-cause mortality. This important evidence has led some authors to postulate that cardiac troponins may be used as the *cholesterol of the third millennium*, despite the fact that management of patients with measurable (but non-diagnostic) values of cardiac troponins remains undefined, especially in the short-term period (*i.e.*, within 1-year).[16,17]

The last and perhaps more debated issue concerns the approach used for estimating the variation of cardiac troponin between two consecutive blood samplings. Two current strategies have been proposed, the former based on absolute variation of cardiac troponin concentration, and the latter on its percentage variation. These two approaches have advantages and limitations, so that a strategy combining both (*i.e.*, the absolute variation when admission values are below the URL and the percent variation when admission values are above such threshold) may yield a better diagnostic performance.[14] Whilst theoretically straightforward, this strategy will need validation in real life scenarios. Interestingly, recent evidence has also been provided that a combined measurement of both cardiac troponins I and T will increase costs, but does not seemingly enhance the diagnostic efficiency of algorithms based on either biomarker alone.[18]

In conclusion, high-sensitivity cardiac troponin immunoassays have almost revolutionized the diagnostic approach to patients with suspected AMI, by increasing the diagnostic performance (especially in patients with non-ST elevation myocardial infarction) and providing useful clinical evidence beyond myocardial ischemia. Nevertheless, some unresolved issues still remain (Table 2), thus paving the way to an advisable update of currently available recommendations for using results of high-sensitivity immunoassays in the emergency room.[19]

Table 1. Leading characteristics of an acute myocardial infarction biomarker.

Characteristic	Percentage met by cardiac troponins
Present at high concentration in the myocardium and absent from non-myocardial tissue	99%
Reflect ischemic myocardial injury	50%
Characterized by a suitable diagnostic window (i.e., early release and prolonged kinetics)	90%
Concentration reflecting the extent of myocardial injury	50-75%
Predict short- and long-term outcomes	50-75%
Influence personalized management	50%
Measurable with rapid and relatively inexpensive techniques	95%
Measurable with standardized diagnostic techniques	10%

Table 2. Current paradigms and unresolved issues of high-sensitivity cardiac troponins.

Cardiac troponins are generic biomarkers of myocardial injury
Cardiac troponins I and T are two different proteins
Standardization of immunoassays remains poor
The time between symptom onset and blood collection is a major determinant of diagnostic performance
Diagnostic performance varies according to the diagnostic thresholds
Diagnostic performance varies when cardiac troponin changes are calculated as absolute or percent variation

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