The never-ending story of cardiac biomarkers: A further step toward a very early detection of ischemic patients?

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Once upon a time. In 1954, Karmen et al. found that serum glutamate oxaloacetate transaminase (SGOT) activity was increased in patients with acute myocardial infarction, suggesting the possible application of these biomarkers in patients with acute coronary syndromes.[1] Then, in 1963 creatine kinase (CK) was found to rise rapidly following an acute coronary syndrome (ACS).[2] In 1966, the superior cardiac specificity of CK-MB was demonstrated[3]; this led to the adoption of CK-MB as the biomarker of choice for the detection of myocardial damage until the early 1990s, when cardiac troponins (cTn) were demonstrated to have both higher sensitivity and specificity in the diagnosis of patients with ACS.

It is a matter of debate whether cTnI and cTnT are released into blood only from irreversible cardiomyocyte damage with complete loss of membrane integrity such as, for example, AMI, or also during reversible damage such as transient myocardial ischemia.

Changing the target: from cell death to transient cell hurt. Some preclinical and clinical studies suggest that not only necrosis but also transient myocardial ischemia might play a role in the release of some biomarkers such as BNP, N-terminal pro B-type natriuretic peptide (NT-proBNP), or cTn.[4–12]

In this view, in this issue of the Journal, Pipikos et al. correlated the behavior of common biomarkers considered to be associated with a critical and prolonged reduction in coronary blood flow, such as NT-proBNP and high sensitivity cardiac troponin T (hs-cTnT) with the presence of myocardial ischemia as assessed by exercise radionuclide myocardial perfusion imaging (MPI).[13] They found that only hs-cTnT levels were significantly different between patients with or without ischemia, although in this study they did not assess the severity of ischemia; however, NT-pro BNP was not able to identify ischemia. The authors made the hypothesis of two possible mechanisms at the basis of hs-cTnT released during ischemia: from the fraction located in the cytosol, even in the absence of cell death,[14] or due to micro-ruptures of non-calcified plaques, suggesting that hs-cTnT might also be used as a marker of vulnerable coronary plaque.[15] At odds with most of the other available studies assessing the value of biomarkers in the detection of ischemia, as determined by MPI, and that evaluated just cardiac troponins or BNP, Pipikos et al. also evaluated additional biomarkers, such as ischemia modified albumin, and neuropeptide Y; however, like NT-proBNP, these biomarkers were not associated with ischemia.[13]

The matter of whether the presence of cTn in the blood is correlated with the presence or severity of ischemia was assessed by several trials that used radionuclide MPI as the reference method for the demonstration of reversible perfusion defects.

In a preliminary study by Thayapran et al. who compared CK-MB and cTnI to exercise stress thallium testing in a small group of 31 patients with known or suspected of coronary artery disease, there were no increases in either cTnT or cTnI in blood samples collected both before and 12 to 24 h after exercise testing in any of the patients, including those with severe ischemia.[16]

However, because of limitations of the analytical performance of troponin assays at very low

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concentrations, it was not easy to address adequately whether there is a quantifiable release of cardiac troponins in the clinical setting of myocardial ischemia.

Recently, a cardiac troponin assay has been developed that has a limit of detection that is at least one order of magnitude lower than current commercial assays (this is highly sensitive (hs)-cTn). The effect of reversible myocardial ischemia on hs-cTnT levels was evaluated by Kurz et al. in a group of 100 patients: reversible ischemia did not induce significant changes of hs-cTnT, baseline concentrations of hs-cTnT were not different in patients with or without perfusion defects, and hs-cTnT levels did not change after 18 min and 4 h.[17] On the other hand, in 120 patients enrolled in the Protein Markers of Ischemia using Proteomic Testing (PROMPT)—TIMI 35 prospective cohort study, hs-cTnI was measured before, immediately after, and 2 and 4 h after stress testing, and correlated with the presence and severity of ischemia as assessed at MPI. The Authors documented a significant rise in circulating hs-cTnI levels in response to stress testing, with a level proportional to the amount of ischemia.[18] Moreover, in another large group of 714 patients, significantly higher levels of hs-cTnI were documented at rest in patients with exercise-induced ischemia compared with those without: using a cut-off value of 1.54 ng/L, sensitivity, specificity, positive, and negative predictive values of 95%, 18%, 26%, and 92%, respectively, were documented. Finally, hs-cTnI was also an independent predictor of exercise-induced myocardial ischemia in multivariable analysis.[19]

The finding that cTn does not increase as a response to reversible myocardial ischemia was also suggested by the experimental results of Fishbein et al. demonstrating, by immunohistochemical staining using antibodies to human cTnT and cTnI, that the loss of cTnT and cTnI by the cells occurs very early following a prolonged ischemic injury and precede the histologic evidence of necrosis, but it does not occur in myocardium that is not necrotic.[20]

