

The Significance of Troponin Elevation in Atrial Fibrillation

Juan Pablo Costabel¹, Lucrecia María Burgos¹, Marcelo Trivi¹

¹Cardiology Department, Instituto Cardiovascular de Buenos Aires, Argentina.

Abstract

Cardiac troponin assays have provided a significant contribution for the early diagnosis of cardiovascular events. There is significant evidence about the association between the absolute value of elevated cardiac troponin levels with the prognosis of patients with chest pain. However, it is well-known that elevated cardiac troponin levels may occur in situations other than acute coronary syndromes, as it happens with atrial fibrillation. The significance and prognosis of this elevation are not entirely clear.

We review the evidence about the meaning of such elevation in the setting of atrial fibrillation.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia in the population and confers a higher risk of morbidity and mortality.^[1] Atrial fibrillation increases the risk of mortality, stroke, heart failure and hospitalizations for cardiovascular causes. Its prevalence increases with patients' age, the presence of coronary artery disease, structural heart disease and elevated cardiac filling pressures, among other phenomena.^[2]

Troponin is a protein that plays a role in myocyte contractile function and determination of its exclusively cardiac-specific form that has provided a significant progress for the early diagnosis of coronary events.^[3] There is significant evidence about the association between elevated cardiac troponin levels and its absolute value with the prognosis of patients with chest pain.^{[4],[5]} However, it is well-known that elevated cardiac troponin levels may occur in situations other than acute coronary syndromes, as it happens with supraventricular tachyarrhythmias.^{[6]-[8]} The situations previously described, which predispose to the development of AF, could also elevate troponin levels. We shall review the evidence about the meaning of such elevation in the setting of atrial fibrillation.

Biology of cardiac troponins and diagnostic assays

Troponin consists of three subunits (troponin I, T, and C), which, together with tropomyosin, regulate the interaction between myosin and actin filaments of muscle contraction. This complex structure is organized in units called sarcomeres. Troponins are also found as a small free pool that exists in the cytosol, which is about 6% for cardiac troponin T (cTnT) and 3% for cardiac troponin I (cTnI). Troponins within the sarcomere exchange with the cytoplasmic pool.^{[3],[9]}

Key Words

cardiac troponin, acute coronary syndrome, atrial fibrillation.

Corresponding Author

Juan Pablo Costabel
Instituto Cardiovascular de Buenos Aires, Argentina.
Blanco de Encalada 1543 Buenos Aires, Argentina.
Telephone: 54 11 47877500
Fax number: 54 11 47877500
E-mail: jpcostabel@icba.com.ar

All the methods for the quantification of cardiac troponins measure troponin plasma levels. Up to now, all these tests use monoclonal antibodies as specific detection methods.^{[10],[11]} Troponin C does not have cardiac specificity and thus no assays have been developed to measure it.^[12] The cardiac isoform of troponin I (cTnI) has a unique post-translational tail of 32 amino acids on the N-terminus. This sequence has made possible the generation of highly specific antibodies without cross-reactivity with other non-cardiac forms.^[10] Three genes control cardiac troponin T transcription, generating different mRNA and producing a series of troponin isoforms. Cardiac muscle contains 4 troponin T isoforms, but only one is characteristic of the normal adult heart. During fetal development, cardiac and skeletal TnT are identical. The skeletal isoforms present in the fetal heart are replaced by the adult isoform late during fetal development. Re-expression of fetal forms, which occurs in cardiac and skeletal tissues in response to damage, produced measuring errors with the first-generation troponin assays. This problem was detected and solved once this antibody was replaced by one with high specificity.^[3]

All this progress that has been achieved means that every time a method detects elevation of Troponin T or I, we may assure that the cardiac isoform is elevated.

