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Review article
Pregledni članak

FALSE POSITIVE TROPONIN – A TRUE PROBLEM

LAŽNO POZITIVNI TROPONIN – ISTINIT PROBLEM

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Summary: Cardiac troponins have a crucial role in diagnosing acute myocardial infarction, but have been considered by some authors to have a high false positive rate. Such opinions may decrease the confidence in troponin with important clinical consequences. The aim of the paper is to analyze three different meanings of the phrase »false positive troponin«: A) analytic (technical) false positive, with no real myocardial damage; B) false positive considering AMI: cardiac injury is present, but there is no AMI; C) false positive considering CAD: there is myocardial damage, but no CAD. The most frequent and the most important source of misunderstanding is the confusion between aspects A) and B). Namely, there has been a relatively small percentage of false positive troponin elevations due to analytic reasons. On the contrary, there has been a relatively large percentage of »false positive« results in patients with myocardial necrosis due to causes other than AMI; for them – instead of »FP troponin elevation« – another phrase ought to be used, e.g., »non-AMI troponin elevation« until the etiopathogenesis in an individual patient is recognized. The phrase »false positive troponin« should be restricted to the artificial increase in troponin due to preanalytic and analytic reasons. By doing so, we may decrease the degree of confusion about troponin and increase the confidence in this highly specific marker of myocardial injury. The possibility of an analytic false positive result should always be kept in mind when one interprets elevated troponin.

Keywords: troponin, false positive, myocardial infarction, acute coronary syndrome

Kratak sadržaj: Srčani troponini imaju ključnu ulogu u dijagnostici akutnog infarkta miokarda, uprkos mišljenju nekih autora da imaju visoku stopu lažno pozitivnih (LP) rezultata. Takvi stavovi mogu smanjiti poverenje u troponin, što može da ima važne kliničke posledice. Cilj ovog rada je da se analiziraju tri različita značenja izraza »LP troponin«: A) analitički (tehnički) LP, bez pravog oštećenja miokarda; B) LP uzimajući u obzir akutni infarkt miokarda (AIM) – srčano oštećenje je prisutno, ali se ne radi o AIM; C) LP u odnosu na koronarnu bolest (KB) – prisutno je oštećenje miokarda, ali bez KB. Najčešći i najvažniji izvor nesporazuma je zabuna između aspekata A) i B). Naime, relativno je mali procenat LP troponina zbog analitičkih razloga. Suprotno tome, relativno je veliki procenat »LP« rezultata u pacijenata sa nekrozom miokarda zbog uzroka drugačijih od AIM; za njih – umesto »LP povećanja troponina« – drugi izraz treba da se koristi, na primer »ne-AIM povećanje troponina« – dok se ne otkrije uzrok u pacijenta. Fraza »LP troponin« trebalo bi da bude ograničena na artificijelno povišenje koncentracije troponina zbog preanalitičkih i analitičkih razloga. Na taj način možemo smanjiti konfuziju oko troponina i povećati poverenje u ovaj visokospecifičan marker oštećenja miokarda. Mogućnost analitički pozitivnog rezultata treba imati na umu kada se interpretira povišena vrednost troponina.

Ključne reči: troponin, lažno pozitivan, infarkt miokarda, akutni koronarni sindrom

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…they have confirmed what clinicians see and struggle with every day – that is, the assays they believe they are supposed to rely on – do not work in the way that the experts suggest they should (1).

Introduction

Cardiac troponin I (cTnI) and T (cTnT) have a central place in the definition of (acute) myocardial infarction (AMI) and consequently crucial medical and scientific as well as high social and legal significance (1, 2).

The high sensitivity of cTn has greatly improved the detection of AMI and thus (recognition of) its incidence increased substantially. Due to high cardiac specificity, cTn also revolutionized the confirmation of myocardial necrosis in the laboratory. Troponin serves as a basis for risk stratification in many diseases, including acute coronary syndrome – ACS (unstable angina versus AMI) and AMI itself, heart failure (both acute and chronic), renal failure, etc. Furthermore, the approach toward invasive diagnostics and therapy in ACS as well as the usage of some drugs (e.g. platelet GP IIb/IIIa inhibitors, low-molecular-weight-heparins – LMWH) all depend on cTn values (3, 4). Thus, it is of great importance to avoid cTn misinterpretation, which may lead to wrong (and even dangerous) clinical decisions (5–6). However, it is sometimes difficult to explain positive cTn, because many diseases can increase it. The differential diagnosis has become extensive and troublesome (2, 3, 7). It produced the feeling that cTn testing has gotten out of hand (8). Due to complaints of false positive (FP) cTn measurements, the U.S. Food and Drug Administration issued a Medical Device Safety Report (9).

