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MINI-REVIEW ARTICLE

Some Common Causes of False Positive Increases in Serum Levels of Cardiac Troponins

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Abstract: Cardiac troponin molecules (cTnI and cTnT) are the most valuable and in-demand biomarkers for detecting various types of myocardial damage (reversible and irreversible, ischemic, inflammatory, toxic, *etc*.) in current clinical practice. These biomarkers are widely used for early diagnosis of acute myocardial infarction (AMI) and risk stratification of patients suffering from a number of cardiac (such as myocarditis, heart failure, cardiomyopathy, *etc*.) and extra-cardiac diseases (such as sepsis, renal failure, pulmonary embolism, neurological pathologies, *etc*.) that negatively affect the cells of cardiac muscle tissue. However, in daily routine clinical activities, internists and cardiologists often encounter cases of false increases in the concentrations of cardiospecific troponins. A false increase in the concentration of troponins contributes to an incorrect diagnosis and incorrect therapy, which can harm the patient. A false increase in the concentration of troponins contributes to an incorrect diagnosis and incorrect therapy, which can harm the patient, therefore, internists and cardiologists should be well aware of the main reasons and mechanisms for false-positive results cTnI and cTnT. This review article mainly focuses on the causes of false-positive increases in serum levels of cTnI and cTnT, which provide helpful clues for the accurate diagnosis of AMI and evidence for the differential diagnosis.

Keywords. Cardiovascular diseases, acute myocardial infarction, biomarkers, troponin T, troponin I, false positive.

1. INTRODUCTION

Troponin molecules are protein compounds that are part of the troponin complex in striated muscle tissues (cardiac muscle tissue and skeletal muscle tissue), but they are absent in smooth muscle tissue. Troponin subunits (Troponin T (TnT), troponin I (TnI), troponin C (TnC)) combine and form a regulatory troponin complex. The key physiological role of troponins is to regulate the contraction and relaxation of striated muscle tissues [1-3]. The key physiological role of troponins is to regulate the contraction and relaxation of striated muscle tissues [3]. Each subunit of troponins performs a strictly defined role:

1) The TnT molecule is a tropomyosin-binding subunit that regulates the interaction between the troponin complex and the actin (thin) filament;
2) The TnI molecule is an inhibitory subunit that binds actin during muscle relaxation (at low cytoplasmic calcium levels) and inhibits the formation of actomyosin;
3) The TnC molecule is a calcium-binding subunit that combines with calcium ions during muscle contraction (at high cytoplasmic calcium levels), which leads to a change in the conformation of the troponin complex, the formation of an actomyosin complex, which is necessary for muscle contraction [4-6].

Structure of molecules (amino acid composition) TnT and TnI in cardiac myocytes and myosymplasts (muscle fibers) are significantly different, and the structure of TnC in cardiomyocytes and myosymplasts is completely identical. Therefore, the cardiac isoforms TnT and TnI (cTnT and cTnI) can be used as cardiospecific biomarkers for the diagnosis of damage to cardiac muscle tissue (most often to identify ischemic myocardial damage associated with acute myocardial infarction (AMI)) [7-11]. In contrast, the TnC molecule is not suitable for this purpose.

The role of cardiac troponins is extremely important and even minor genetic (hereditary) mutations (altering only one or several amino acids) can cause severe hereditary cardiac pathologies - cardiomyopathies (hypertrophic cardiomyopathy, restrictive cardiomyopathy, dilated cardiomyopathy) [12-15]. These hereditary cardiomyopathies are accompanied by severe disorders of contractile function and relaxation of cardiac muscle tissue, leading, as a rule, to terminal heart failure and death in these patients.