Troponin assays have improved over the past 10 years, and cTn high-sensitivity (hs) assays have been introduced in clinical practice since 2012. High-sensitivity cTn assays have two main differences with the other assays. Firstly, their ability to reliably detect very low troponin levels in plasma, enabling the early detection of troponin release and allowing an earlier diagnosis. Secondly, the absolute coefficient of variation is much lower, which enables the reliable detection of small variations over the time and differentiates chronic elevations from those acute.^[4]

Mechanisms of troponin release

The mechanisms of elevated troponin levels in the bloodstream are multiple. Myocyte necrosis produces enzymatic degradation of the internal structures and sustained release of high amounts of troponin. However, as it has been previously mentioned, small amounts of Troponin T and Troponin I are free in the cytoplasm and exchange

with those in the sarcomere. It would be expected that if there is release from this pool that the troponin would be released quickly and that blood levels would fall with rapid washout. The half-life of cTnT and cTnI in the blood is about 2 h. Rapid rise and fall within 24 h may therefore be consistent with release of this pool and reversible myocyte damage rather than myocyte necrosis, where a time-dependent fall over a longer period (4 to 10 days) would be expected because of gradual degradation of myofibrils and release of the troponin complex.^[13]

The release of this pool would take place in situations in which the permeability of the cell membrane has been altered. Inflammation could not only alter the permeability of the cell membrane, but also induce necrosis, as it happens in myocarditis. Transient ischemia could also produce the same phenomenon.^[14]

Another potential cause of troponin release during ischemia could be associated with cellular release of proteolytic troponin degradation products. Thus, proteolysis to create small fragments could allow these fragments to pass through a cell membrane with normal membrane integrity. Only 15 min of mild ischemia has been shown to cause development of cTnI degradation products.^[15] The same mechanism could justify troponin elevation in heart failure with or without myocardial ischemia, and only be associated with elevated filling pressures.^[16]

A study by Turer et al. demonstrated that rapid atrial pacing increased troponin levels in patients with and without coronary artery disease, with or without induced ischemia, which could be explained by the release of troponin after excessive myocardial fiber stretching, altering the structure of certain integrins and allowing release of troponin from the cytosolic pool into the bloodstream.^[17]

Another potential mechanism of troponin release is normal myocyte cell turnover. Study of the integration of carbon-14 into the DNA of myocardial cells, generated by nuclear bomb testing, has shown that cardiac myocytes regenerate.^[18] There is a decrease from 1% annual turnover at the age of 25 to 0.45% at the age of 75 years with approximately 50% of cells exchanged during a normal life span. Whether such low-grade turnover results in release of troponin to the systemic circulation is unknown.

Active secretion of vesicles (blebs) or membrane expression with shedding has been hypothesized to be a mechanism to enable troponin to be released from cardiac cells. These may be released into the circulation without rupture of the plasma membrane. There are also likely to be unknown causes of troponin elevations. It is not known as to why sepsis causes the release of troponin from cardiac myocytes, although heat shock proteins and tumor necrosis factor have been implicated.^[19] It is thought that increased troponin levels with renal failure are not related to decreased renal excretion^[13], but rather to toxic products, and supply and demand issues probably also play a role. It is also possible that there are low-grade reparative processes compensating for myocyte loss due to various causes.

Prognostic value of elevated troponin levels

Cardiac troponin is a sensitive and specific marker of myocardial damage.^{[1],[2],[3]} Patients with elevated levels of troponin are considered to have an increased risk for major cardiac events. Multiple studies have shown the prognostic significance of minor troponin elevations in multiple cardiac patient populations, such as acute coronary syndromes and heart failure.^{[20],[21]} Furthermore, it appears that even troponin levels that are just above the detection limit significantly influence the risk for future cardiac events even in healthy patients.^[22]

In the scenario of AF, van den Bos et al reported that circulating cTnI levels were associated with mortality and major adverse cardiac events in a cohort of hospitalized patients. After adjustment for all baseline variables, minor troponin I elevation as well as a positive troponin I were independently correlated with death (HR: 2.35, 95% CI: 1.17–4.73 for minor elevation and HR: 3.77, 95% CI: 1.42–10.02 for positive troponin I). There was an independent association between the combined endpoint of death/MI and both a minor elevation in troponin I and a positive troponin I (HR: 1.99, 95% CI: 1.05–3.80 for minor elevation and HR: 3.03, 95% CI: 1.24–7.37 for a positive troponin I). Cumulative 3-year survival rates were 78% in the non-detectable troponin I group, 62% in the minor elevation group, and 57% in the positive troponin I group (log-rank $P < 0.001$).^[23]