For sure, not all colleagues are quite familiar with the terms: »positive predictive value« (PPV), »false positive«, etc. Even if one is, he/she might get confused by different meanings of the same phrase. Namely, there have been three different »standards« as references to calculate cTn sensitivity, specificity, etc: A) myocardial damage; B) AMI and C) coronary artery disease (CAD). Accordingly, there are three possible different meanings of the phrase »FP cTn« in contemporary medical literature and practice:

A) Analytic (technical) FP, with no real myocardial damage;

B) FP considering AMI: cardiac injury is present, but there is no AMI;

C) FP considering CAD: there is myocardial damage, but no CAD (angiographically).

A) Analytic (technical) FP, with no actual myocardial damage

What are the causes of analytic, no actual myocardial damage FP cTn?

Preanalytic and analytic problems can induce elevated and reduced values of cTn (10). There is a group of clinical conditions and no obvious myocardial diseases, like: sepsis /critically ill patients, hypovolemia, cerebrovascular accidents, acute cholecystitis (11) with potentially FP cTn. However, some of these case reports cannot exclude the influence of analytic interference on cTn values. A great deal of evidence showed trouble with FP cTnT in renal failure and in different skeletal muscle diseases and seriously reduced diagnostic significance of this biomarker (12). For example, there are forms in the diseased skeletal muscle which may raise concentrations of cTnT and could reflect reexpressed isoforms (12).

Analytic FP may result in assay interference from heterophile (13) and human antimouse antibodies (HAMAs) that can be identified: by demonstrating a lack of recovery upon dilution, by showing a different result when testing the sample on a different manufacturer's assay, and by using antibody blocking reagents to remove the interferents (14). Sources of circulating antibodies include: immunotherapies, vaccinations, blood transfusions or the use of mouse monoclonal antibodies in diagnostic imaging and cancer therapy, exposure to microbial antigens, exposure to foreign animal proteins, and autoimmune diseases such as rheumatoid arthritis (15, 16).

The list of analytic FP causes includes: fibrin clots, microparticles in the sample, heterophile and human antianimal antibodies, autoantibodies, rheumatoid factor (RF), interference by endogenous components in blood (bilirubin, hemolysis, lipids), elevated alkaline phosphatase activity, macro immunocomplex formation, and analyzer malfunction (1, 17, 18).

Rheumatoid factor, another cause of interference in the immunoassays, has been reported in 5% of healthy persons, and approximately 1% of patients with elevated cTnI levels may have this elevation solely because of the RF (16). It was published in 1999 that a high percentage of FP cTnI resulted in patients with RF (19). Although only recently discovered for cTn, autoantibodies to other serum biomarkers have been known for decades (20). Circulating autoantibodies against cTnI were found in a substantial number of one study participants (21). Macromolecular enzymes tend to have persistently abnormal activities in blood because of the reduced clearance rate of these high-molecular-weight complexes. As such, their presence can lead to FP test results (20).

Probably a better term, antianimal antibodies can bind to immunoglobulins of many animals (mouse, sheep, cow, etc.). Some 10–40% of humans possess antianimal antibodies (IgG, IgA, IgM, IgE class). Circulating antibodies can reach gram per liter concentrations and may persist for years (21).

Several sources have been implicated as possible causes for inducing heterophile antibodies in humans, including exposure to animals, special diets, deliberate immunization, rheumatoid factors, blood transfusions, autoimmune diseases, dialysis, certain medications, and cardiac myopathy (21).

Moreover, a case report was published, which reveals the fluctuation of falsely elevated cTn. Cardiac troponin correlated with hemoglobin, which – in turn – served as a marker of heterophile antibody levels (21).