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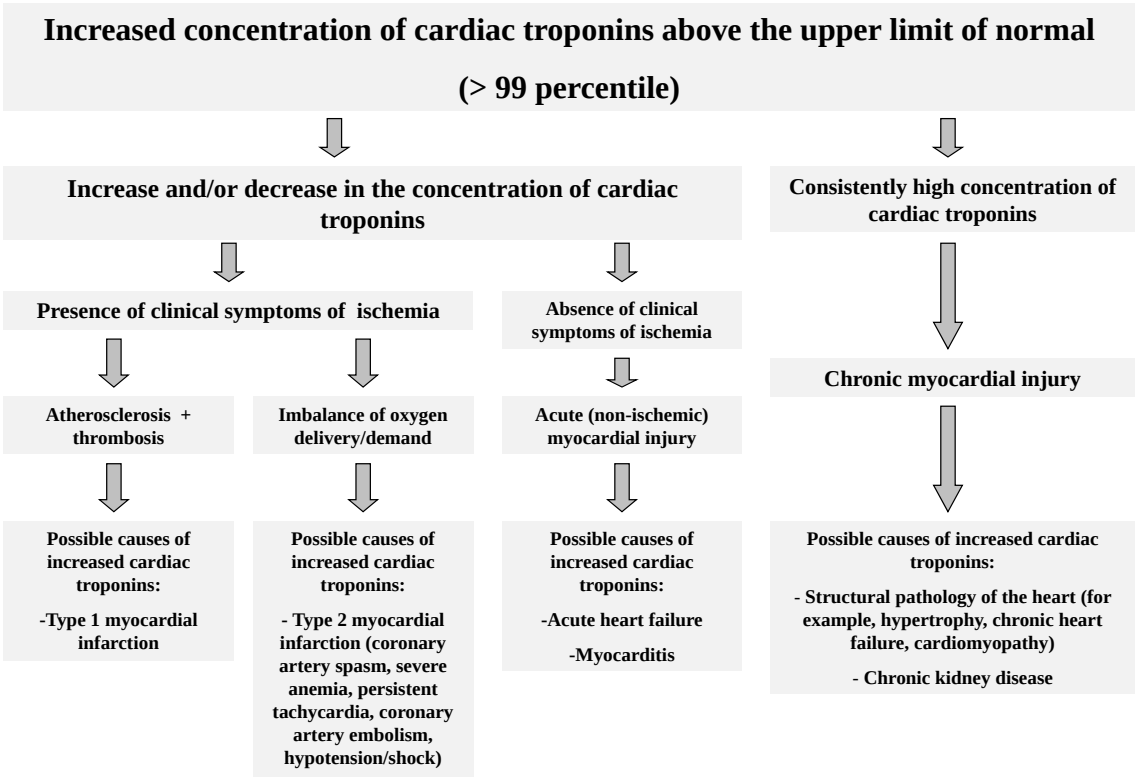

Fig. (1). Localization of cTnI and cTnT molecules in myocardial cells: cytoplasmic and structural fractions.

A small part of troponin molecules (about 4-7% of the total troponin content in cells) is localized in the cytoplasm of cardiomyocytes and does not participate in the contraction of cardiac muscle tissue (Fig. **1**) [16].

Many researchers believe that the cytoplasmic fraction of cTnT and cTnI can be released into the bloodstream in healthy people (in small amounts, less than 99 percentile), as well as with reversible damage to myocardial cells (for example, during physical exertion and/or psychoemotional stress) [17-19]. The concentration of cTnT and sTpI in healthy people or athletes after physical exertion, as a rule, slightly exceeds 99 percentile (no more than 3-5 times), is not associated with an unfavorable prognosis and relatively quickly returns to normal limits. A slight increase in cTnT and sTpI levels is explained by the low content of cytoplasmic fractions of cTnT and cTnI molecules. In AMI, the concentration of cTnT and cTnI significantly exceeds the upper limit of 99 percentile (more than tens and hundreds of times, depending on the time after the development of AMI) [16-18, 20]. With irreversible damage (for example, with AMI), damage (lysis) of the proteins of the structural fraction cTnT and sTpI occurs and the release of these molecules; therefore, the concentration in the blood serum will be significantly higher compared to reversible damage to myocardial cells. Thus, the degree of damage to cardiomyocytes is associated with the degree of increase in serum levels of cardiac troponins.

2. DIAGNOSTIC SIGNIFICANCE OF CARDIAC TROPONINS

Cardiac troponins (troponin T and troponin I) are the main and most specific biomarkers for the early diagnosis of acute myocardial infarction (AMI) [21-24]. In accordance with the main guidance document (Fourth Universal Definition of Myocardial Infarction), the main criteria for AMI are the following:

1) Myocardial damage detected using cardiac troponins;
2) Symptoms of myocardial ischemia;
3) Ischemic changes on an electrocardiogram and, in particular, the appearance of a pathological Q wave;
4) Identification of areas of non-viable myocardium using imaging methods;
5) Detection of a blood clot in the coronary arteries using coronary angiography or autopsy [21].

