High-Sensitivity Cardiac Troponins. Don't Bite off More Than You Can Trade

Troponinas de alta sensibilidad. Quien mucho abarca, poco aprieta

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In this issue of the Argentine Journal of Cardiology, Víctor Mauro et al. analyze the prognostic value of high-sensitivity cardiac troponin levels in a selected population of patients with non-ST segment elevation acute coronary syndromes, excluding high-risk patients (heart failure, chronic kidney failure, sepsis, gastrointestinal bleeding). The authors have accurately concluded that plasma levels of high-sensitivity cardiac troponins can only be considered as an additional parameter in risk stratification algorithms and do not necessarily imply adopting an aggressive treatment strategy. (1)

WHAT ARE HIGH-SENSITIVITY CARDIAC TROPONINS?

High-sensitivity cardiac troponins (cTnT, cTnI) are only found in the myocardium and changes in their plasma levels reflect changes inside the cardiomyocytes. Cardiac troponins are released to the bloodstream only in case of (apparently) severe myocardial injury or cardiomyocyte death, when there is loss of cell membrane integrity. Normal plasma levels are generally defined by the value observed in 99% (99th percentile) of the healthy population, but a certain plasma level can be detected in normal subjects as a result of "physiological" cell death if the sensitivity of the assay used can detect very low levels of cTn (cardiomyocytes do die, do not live forever, and they do regenerate).

Cardiac troponin assays are very specific, but differ in terms of sensitivity. When speaking about traditional cardiac troponins (cTnT, cTnI), high-sensitivity (hs-cTnT, hs-cTnI) and ultra-sensitivity cardiac troponins, we are referring to the sensitivity of the assay used to determine troponin levels. In theory, the most sensitive method is the one that can detect troponins in normal subjects. (2) The most sensitive methods can detect plasma levels of troponins even 1000 times lower than those detected by traditional methods. One disadvantage is that different commercial manufacturers offer different assays with very dissimilar sensitivity and completely different normal range limits, and require local calibration. While this issue does not interfere much with clinical practice, it complicates multicenter studies, the definition of acute myocardial infarction and the recommendations of clinical practice guidelines.

THE GREATEST ADVANTAGE OF HIGH-SENSITIVITY CAR-DIAC TROPONIN ASSAYS

The advantage of this type of troponin assays is the extraordinary sensitivity to determine myocardial injury. If plasma troponin levels detected with a truly high-sensitivity assay are below their upper reference limit (usually the 99th percentile of a healthy population), an acute coronary syndrome can be reasonably ruled out. As usual in biology, reliability will not be 100% and the diagnosis of unstable angina will remain uncertain (if this term can still be used, bearing in mind the other considerations made in this editorial), particularly if the episode is not associated with electrocardiographic changes suggestive of ischemia and the ECG is normal. This is even better if two ECGs, one with and another without chest pain are available.

This concept partially differs with the observation of Mauro et al. who reported that 35% of the subjects with a diagnosis of acute coronary syndrome had normal cardiac troponin levels, below 14 ng/L (pg/mL) detected using a high-sensitivity assay. (1) Yet, the assay used was not the most sensitive available.

The second advantage is that elevated high-sensitivity cardiac troponin levels can be detected early after an episode of myocardial ischemia or injury, allowing a more rapid approach in the management of patients with chest pain in the emergency room. The time required to consider that troponin levels are normal and will not increase can be reduced from the traditional 6 h to 3 h or even 1 h.

THE GREATEST DISADVANTAGE OF HIGH-SENSITIVITY CARDIAC TROPONIN ASSAYS

The lack of specificity for the diagnosis of acute coronary syndrome is the greatest disadvantage of high-

REV ARGENT CARDIOL 2018;86:307-309. http://dx.doi.org/10.7775/rac.v86.i5.14044

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sensitivity cardiac troponins. The first problem is that high-sensitivity cardiac troponins can be elevated in many clinical situations (Table 1). The reason for this elevation in systemic diseases and non-ischemic heart diseases is multiple. (3) High-sensitivity cardiac troponin levels may increase due to direct cardiomyocyte injury in case of myocarditis, chemotherapy-induced toxicity or infiltrative diseases, or to left ventricular pressure or volume overload with increased ventricular stress in patients with valvular heart disease, hypertension, heart failure or kidney failure. Other clinical situations with multifactorial cause include anemia, hypotension, sepsis, stroke and diabetes. Therefore, a rise and/or fall of high-sensitivity cardiac troponin values are required for the diagnosis of myocardial infarction (or non-ST segment elevation acute coronary syndrome). (4)