False positive cTn elevation may be transitory in the same patient – it may disappear following the decrease of antibodies (22, 23). Whether a cTn rise is true positive or FP (technical FP, biochemical FP, analytic FP, »true« FP) may depend on the type of cTn measured. Sometimes, for example, cTnT is FP, but cTnI is not (24). Renal failure is one of the most important conditions with diverse cTnT and cTnI results. Also, a rapid cTnI assay can lead to more FP results and is not optimal for the determination of cTn status and prediction of subsequent cardiac events at suspicion of ACS (25). In addition, percentage of FP results may depend upon the cTn generation assay: some problems occurred about the specificity of the first-generation cTnT assay, using an antibody showing significant cross-reactivity with skeletal isoforms of cTnT (26). Rate of FP may depend even on the numerical result of cTn measurement: interference should be highly suspected in serum specimens where the initially measured cTnI concentrations are in the range of 2,000–25,000 ng/L when using the Abbott AxSYM (18). The type of specimen (plasma/serum) used for analysis of cTn may also be a contributing factor to spurious cTn test results (18). The potential effects of all drugs, currently used in ACS management, upon cTn values have not been studied adequately still. Use of high-sensitive (hs), new generation tests for cTn improves sensitivity and specificity (AUC from 0.95 to 0.96, depending on manufacturers) vs. standard assay (AUC 0.90; confidence interval 0.86 to 0.94) (27). Simultaneously, with the increase in test sensitivity, the possibility for FP cTn increases as well, and this fact, associated with a low index of individuality for cTn, indicates that population-based reference and cut-off values are less useful for interpreting cTn results than following serial changes in values in individual patients (28, 29).

The terms »troponin positive« and »troponin negative« should be avoided. »Detectable« levels will become the norm and will have to be differentiated from »elevated« levels (30). Despite evident progress in decreasing analytic FP cTn elevations, even with an ultrasensitive 3-site sandwich cTnI immunoassay, this remains the problem occasionally (31). Case reports of FP cTn have been continuously published (32).

How can we decrease the percentage of analytic FP?

The ultimate goal will be to have all cTn assays attain a 10% CV at the 99th percentile reference limit – to reduce any potential of FP analytic results attributable to imprecision in the low concentration range (33).

On the other hand, the easiest way to meet the 10% CV metric would be to increase the assay threshold, thereby decreasing its clinical sensitivity. The sensitive assay with slightly more imprecision will correctly identify more patients at risk than an insensitive one with excellent precision (34).

The operative threshold was defined as the 99th percentile of the values for a reference control group and was based on the consensus that an acceptable FP rate would be ≈1% (35). Assays with CV 20% at the 99th percentile upper reference limit should not be used (10).

False positive results and analytic difficulties should be published openly in a forum, in which their tabulation can aid laboratories and, subsequently, clinicians (36). Lum et al. (17) gave eight suggestions to avoid technical FP results. On the other hand, causes of analytic FP cTn were not discussed in the crucial document (2). The National Academy of Clinical Biochemistry recommends that plasma should be the specimen of choice for analysis of all biochemical cardiac markers (37). Unfortunately, the use of plasma for cTnI analysis is not without shortcomings. Reports of significantly lower results in heparin plasma compared with serum have been described, and use of heparin plasma is discouraged for some cTn methods. In addition to heparin plasma, other studies report significantly lower cTnI results in specimens collected in EDTA plasma compared with serum (23).

Beyne et al. (38) concluded that a single centrifugation of collection tubes containing thrombin as a clot activator was insufficient to avoid FP cTnI results on the Access analyzer. Repeat centrifugation decreases FP results, as well as use of ultracentrifugation, which decreases rate of FP CTnI from 3.6% (after classical centrifugation) to 1.1% (after ultracentrifugation, $p<0.0005$) (39). Thus, some institutions have a policy of repeating all abnormal cTnI assays to reduce FP (40). A recent study recommends the use of rapid serum tubes (RST) because RST significantly reduce the incidence of FP cTnT (39, 41). Recognizing the significance of interference by heterophilic antibodies, the manufacturers recommend using the antibody blocking agents along with their cTn immunoassays whenever this interference is suspected. Other preventive activities can include dilution, use of heterophilic blocking tubes, immunoglobulin-inhibiting reagents and precipitation with polyethylene glycol (15). However, the results of these blocking agents are not very convincing (16). With the more specific second-generation cTnT assays for AMI, no cross-reactivity with cTnT purified from skeletal muscle could be detected and no FP cTnT was measured in sera of healthy marathon runners or patients with severe skeletal muscle damage (24).

