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Troponin elevation: is it ischemia?

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Abstract: Cardiac troponin is the preferred biomarker for myocardial infarction, thanks to its sensitivity and absolute specificity for the heart. The availability of high-sensitivity assays (hs-cTnT and hs-cTnI), capable of measuring with excellent analytical precision very low levels of circulating troponin, raised the issue of whether transient ischemia is a sufficient stimulus for troponin release. For this purpose, in a series of patients submitted to a stress test (exercise ECG/echo test; dipyridamole echo test; dobutamine echo test), we measured plasma levels of hs-cTnT at baseline and 6 hours after the end of the test. Plasma concentrations of hs-cTnT significantly increased in the vast majority of patients after the test. Significant elevations were documented in response to each stressor, regardless of the test result, after both positive and negative tests. Moreover, troponin significantly increased in response to the stress, both in patients with and in patients without obstructive coronary artery disease. Despite a good sensitivity (80% and 89%), troponin showed a very low specificity (32% and 47%) for stress-induced ischemia and coronary artery disease, respectively. Myocardial release of troponin is a multifactorial process, mediated not only by cardiomyocyte necrosis, but also through several different mechanisms such as myocardial ischemia, increase in cardiac work, and hemodynamic overload. Transient elevation of high sensitivity cardiac troponin is not a useful tool for detecting spontaneous or stress-induced ischemia. ■ *Heart Metab*. 2020;81:7-11

Keywords: cardiac biomarker; cardiac troponin; high-sensitivity cardiac troponin t; myocardial infarction; myocardial ischemia

Background

Troponin is universally accepted as the reference biochemical marker for myocardial infarction (MI), because of its high sensitivity and almost absolute myocardial specificity. Simple, low-cost laboratory methods are now available for measuring,with high analytical precision, two cardiac troponin subunits: T (cTnT) and I (cTnI).[1,2] In the last 15 years, high-sensitivity methods (hs-cTnT and hs-cTnI) have also been developed, capable of identifying very low levels of circulating troponin, in the order of a few nanograms/liter, with a negligible imprecision rate.[3] The availability of accurate methods for troponin measurement has drastically changed the laboratory diagnosis of MI, historically based on the blood dosage of cardiac necrosis enzymes, such as the MB fraction of creatinkinase (CK-MB) and traditional markers such as myoglobin, all of these having a poor myocardial specificity.

The availability of a biomarker such as hs-cTnT and hs-cTnI has profoundly changed the diagnostic criteria for MI, that until a decade ago were equally based on symptoms, electrocardiogram, and laboratory markers. The Fourth Universal Definition of Myocardial Infarction 2018 now reports such a definition of MI: "Detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL," in the setting of evidence of acute myocardial ischaemia."[4]

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Two distinct pools of cardiac troponins are found within cardiac myocytes: 92% to 95% in a structural form, bound to myofibrillar filaments, and approximately 5% to 8% in a free cytosolic pool.[5] As a consequence of myocardial injury, cardiac troponins as released from the cells into the plasma following two distinct release kinetics: the first resulting from the cytosolic pool liberation and the second one, more elevated and sustained over time, due to degradation of the contractile apparatus.[6] The early pool release has been attributed to changes in cell membrane permeability and may be observed in the absence of cell necrosis. Several, non-necrotic mechanisms of troponin release have been described, including transient myocardial ischemia or simply myocardial cell stretching.[5,7]

The wide diffusion of a simple, accurate, and highly sensitive assay has raised the issue as to whether such "high-performance" troponin may be used for detecting minimal myocardial necrosis or reversible ischemia.[6,8] The availability of a laboratory method to combine with symptoms, electrocardiogram, myocardial contractility, and perfusion, would be of great help to improve diagnostic accuracy both in spontaneous and in stress-induced ischemia. Currently, however, it is uncertain whether troponin could help in diagnosing transient ischemia.[9]

In a recent, original experiment by our group, we investigated whether stress-induced ischemia in patients undergoing both exercise (ECG/echo exercise) and pharmacological (echo dipyridamole, echo dobutamine) stress tests, could induce plasma release of hs-cTnT.[10]

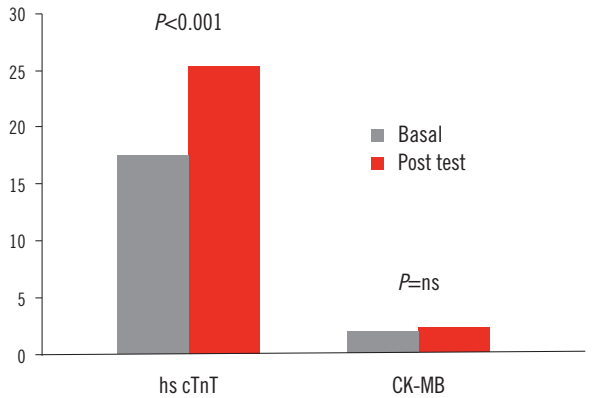

Figure 1 *Plasma levels of hs-cTnT and CK-MB at baseline and post stress in the whole population.*
CK-MB: MB fraction of creatinkinase (ng/mL); hs-cTnT: high sensitivity cardiac troponin T (ng/L)