A very interesting and special situation is the case of elevated cardiac troponins in the "normal" population. High-sensitivity cardiac troponins can be elevated in subclinical conditions and completely normal persons. Troponin elevation can occur after strenuous exercise activities such as marathons, Ironman competitions and other extreme sports and has no relation with myocardial infarction or acute coronary syndromes. (5) Interestingly, moderate exercise may also be associated with a transient increase in high-sensitive cardiac troponins, especially in untrained persons. Its clinical relevance has not been established yet, but even an increase in troponin values within the normal range could be associated with higher cardiovascular risk. (5)

PROGNOSTIC VALUE

Elevated cardiac troponin levels imply myocardial injury and are associated with an adverse outcome in all clinical situations, with or without heart disease. However, they are not the only predictive parameter and cannot be modified directly; they only predict events. Risk scores in acute coronary syndromes, as the TIMI or the GRACE risk scores, include a high number of parameters apart from cardiac troponins that are independently related with the outcome. It would be unwise to ignore troponin or any of the other factors.

Once risk has been identified, in general the benefit of aggressive strategies is greater in high-risk groups, but may not exist in very low-risk groups, especially if the aggressive strategy has side effects, as "invasive" approaches have. Global risk assessment must be carried out in all patients in order to make the appropriate decisions, which are never identical for all the patients; otherwise, risk assessment would not be necessary. (6) On the other hand, the most "ultra-super-sensitive" troponin level to exclude the risk of myocardial ischemia has not been established yet, not even to be 100% sure that an episode of chest pain is not due to ischemia.
 Table 1. Some clinical situations that can elevate high-sensitivity cardiac troponin levels

1. Ischemic heart disease:

- Acute coronary syndromes. ST-segment elevation and non-ST segment elevation myocardial infarction.
- Stable angina.
- Chronic myocardial ischemia without angina.
- Anemia.
- Hypotension.
- Hypovolemia.
- 2. Other heart diseases (not associated with myocardial infarction or ischemia):
- Myocarditis.
- Any cardiomyopathy.
- Cardiac trauma.
- Heart surgery.
- Cardioversion.
- Catheter ablation.
- Pacemaker implant.
- Percutaneous cardiac interventions.
- Endomyocardial biopsy
- Heart failure.
- Arrhythmias (atrial fibrillation).
- Valvular heart disease.
- Aortic dissection.
- Chemotherapy.
- Antiretroviral drugs.
- Alcoholism.
- 3. Systemic diseases:
- Kidney failure.
- Stroke.
- Sepsis.
- Cardiogenic shock of any cause.
- Hypertensive crisis
- Pulmonary embolism.
- Severe pulmonary hypertension.
- Cancer (before chemotherapy).
- Sarcoidosis.
- Hemochromatosis.
- Rhabdomyolysis.
- Hypothyroidism.
- Severely burned patients.
- End-stage diseases.
- 4. Normal population*.
- Strenuous exercise activity.
- Moderate exercise in untrained patients.
- Stress.

*Levels of high-sensitivity cardiac troponins can be detected in the normal population. Levels above the 99th percentile are considered abnormal.

REAL USEFULNESS

Cardiac troponins are highly specific of a tissue (the myocardium), but not of a disease. High-sensitivity cardiac troponin assays provide greater certainty to exclude severe acute heart disease but greater difficulties in differential diagnosis.

Elevation of cardiac troponin levels is associated with the outcome, but is not the only parameter to consider, does not have greater value than the other clinical parameters, cannot be corrected and does not have a specific treatment.

Therefore, high-sensitivity cardiac troponins are useful in clinical practice when the observer has adequate knowledge and clinical judgment but should not guide decision-making as a single parameter. Don't bite off more than you can trade.

Conflicts of interest

None declared.

(See authors' conflicts of interest forms on the website/Supplementary material).

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