Due to modern ultra-sensitive tests, medical practitioners got the opportunity to diagnose AMI (within the first two hours from admission of the patient) through the evaluation of dynamic changes of cardiac troponins early. The changes (increase) in the concentration of cardiac troponin molecules within the first two hours are very small (may amount to as little as several ng/l) and cannot be detected by moderately sensitive test systems. It should be noted that due to a number of multicenter studies, there have been validated algorithms of early diagnostics (0 → 1 hour and 0 → 2 hours) of non-ST-segment elevation AMI (NSTEMI) for ultra-sensitive test systems of various manufacturers (Table **1**) [24].

In addition, cardiac troponins can be used to assess the prognosis of patients suffering from many non-cardiac pathologies that damage cardiac myocytes [25-35]. Besides, along with the necrosis of cardiomyocytes, there are other mechanisms of cardiac troponin release from myocardial

Table 1. Current diagnostic algorithms for confirmation/exclusion of NSTEMI (0 → 1 hour and 0 → 2 hours), approved by the ESC (2021) [24].

One-Hour NSTEMI Diagnostic Algorithm					
Troponin immunoassay, company (manufacturer)	Biomarker concentration that indicates an extremely low probability of an NSTEMI diagnosis, ng/L	Biomarker concentration that indicates a low probability of an NSTEMI diagnosis, ng/L	Changes in biomarker concentration after 1 hour at which a diagnosis of NSTEMI should be excluded, ng/L	Biomarker concentration that indicates a high probability of an NSTEMI diagnosis, ng/L	Changes in biomarker concentration after 1 hour at which a diagnosis of NSTEMI should be confirmed, ng/L
High-sensitivity cardiac troponin T (Elecsys; Roche)	<5	<12	<3	≥52	≥5
High-sensitivity cardiac troponin I (Architect; Abbott)	<4	<5	<2	≥64	≥6
High-sensitivity cardiac troponin I (Centaur; Siemens)	<3	<6	<3	≥120	≥12
High-sensitivity cardiac troponin I (Access; Beckman Coulter)	<4	<5	<4	≥50	≥15
hs-cTn I (Clarity; Singulex)	<1	<2	<1	≥30	≥6
hs-cTn I (Vitros; Clinical Diagnostics)	<1	<2	<1	≥40	≥4
hs-cTn I (Pathfast; LSI Medience)	<3	<4	<3	≥90	≥20
Two-Hour NSTEMI Diagnostic Algorithm					
Troponin immunoassay, company (manufacturer)	Biomarker concentration that indicates an extremely low probability of an NSTEMI diagnosis, ng/L	Biomarker concentration that indicates a low probability of an NSTEMI diagnosis, ng/L	Changes in biomarker concentration after 2 hours at which a diagnosis of NSTEMI should be excluded, ng/L	Biomarker concentration that indicates a high probability of an NSTEMI diagnosis, ng/L	Changes in biomarker concentration after 2 hours at which a diagnosis of NSTEMI should be confirmed, ng/L
hs-cTnT (Elecsys; Roche)	<5	<14	<4	≥52	≥10
hs-cTnI (Architect; Abbott)	<4	<6	<2	≥64	≥15
hs-cTnI (Centaur; Siemens)	<3	<8	<7	≥120	≥20
hs-cTnI (Access; Beckman Coulter)	<4	<5	<5	≥50	≥20
hs-cTn I (Clarity; Singulex)	<1	to be determined	to be determined	≥30	to be determined
hs-cTn I (Vitros; Clinical Diagnostics)	<1	to be determined	to be determined	≥40	to be determined
hs-cTn I (Pathfast; LSI Medience)	<3	to be determined	to be determined	≥90	to be determined