Troponin elevation: is it ischemia? - Our experience

One hundred twenty-five patients (90 males; mean age 66.7±11.1 years), with known or suspected stable ischemic heart disease, were submitted for diagnostic purposes to a stress test (ECG or echo exercise test, echo dipyridamole test, echo dobutamine test).[10] Plasma levels of hs-cTnT were measured in peripheral blood at baseline (1 to 3 hours before the test) and 6 hours after the end of the tests. Plasma levels of CK-MB were also determined in each patient at the same time intervals. In our laboratory, the upper normal limit of hs-cTnT is 14 ng/L. Only patients presenting with a hs-cTnT value within the normal limits or only slightly increased (<50 ng/L), were effectively included in the study. Patients with acute coronary syndromes, heart failure or severe left ventricular dysfunction, dilated and hypertrophic cardiomyopathies, valvular heart disease, and chronic kidney disease at

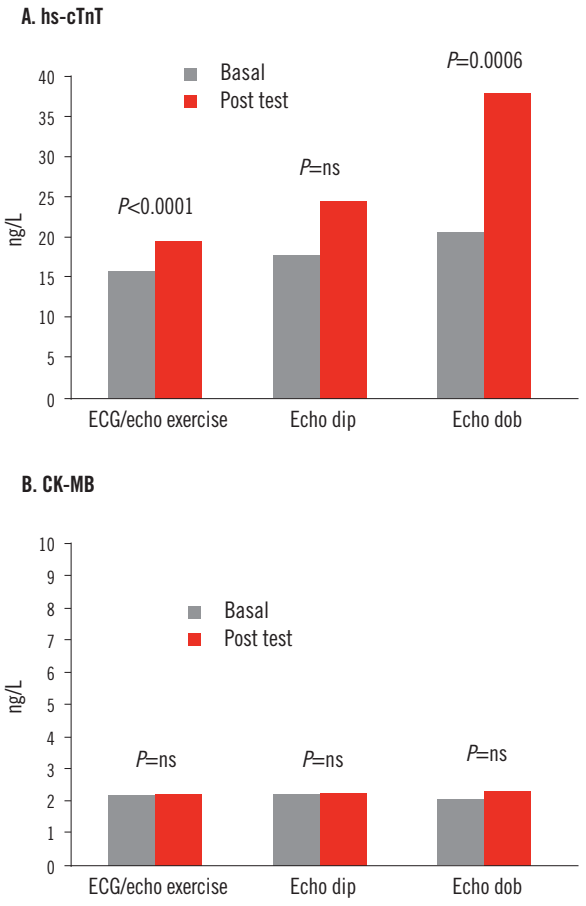

Figure 2 *Plasma levels of hs-cTnT (panel A) and CK-MB (panel B) at baseline and post stress, for each stress test.*
CK-MB: MB fraction of creatinkinase (ng/mL); dip, dipyridamole; dob, dobutamine; hs-cTnT: high sensitivity cardiac troponin T (ng/L)

stages 3 to 5, were also excluded from the study. Fifty out of 125 patients underwent coronary angiography; the indications for coronary angiography were based upon the clinical profile and the result of stress tests.

Results

Among the 125 patients, 53 underwent an exercise ECG or echo test, 42 a dipyridamole test, and 30 a dobutamine test. Plasma concentrations of hs-cTnT increased, 6 hours after the test, in 90 out of 125 patients (72%). Conversely, a significant increase of CK-MB was documented in only 31 out of 125 patients (25%), *P*<0.0001. As depicted in *Figure 1*, hs-cTnT increased from 17.5±16.9 ng/L at baseline to 25.5±27.9 after the tests (*P*<0.0001). Conversely, no significant changes were observed in CK-MB plasma levels (2.15±0.9 ng/mL at baseline; 2.20±1.0 after the tests; *P*=ns). Increments of hs-cTnT were documented after exercise tests, after dipyridamole tests, and after dobutamine tests (*Figure 2*, panel A). Again, none of the three stressors caused significant increments in CK-MB levels (*Figure 2*, panel B). No patient had persistent ST-T changes or developed new Q waves on the electrocardiogram nor new persistent echocardiographic asynergies after the tests.

Out of 125 tests, 84 resulted negative, and 41 positive for myocardial ischemia. Hs-cTnT increased similarly after both negative (from 18.6±19.2 ng/L to 27.1±32.1 ng/L, +46%; *P*=0.0018) and positive tests (from 15.2±10.8 ng/L to 22.3±16.2 ng/L, +47%; p=0.0005) *(Figure 3).* No change in CK-MB levels was seen both in negative and positive tests. The elevation of troponin resulted 80% sensitive and 32% specific for stress-induced ischemia.