The incidence of interference varies considerably in the literature, ranging from 0.17 to 40% (16). That is quite pronounced variability. Others find less

variability: because of the many manufacturers of cTnI assays, it is difficult to estimate the prevalence of FP cTnI results, but reported percentages range from 0.17% to 3.1% (17). The overall prevalence of FP serum cTnI was 3.1% (95% confidence interval [CI] 2% to 4.4%) of the total population: 14.8% (95% CI 9.9% to 20.9%) of patients with positive cTnI, and as many as 37.5% of patients with elevated cTnI and normal range creatine kinase (23). Inaccurate quantification of cTnI is prevalent, but with further sample manipulation, such FP results may be eliminated without significant risk of clearing true-positive results. Evidently, as biochemical analysis comes to play a more central role in the assessment of the cardiology patient, more data concerning the potential for nonantibody-related FP results is urgently required for each of the many immunoassay systems in clinical use (23).

B) No-AMI cardiac injury

Cardiac troponins I and T are highly sensitive and specific biochemical markers for myocardial necrosis and were generally believed not to be elevated in cases other than AMI, as Lum et al. wrote in the excellent paper: »FP cTn results in patients without AMI« (17). Cardiac troponin is often (but erroneously) considered a specific marker for the diagnosis of ACS (42). The tissue specificity of cardiac cTn should not be confused with specificity for the mechanism of injury (e.g., AMI vs. myocarditis) (43, 44).

Elevated cTn levels are commonly seen in several non-ACS patient presentations and are often assumed to represent »FP« test results (6). In addition, symptoms compatible with myocardial ischemia are notoriously common, resulting in substantial likelihood of FP diagnoses of AMI based only on symptoms and biomarkers (45). Raised cTn without myocardial ischemia should be considered »false false-positive«, as Jaffe suggested (46). In other words, elevated cTn is true positive, because it resulted from a myocardial injury caused by a disease other than AMI.

In general, the higher the cTn concentration – the higher the probability of significant cardiac pathology (47) and the higher the likelihood of an AMI (1). Indeed, cTn concentrations in patients with myocarditis are commonly even higher (48).

Clinicians should be cautious about straightforward diagnosing AMI in patients with raised cTnT levels, because many other diseases can also raise cTn (49). Recent recommendation that serial cTn testing can be useful in differentiating AMI from nonischemic increase in cTn (50) can help in solving many ambiguous cases. Namely, no-AMI cardiac injury with a positive first value of cTn, after subsequent serial samples were not significantly increased or decreased from baseline, as opposed to typical findings in cTn kinetics for AMI. Keller et al. (51) showed that the positive predictive value for hs-TnI, for ruling in AMI, increased from 75.1% (determined only on admission) to 95.8% (determined at admission and with the serial change in cTn concentration after 3 hours), and for cTnI increased from 80.9% at admission to 96.1% combining with other TnI value after 3 hours.

In an Observational Prospective Cohort Study, Myint et al. (52) found 54% patients with a raised cTnI due to non-ACS illnesses. In the emergency department, there were 42.2% patients with positive cTnI levels. In terms of the diagnosis of AMI, the sensitivity was high enough (94.6%), but its specificity was relatively low (61.9%) (53). Patients without ACS but with raised levels of cTnT comprised 38% of all hospitalized patients found to have raised cTnT. These patients had a worse in-hospital and 6-month outcome than those having ACS with raised levels of cTnT (49). The best clinical cTnT cut-off value for diagnosing ACS was ≥90 ng/L, with sensitivity 77% and specificity 75% (49).

Rate of FP considering AMI depends on the definition of AMI used. Several years ago, by applying the WHO diagnostic criteria for AMI, ≥30% of cTnT positive patients were classified as FP (26). The overall PPV of cTnT for ACS diagnosis was only 56% (95% CI, 52%–60%). The PPV of cTnT level >1,000 ng/L in the presence of normal renal function was 90%, but was as low as 27% for values of 100–1,000 ng/L for elderly patients with renal failure (42). Thus, the rate of »FP« in terms of AMI directly depends upon the cTn cut-off value used. An increase in the analytical sensitivity of cTn assays with the subsequent lowering of the cut-off concentration will result in a higher percentage of non-ACS patients who have abnormal cTn results (14). Very important for the differentiation between acute and chronic cTn elevation is a rising (or falling) cTn pattern in AMI (2).