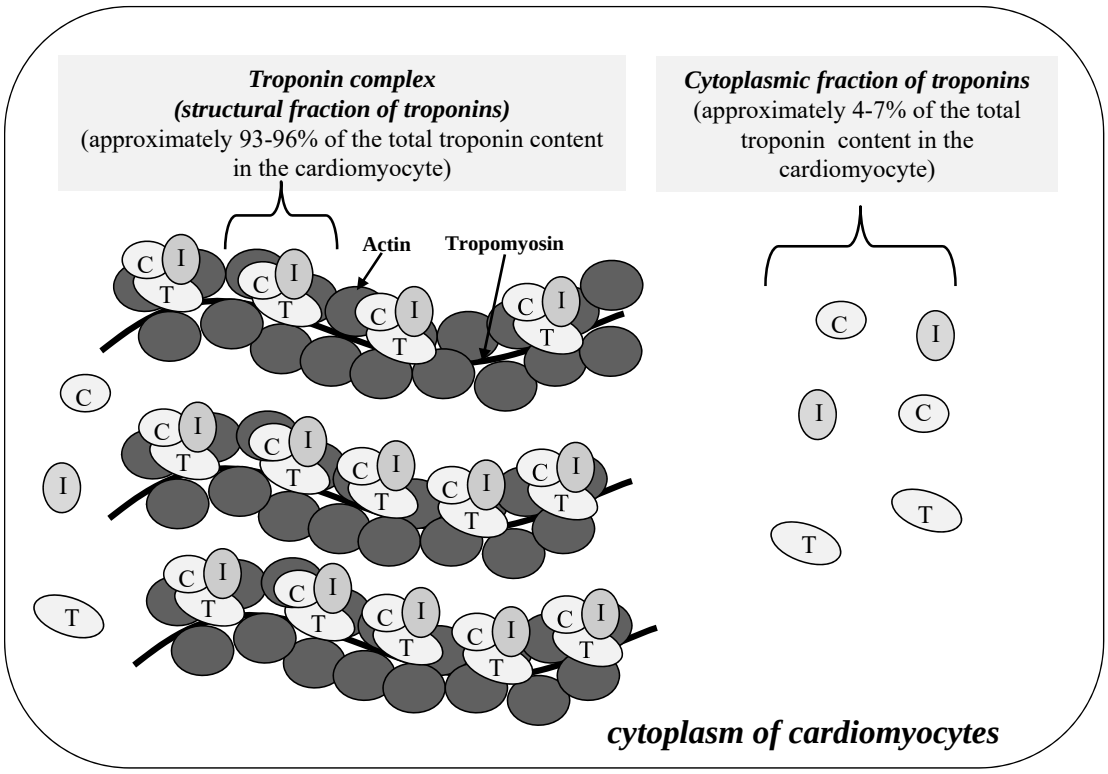

Fig. (2). Interpretation of the results of laboratory diagnostics of AMI.

cells and/or the increase of cardiac troponin concentration in blood serum. Thus, several clinical studies give evidence of a very frequent increase in cardiac troponin concentration in various pathologies. At the same time, the mechanism of troponin increase in these diseases is not associated with the ischemic necrosis of myocardial cells — the main mechanism of troponin levels increase in AMI. The study by G. Lindner *et al*. is quite representative in this respect. The researchers have conducted a detailed analysis of the reasons (the diseases) causing an increase in cardiac troponin T levels in patients admitted to the emergency department. In total, the study included 1573 patients, and only 10% of them had the increased level of cardiac troponin T associated with AMI, while all the rest (about 90%) showed no signs of AMI, and their increased levels of troponin T were induced by other diseases causing the increase of troponin T serum levels by non-ischemic mechanisms. The most common reasons for troponin T increase were the following: pulmonary embolism, renal failure, acute aortic dissection, heart failure, acute myocarditis, rhabdomyolysis, application of cardiotoxic chemotherapeutic agents, acute exacerbation of chronic obstructive pulmonary disease, sepsis and infiltrative cardiac pathologies (for example, amyloidosis) [31]. The interesting fact revealed by this study was that in 30% of cases, the increased levels of troponin T were not connected with any previously described causes of cardiac troponin increase [25]. There is a high probability that these reasons might be connected with the false-positive mechanisms or they have been induced by the factors the researchers and medical practitioners have not paid attention to and have not described yet. Thus, the interpretation of the results showing the increased levels of cardiac troponins is an extremely complicated and sometimes even impossible task of modern clinical practice. Therefore, it is important to remember that the troponin test itself is not "the gold standard test" for AMI diagnostics, but it can become one only for those patients who show typical clinical symptoms of myocardial ischemia, and have corresponding ischemic changes on the electrocardiogram, echocardiogram, *etc*. Generally, when interpreting possible reasons for the increase of cardiac troponins in blood serum, one should be guided by the following schematics (Fig. **2**) [21].

However, in some cases, elevated (positive) troponin concentrations cannot be explained, even after careful clinical examination and exclusion of all possible pathologies that may cause cardiomyocyte damage [31]. Such cases are called false positive and are most often associated with the following reasons: fibrin clots, heterophile antibodies, alkaline phosphatase, rheumatoid factor, cross-reactions of diagnostic (anti-cTn) antibodies with troponin molecules released from skeletal muscle [36-48]. Knowledge of the main causes and mechanisms of a false positive increase in cardiac troponin concentrations is important in clinical practice, since many physicians may make incorrect diagnoses and prescribe unnecessary treatment based on laboratory results, which can be harmful to the patient and lead to unnecessary economic costs. The main causes and mechanisms of false-positive troponin elevations, as well as ways to combat these types of interference are sequentially discussed below.