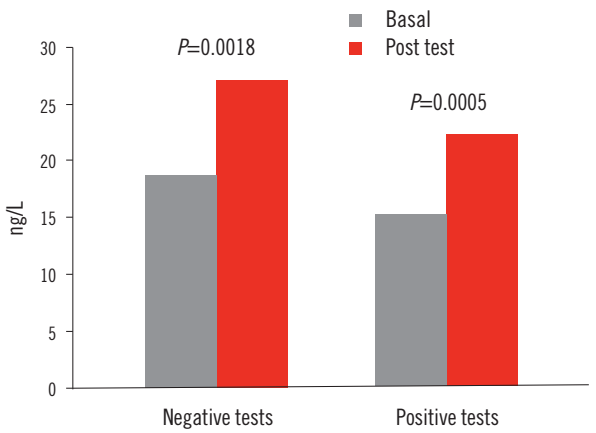

Figure 3 *Plasma levels of hs-cTnT at baseline and post stress according to the test result.*
hs-cTnT: high sensitivity cardiac troponin T

Fifty patients underwent coronary angiography. Obstructive coronary artery disease (CAD) was documented in 35/50 patients. The elevation of troponin levels was more frequent in patients with (31/35 patients, 89%), as compared with patients without obstructive CAD (8/15 patients, 53%); *P*=0.01. Stress-induced elevation of troponin showed 89% sensitivity but only 47% specificity for obstructive CAD. Furthermore, the magnitude of troponin increase was more pronounced in patients without CAD (from 12±4.5 to 25.3±32.5 ng/L, +111%), as compared with patients with obstructive CAD (from 15.7±9.8 to 28.9±34.2 ng/L, +84%). No difference was found in the rate of CK-MB increments, depending on CAD.

The many reasons for troponin elevation

Any blood elevation of troponin is perceived as expression of myocardial injury.[2,4] Since the availability of high-sensitivity assays, capable of measuring very low levels of circulating troponin,[3] and considering the pathophysiology of troponin release,[5] we have specifically addressed two issues: (i) is reversible ischemia a sufficient stimulus for troponin release from cardiomyocytes?; (ii) could hs-cTnT be helpful in diagnosing spontaneous or stress-induced ischemia?

The answer to the first question is undoubtedly yes. Significant amounts of cardiac troponins, mainly deriving from the free cytosolic pool,[5] may be released in the blood not only as a consequence of myocardial cell necrosis, but also for reversible ischemia, becoming measurable with high-sensitivity assays. It is remarkable that in our experience stress-induced release of troponin was not associated with any other evidence of myocardial necrosis (no changes in CK-MB; no persistent ST-T changes nor development of new Q waves; no persistent new echocardiographic asynergies).

Conversely, the answer to the second question is undoubtedly no. Despite a good sensitivity (80%), troponin elevation showed in our experience a very low specificity (32%) for stress-induced ischemia, failing to meet the goal of representing a useful tool for detecting ischemia in a clinically useful manner.[10] Indeed, we observed a significant increase of circulating hs-cTnT in the majority of patients undergoing a stress test, irrespective of the result, positive or nega-

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tive, of the test. The elevation of circulating troponin was similar for frequency and magnitude in negative as compared with positive tests, thus resulting in a wide overlap of troponin changes among ischemic and nonischemic patients. Moreover, the magnitude of troponin increments were even more marked in the absence (111%) than in the presence (84%) of obstructive CAD. Even in this respect troponin, despite a good sensitivity (89%), showed a very low specificity (47%) for CAD.

Whether troponin is released in the setting of transient ischemia is still a matter of continuing debate.[11] In the past decade, some authors have not been able to document any rise of circulating troponin in exercise or pharmacological stress-induced ischemia.[12-14] Conversely, other authors found a significant association between transient ischemia and troponin release.[15-17] In our cohort of patients submitted for diagnostic purposes to an exercise or a pharmacological stress test, we documented a significant release of troponin that was not limited to patients with stress-induced ischemia and obstructive CAD, but that also involved patients with negative tests and normal coronary arteries. Troponin release was more pronounced after exercise and dobutamine stress, responsible for a greater increase in heart rate, blood pressure, and cardiac inotropism, as compared with dipyridamole stress, mainly acting by a mechanism of inappropriate vasodilation.

Myocardial release of troponin can occur even in physiological conditions. Many works have reported significant increase of circulating hs-cTnT and hs-cTnI after prolonged treadmill exercise and sport endurance in healthy young and competitive athletes.[18,19]

Altogether, these findings support the hypothesis that myocardial release of troponin is a multifactorial process, not limited to cardiomyocyte necrosis, but including a number of mechanisms, such as transient ischemia, hemodynamic overload, and the increase in cardiac work.[7] Hs-cTnT and hs-cTnI are the preferred biomarkers for MI.[20] However, even transient and marked troponin elevations may not be pathognomonic for MI, but identical in cases of pulmonary embolism, acute respiratory distress, myocarditis, nonischemic pulmonary edema, noncardiac shock, etc.[21]

Considering such multiple potential mechanisms, it is evident that any elevation of circulating troponin, despite its absolute specificity for the heart, can occur in several cardiac and noncardiac pathological settings, as well as in healthy subjects. The problem has become even more critical after the introduction of the high-sensitivity methods, because the gain in sensitivity has been inevitably obtained at the expense of the low specificity. Any increase of circulating troponin must therefore be interpreted in the light of the clinical context, taking into account the electrocardiographic, mechanical, and perfusion findings in individual patients. ■

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