When there is a mild cTn elevation and the clinical situation makes an acute cardiovascular problem very unlikely, we should consider the cost of all the unnecessary stress tests ordered, coronary angiograms performed, and antiplatelet agents prescribed (8). In such situations, some of the patients with FP cTn elevation would likely have been told they had suffered myocardial injury and others would have been unnecessarily admitted to the cardiac intensive care unit. In addition, it is impossible to measure the effects of loss of confidence by clinicians in the utility of cTn test as a consequence of these FP results (18). The diagnosis of AMI should still mostly be based on the clinical presentation (42). Fye suggests that we should think twice before attaching the NSTEMI label to a patient with a mild cTn elevation, much more likely to be due to one or more of the nonischemic conditions (8).

C) (Angiographically) no-CAD myocardial injury

As ACS is an emergent, life-threatening disease, it has become routine practice in many institutions that raised cTn directs patients toward urgent or early-invasive cardiac catheterization, even if this approach produces a significant number of »FPs« (48).

There have been patients with suspected ACS, elevated cTn and no significant stenosis on coronary angiography. The prevalence of myocardial infarction with normal coronary arteries (MINCA) is higher than previously believed (7%). It is found in 1/3 women with MI, which is usually smaller. MINCA patients had thromboembolism more frequently (54).

Some such patients actually have myocarditis. Most of them had AMI, but either plaque rupture had occurred on non-significant stenosis or the pathophysiologic mechanism was different: spasm, embolism, etc. (known as type 2 AMI) (2). This understanding of cTn false positivity is possible in patients with »FP catheterization laboratory (cath-lab) activation for STEMI«. Unnecessary cath-lab activation leads to potential exposure of patients to needless risk, to unwise costs, etc; on the contrary, omission of cath-lab activation precludes life-saving intervention for some patients. Therefore, it is important to optimize the criteria for cath-lab activation (55–57).

Namely, suspected STEMI leads to on-call activation of catheterization laboratory in many countries, to provide the mechanical revascularization (primary PCI). If performed timely, this is considered to be the optimal strategy for most STEMI patients. Indeed, patients with suspected STEMI usually have elevated cTn values. In many papers cath-lab activations have been considered FP if the angiographic finding was not compatible with STEMI (e.g. coronary artery thrombosis, etc) (55, 56).

If elevated in a patient with FP cath lab activation, cTn is indirectly considered as FP, too. Indeed, this in suboptimal terminology. FP cath-lab activation does not mean necessarily that there was a mistake of sending a patient (e.g. with pericarditis) urgently to cath-lab. It only means that the typical finding for STEMI was missing at the time when coronary angiography was performed. Thus, in many patients with the so-called FP cath-lab activation, elevated cTn is actually due to myocardial necrosis, despite of the term FP. Moreover, in many (probably in most) patients with ST-segment elevation who underwent urgent coronary angiography, cTn raise is due to ischemic causes, such as prolonged coronary artery spasm, or thrombosis or embolus, which resolved prior to angiography. Thus, probably in a majority of patients with the so-called FP cath-lab activation, cTn elevation is caused by ischemic myocardial necrosis, which is AMI by definition. Thus, it is not FP cTn elevation.

There has been not so small a number of such patients as one might expect: in ESC Guidelines for the diagnosis and treatment of NSTE ACS, their prevalence was estimated to be up to 15–20% (44, 58).

On the other hand, important papers have accumulated in the last few years that suggest another aspect of the relation between cTn and CAD. In persons without acute illness, cTn was found in low concentrations (less than needed for AMI diagnosis), so-called »detectable« concentrations. Long-term follow-ups were organized and the results have been very important. For example, a detectable baseline concentration of cTn is often a marker of the presence of underlying CAD and perhaps even its subsequent proclivity to instability (59). In 2006, Zethelius et al. (60) published the paper: »CTn I as a predictor of CAD…« In another study, baseline cTnI was of value in detecting CAD and also in predicting the need for revascularization during follow-up (59). cTnI concentrations increased with age in subjects free from clinical signs of CAD, suggesting silent myocardial damage. cTnI predicted death and first CAD event in men free from cardiovascular disease at baseline, indicating the importance of silent cardiac damage in the development of CAD and mortality (60). A detectable cTn value alone had 65% predictive accuracy, which was comparable to the 70% provided by imaging stress testing and more than the accuracy provided by the electrocardiogram recorded during the stress testing (53%). There was synergism with improvement in overall accuracy to 85% when imaging stress testing and cTnI were used conjointly. Detectable levels of cTn were prognostic for future events in this study, too (59).