However, the exact mechanism for the discharge of cTn is still debated. Considering that the transport across the cell membrane is a prerequisite for the release of troponin from viable cardiomyocytes, the smaller size of cTnI (approximately 26 kDa) compared with cTnT (37–39 kDa) could make cTnI a superior biomarker to detect reversible ischemia. As a matter of fact, while hs-cTnI concentrations have been found to be selectively increased in patients with reversible myocardial ischemia,[18] hs-cTnT does not.[21,22]

In an experimental animal model, cTnI values after brief reversible ischemia increased between 3 and 24 hours following restoration of flow. Although brief ischemia did not produce any pathologic evidence of necrosis or infarction, regional apoptosis of single dispersed myocytes transiently increased at 1 hour and normalized 24 hours after reperfusion. This fact is in contrast with the pattern of myocyte necrosis that occurs in myocardial infarction and provides a possible mechanism by which cTnI is released into the circulation: cTnI elevations do not reflect the early release of an exchangeable pool of cTnI from viable myocytes but arise from delayed programmed myocyte death from apoptosis.[23]

Another variable to be taken into account when assessing molecules as biomarkers of ischemia is the degree of exercise or the duration of the ischemic event during a stress test. Cardiovascular biomarkers (cTnT, hs-cTnT or hs-cTnI, BNP, NT-proBNP, and D-dimer) that are currently used in clinical diagnosis of ACS and heart failure are influenced by the presence of strenuous exercise. For this reason, it is necessary to take the occurrence of physical exercise into account when a cardiac emergency is suspected. In a review of 33 studies, including 1045 athletes, the response in cTnT concentration after strenuous exercise was evaluated: in 51% of subjects cTnT increased above the cut-off value. The exercise-induced increase in troponins could be due to the release of cytoplasmic cTnT and cTnI, because exercise may increase membrane permeability of cardiomyocytes.[24,25] This reversible membrane leakage might be also due to increased mechanical stress on the cardiomyocytes, overload with free radicals, increased body temperature, or prolonged acidosis.[24,26] However, the reason for the release of non-structurally bound cTn through reversible membrane leakage in apparently healthy athletes remains controversial.

B-type natriuretic peptide (BNP) is one of the biomarkers linked to heart failure; its usefulness as a marker also of ischemia is still controversial. In 63 patients (62% with known coronary disease) undergoing exercise stress single-photon emission computed tomography (SPECT), plasma BNP values, at baseline or after exercise, were not associated with myocardial ischemia.[27] These results are in agreement with those reported by Pipikos et al. that also documented that reversible ischemia was not associated with changes in NT-pro BNP values.[13]

Many transient cTnI elevations probably occur without demonstrable ECG changes or chest pain, since these are insensitive indices of brief ischemia, and might justify the presence of elevated levels of hs-cTnI in resting conditions in patients that will manifest stress-induced ischemia. However, mechanisms other than repetitive ischemia have been also postulated. In 378 patients with stable angina and unknown CAD and enrolled in the Evaluation of Integrated Cardiac Imaging (EVINCI) study, hs-cTnT and NT-proBNP were measured. All patients underwent stress imaging to detect and quantify myocardial ischemia and coronary computed

tomographic angiography to define the presence and characteristics of coronary artery disease. In this group of patients, the presence and extent of coronary atherosclerosis was related with circulating levels of hs-cTnT, also in the absence of ischemia, suggesting an ischemia-independent mechanism of hs-cTnT release; furthermore, only patients with CAD and ischemia showed significantly higher levels of NT-proBNP.[28]

The article by Pipikos et al. is another piece of the conundrum about the role of biomarkers, and hs-cTn in particular, in the diagnosis of ischemic heart disease other than ACS. The data presented in this study also continue the debate concerning the different mechanisms responsible for biomarkers released in response to transient ischemia vs. prolonged ischemia leading to necrosis. Understanding the basis for the release of cardiac marker will have an impact on how these tests can be used in the clinical setting and for patients' management. It is now important to assess the short-term risk of cardiac events for non-AMI patients who present to the ED with a history of acute chest pain. In this case, the use of a cardiac marker that is increased, also as result of a reversible ischemic event, might be of help in identifying high-risk subjects. It may be possible that cardiac troponin can be used for both reversible ischemia and irreversible necrosis if one accepts the concept of continuum spectrum for ischemic heart disease, with low blood concentrations indicating the former and higher concentrations the latter. Thus, two cut-off concentrations might be necessary to differentiate between these two events.

While it seems, according to most reports, that NT-proBNP is not ideal as a marker of ischemia, several issues about troponins are still matter of debate: What is the role of elevated hs-cTn at rest (and at which cut-off point) in identifying patients with coronary artery disease and prone to more severe ischemia and thus at higher risk? Is the increase in hs-cTn related to the amount of ischemia and how long elevated blood levels are detectable after an ischemic episode? Can a single sample be used at the emergency department to rule out patients with suspected IHD? Which hs-cTn (hs-cTnT or hs-cTnI) performs better?

Other studies are necessary to answer these critical points.

Disclosure

None declared.

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