A sub-study of the Randomized Evaluation of Long-Term Anticoagulant Therapy trial (RE-LY), performed in 6189 patients with AF and treated with either warfarin or dabigatran, found that cTnI was predictive of thromboembolic events and cardiovascular mortality, and even after adjustment by potential confounding factors, the risk of stroke or systemic embolism was doubled to fivefold higher for cardiovascular mortality, in patients with the highest quartiles. Hijazi et al. demonstrated that persistent elevation of troponin I was seen in nearly half of the patients in the RE-LY study cohort comprising of patients with anticoagulated AF with ≥ 1 risk factor for stroke. As compared with none or transient elevation, persistent elevation of this biomarker over 3 months conferred a greater risk of stroke and vascular death over a period of 2 years.^[24] Similar results have been shown in the Apixaban for the Prevention of Stroke in Subjects with Atrial Fibrillation (ARISTOTLE) biomarker study.^[8] The sub-study results verified that the troponin levels were related to the risk of stroke and death, in a continuous fashion, independent of baseline characteristics and other biomarkers. Consequently, an even larger proportion of patients, 73%, were identified to have detectable levels. During a median 1.9 year period, the annual rates of stroke or systemic embolism ranged from 0.87% in the lowest hs-cTnT quartile to 2.13% in the highest hs-cTnT quartile (adjusted hazard ratio [HR]: 1.94; 95% confidence interval [CI]: 1.35 to 2.78; $p = 0.0010$). Adding hs-cTnT levels to the CHA₂DS₂-VASc score improved the C statistic from 0.620 to 0.635 for stroke or systemic embolism ($p = 0.0226$), from 0.592 to 0.711 for cardiac death ($p < 0.0001$), and from 0.591 to 0.629 for major bleeding ($p < 0.0001$)^[7]. These results were confirmed in the study by Roldan et al^[25], in a stable and chronic anticoagulated AF cohort, whereby increased plasma hs-cTnT levels were associated with an adverse prognosis in AF patients, with regard to cardiovascular events and mortality. Patients with levels above the 50th percentile of the troponin distribution in an AF population had an increased risk of stroke, other ischemic events, and a higher mortality regardless of their risk as estimated by the CHADS₂ and CHA₂DS₂-VASc scores.

Elevated levels in patients with AF is a relevant issue, and even more important in those who present with angina pectoris or dyspnea. There are few existing studies that discuss the significance and diagnostic value of cardiac troponins in these patients. The first study evaluating the role of cTnI in AF patients in the acute setting was performed by Parwani et al, who evaluated 354 consecutive patients with the primary diagnosis of AF and clinical symptoms suggestive of myocardial ischemia presenting to an emergency department.^[26] Fifty-one patients (14.4%) showed an elevated cTnI with a mean

value of 0.37 µg/L (range, 0.09 – 3.14), 45% underwent coronary angiography, and 6 of these patients (26%) had a significant coronary artery stenosis necessitating coronary intervention. There was no difference in mean cTnI between those with or without coronary artery disease (CAD), $p = 0.69$. The rest of the patients with elevated cTnI did not undergo coronary angiography because of low pretest likelihood for CAD, and non-invasive testing in these patients was negative. Patients with elevated cTnI complained significantly more often of angina pectoris. The type of AF (paroxysmal vs. persistent) did not have an influence on cTnI level. Multivariable analysis revealed that patients with AF and elevated cTnI showed higher heart rate, lower left ejection fraction, elevated serum creatinine, lower hemoglobin and were more likely to present with angina pectoris. In this setting, cTnI has a low positive predictive value regarding relevant coronary stenosis.