Advances in cTn research and outstanding effort led to development and usage of hs-cTn, with sensitivity to cardiomyocyte damage improved even 100 times (in comparison to previous generations of cTn analyzers). Value of hs-cTnT 14 ng/L is used as the 99th percentile of the control (healthy) population (61).

Generally, a cut-off level for cTn representing 99% of the healthy population has been recommended to reduce the frequency of FP results (62). The 99th percentile cTn value depends on age, and can be almost 4 times higher in patients over 70 years, in comparison to a young population (63, 64). Thus, if we do not take into account the higher values of hs-cTn in the older population, it will result in a higher percentage of »FPs« – as far as AMI is concerned. For example, using the cut-off value of 86.8 ng/L (instead of the currently recommended 14 ng/L), hs-cTnT »FPs« (for AMI diagnosis) in the reference population >75 years were diminished by ≈90% (65).

In the majority of patients, hospitalized due to non-cardiac disease, concentrations of hs-cTnT exceeding the 99th percentile were measured, and were a powerful and independent marker of mortality (66).

There are a large, and increasing, number of conditions with elevation of cTn, which is not associated with ACS. In many cases (but not in all), there is a high probability of associated atherosclerotic disease, which may contribute to the pathophysiologic process (67). Outpatients with stable CAD have significantly higher cTn than controls ($p<0.001$) (68). Detectable values below the 99th percentile may identify individuals with chronic CAD at risk for subsequent cardiac events (59). Vice versa, it must always be remembered that a negative cTn result does not rule out a flow limiting stenosis of the coronary artery (67). In the future, screening of the population without diagnosed CAD by measuring hs-cTn may be performed in order to detect patients who actually have undiagnosed stable CAD (or will have manifest CAD, or a main adverse cardiac outcome during the follow-up) (63, 69). For example, in the Atherosclerosis Risk in Communities Study (ARIC), there was an almost 3.5 mortality gradient between the highest and lowest cTn category among 11,193 participants (70).

As with any prognosticator, FP hs-cTn might appear (meaning that, although an individual has increased hs-cTn, no CAD is detected during the defined follow-up). But, it is not still a real problem, and there are more important things to improve in our cTn considerations about the problem when to say that cTn is FP.

Discussion

Thus, we analyzed three FP aspects (A, B and C). The rate of FP clearly depends on which of the aspects is used: the FP number is lowest if we consider an analytic source (aspect A – the presence of myocardial injury). All three aspects of »FP« are involved in a not so rare aforementioned clinical situation, found in 6% to 20% of AMI patients (44, 71, 72). Namely, increased cTn levels may be observed in patients (who present with chest pain and are subsequently found to have minimal angiographic CAD). Of such patients, 50% are women (compared with only 30% of the cTn-positive patients with angiographic CAD, $p=0.017$) (71). There is frequently confusion over whether such presentations represent an »fp« result or an ischemic event (73).

Since such patients have increased cTn but no significant CAD angiographically (aspect C – CAD), one may suspect either:

- there is positive cTn due to non-AMI causes (aspect B – presence of AMI), e.g. myocarditis or
- no myocardial injury, but positive cTn due to analytic error (aspect A – presence of injury).

Many clinicians simply assume that these represent biochemical FP assays. It is impressive that the investigators (Assomull et al), using magnetic resonance imaging (MRI), come to the opposite conclusion (45). Besides, analytic FPs seem less likely, because prognosis is not good for such patients (71, 74).

Despite the absence of significant coronary stenosis, this group of patients had a 3.1% incidence of death, reinfarction, or rehospitalisation for ACS at six months, compared with 0% in cTn-negative patients without angiographic CAD (71).