A study by Conti sought to investigate the presence of coronary atherosclerosis and adverse outcomes in patients with AF.^[27] Consecutive patients with recent onset AF and without severe comorbidities were enrolled between 2004 and 2013. Patients with a troponin rise or with adverse outcomes were considered for coronary angiography. A propensity score matching was performed to adjust for baseline characteristics. The primary end point was the composite of acute coronary syndrome, revascularization, and cardiac death at 1, 12 month and 10 year follow-up. Of the patients enrolled, 3541 completed the study; 202 (6%) showed troponin rise; and 91 (3%), an adverse outcome. The value > 0.50 ng/L was associated with 55% sensitivity and 75% specificity in detection of critical stenosis and revascularization. In the matching cohort, the OR of troponin rise was 10 (CI, 4-22; $p < 0.001$). Patients presenting with a recent-onset AF and a troponin rise were more likely to achieve adverse coronary events, both in the short (9%) and long terms (9%), when compared with patients without troponin rise (1% and 1%, respectively; $p < 0.001$). Overall, during the follow-up of 10 years, 49% of patients with troponin rise who were submitted to coronary angiography underwent revascularization compared with 31% of patients without troponin rise ($P < .001$).

In contrast, a recent publication by Alghamry et al, reported the results of a retrospective cohort, which included 231 patients who presented with symptomatic AF (chest pain, dyspnea or palpitations) and had serial troponin measurements.^[28] Cardiac TnI elevation above standard cut off was not predictive of CAD after adjustment for other predictors (OR 1.62, 95% CI 0.79-3.32, $p=0.19$). A ROC curve analysis for classification of CAD from cTnI peak was performed, showing an area under the curve value of 0.67 (95% CI 0.58-0.76), that indicates that cTnI peak as a diagnostic test is inadequate in discriminating between those with CAD and those without CAD. However, the highest cTnI concentration value (cTnI peak) was predictive of CAD (OR 2.02, 95% CI 1.02-3.97, $p=0.04$). Dyspnea on presentation (OR 4.52, 95% CI 1.87-10.91, $p=0.001$), known coronary artery disease (OR 3.44, 95% CI 1.42-8.32, $p=0.006$), and ST depression on the initial electrocardiogram (OR 2.57, 95% CI 1.11-5.97, $p=0.028$) were also identified as predictors of CAD in their cohort.

Our group performed a prospective study where 100 patients were consecutive included with a primary diagnosis of tachyarrhythmia.^[6] Mean age was 64 ± 12 years and 59.8% were men. The most common arrhythmia at admission was atrial fibrillation (68%), followed by atrial flutter (16%) and reentrant tachycardia (16%). The results of

the first determination of hs-cTnT were positive (> 14 ng/l) in 44.2% of the patients and the second determination, separated by 3 hours, was positive in 50.7% of the cases. The variation between the first and the second troponin levels was 1 (0-5) ng/l, and was > 7 ng/l in 24.6% of the cases, with a clear trend toward higher troponin values in reentrant tachycardias. Four cardiovascular events were reported in 30 days. In all the cases the patients had presented AF and there were no significant differences in hs-cTnT values. We concluded that there is a significant number of patients with supraventricular tachyarrhythmias who present elevated hs-cTnT levels. The association of this elevation with cardiovascular events seems to be very low.

The relationship between troponin elevation and heart rate was also explored in the work by Ulimoen et al. who reported that cTnT levels were significantly reduced both by β -blockers and calcium channel blockers.^[29] They demonstrated that lowering the heart rate is associated with lower release of cTnT even in patients with permanent AF and heart rates well below 100 bpm, and may potentially challenge the findings of the RACE II study.

All this data is not conclusive about the meaning of troponin elevation in the setting of atrial fibrillation. Perhaps troponin increase is due to AF per se, or is caused by coexistent cardiovascular risk factors or may simply reflect a 'sick heart'. Thus, there is no established explanation for the association between high troponin and stroke.

Conclusions

Cardiac troponins are elevated in a significant proportion of patients with atrial fibrillation that predicts a worse outcome and greater cardio-embolic risk independently of the other known risk factors. Such elevation does not necessarily represent the expression of an ongoing acute coronary event. Future prospective studies with a larger number of patients might clarify this matter.

Conflict Of Interests

None.

Disclosures

None.

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