In fact, 65% of cTn elevations in patients with negative coronary angiograms represent a true positive for heart disease, although most of these patients do not have AMI (75–78). Recent guidelines also consider those cTn elevations not to be FP (58). The mechanism underlying this adverse outcome is uncertain (73). The study of Christiansen et al. (73) demonstrates that 30% of patients who presented with a cTn-positive ACS and minimal angiographic CAD had evidence of a myocardial scar as assessed by contrast-enhanced cardiac MRI. It seems that elevated levels of cTn in patients with suspected ACS without significant CAD (sometimes labelled as »FP« – aspect C – no CAD) are the result of myocardial injury, and that these patients are candidates for aggressive preventive therapies (71).

Moreover, DeFilippi et al. (79) studied patients with chest pain but no ischemic ECG changes, anticipated to have low prevalence of CAD and a good prognosis. In the subgroup with an elevated cTn level CAD was found in 90% vs. 23% in cTnT-negative patients who underwent angiography ($p<0.001$), and multivessel disease was found in 63% vs. 13% ($p<0.001$). The cTnT-positive subgroup had a significantly ($p<0.05$) higher percent diameter stenosis and a greater frequency of calcified, complex and occlusive lesions. The cumulative adverse event rate was 32.4% in cTnT-positive patients vs. 12.8% in cTnT-negative patients ($p=0.001$) (79).

Out of three actual different »standards« as references to calculate cTn sensitivity, specificity, etc. (A. myocardial damage; B. AMI and C. angiographically proven CAD), and three possible meanings of »FP cTn elevation«, the first two (aspect A – injury and aspect B – AMI) have been widely used. To our opinion, the phrase »FP cTn« should be restricted to the analytic source (aspect A – injury). Thus, we believe that the main source of confusion arises from reporting »FP cTn elevation« when patient has no AMI (aspect B – AMI). As many such patients do have myocardial injury (myocarditis, etc), instead of »FP cTn elevation« another phrase ought to be used, e.g., »non-AMI cTn elevation« until the etiopathogenesis in an individual patient is recognized.

The importance of FP cTn is obvious. Unstable ACS patients showing cTn elevations could benefit from some therapy to reduce their risk of major cardiac events. It is a great progress in our understanding of cTn that laboratory information, classified as

FP only ten years before, now has therapeutic implications in ACS patients (26). The attendant desire to avoid FP tests is one of the reasons that the currently recommended cut-offs for cTn (99th percentile and 10% CV) are more stringent than the 97.5th percentile and 20% CV commonly used for other laboratory tests (77). With increasing cTn sensitivity, even more non-ACS and chronic cTn elevations are found (14, 61, 66, 80, 81). For example, cTnT was detectable in 10.4% of the analyzed population with the cTnT assay (detection limit ≤10 ng/L) compared with 92.0% with the new high-sensitive cTnT assay (≤1 ng/L) (82, 83) and as low as 0.1 ng/L.

New discoveries in this very interesting and important field might change our understanding of what is FP (considering even the existence of myocardial injury, not only the causative factor). For example, Buschmann et al. conclude that increases in cTn in hypothyroidism are not necessarily FP, as assumed widely in previous reports, but in contrast reflect actual diffuse myocardial injury (84).

It is also important to put the problem of FP cTn into context. Namely, if pre-test probability for a certain disease (e.g. AMI) is very high, post-test probability will stay high even if the cTn concentration is normal. Therefore, false positivity does not produce as much harm in patients with very high pre-test probability for a disease (35).

Indeed, one of the most important goals of cTn usage is to diagnose AMI. For this purpose, as well as to differentiate AMI from non-AMI causes of cTn increases, serial cTn testing (especially from admission to 3 hours later) can be a useful tool.

Conclusion

1. In contemporary medical literature and practice, there are three meanings of the phrase »false positive troponin«: A) analytic (technical) false positive, with no real myocardial damage; B) false positive considering AMI: cardiac injury is present, but there is no AMI; C) false positive considering CAD: there is myocardial damage, but no angiographically significant CAD.
2. Troponin is »myocardial injury-specific«, not »AMI-specific«; therefore, the phrase »false positive troponin« should be restricted to artificially increased troponin due to preanalytic and analytic (methodological – technical) reasons.
3. The possibility of (pre)analytic false positive troponin should always be kept in mind and checked, especially in clinical situations without an obvious cause of myocardial injury and when confirmation of myocardial necrosis by means of ECG, echo, other laboratory tests, etc. is missing.

Conflict of interest statement

The authors stated that there are no conflicts of interest regarding the publication of this article.

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