3. FIBRIN CLOTS

Fibrin clots are one of the most important factors causing interferences in laboratory studies of blood serum. Fibrin clots are formed due to incomplete blood clotting under the action of coagulants added to the test blood to obtain serum. Standard biochemical test tubes (vacuum tubes with a red lid) use a dry clot activator (silica) applied to the inner sur-

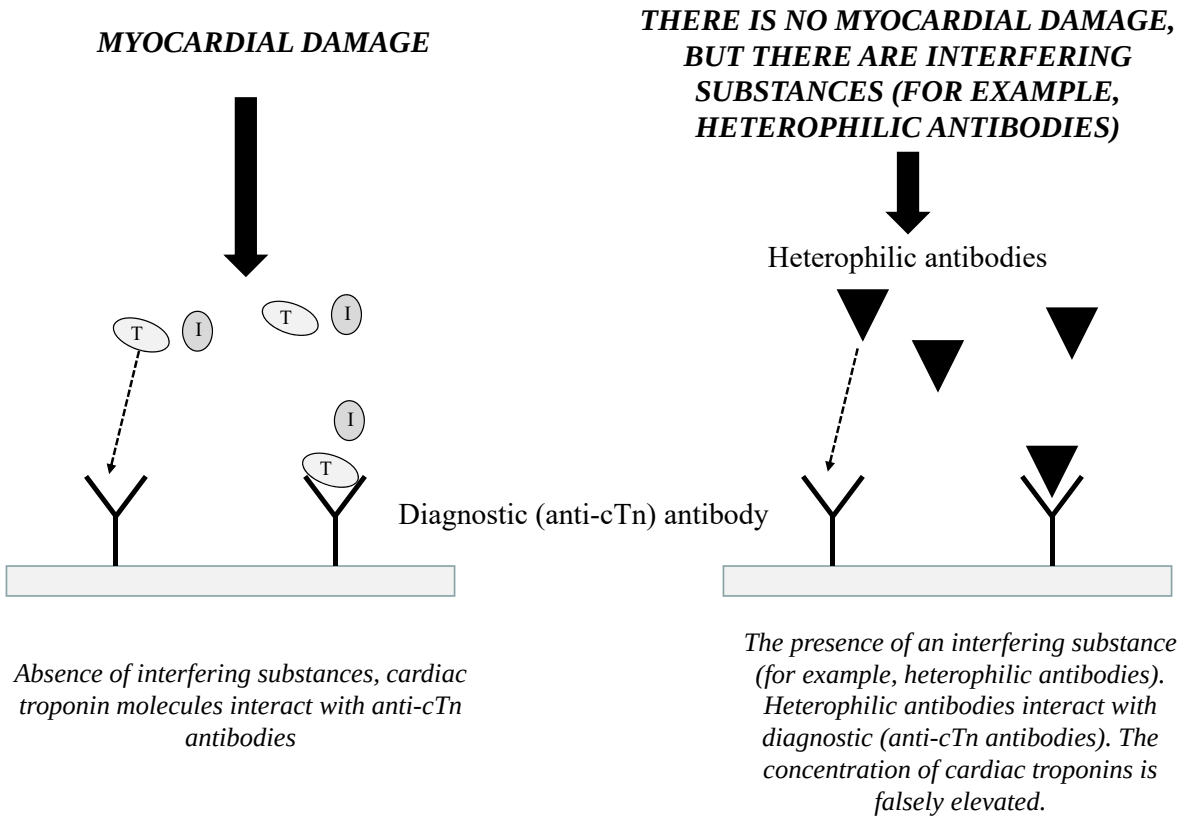

Fig. (3). Mechanism of false increase in cardiac troponin levels due to interfering factors (heterophilic antibodies).

face of the test tube wall as a coagulant. The main reason for the formation of fibrin clots is incomplete clotting of blood prior to centrifugation. Most often, this occurs in patients with coagulopathies or against the background of anticoagulant therapy [23, 49, 50]. In addition, extra-laboratory errors (violation of blood collection technique) and intra-laboratory violations (reduction of recommended time from blood receipt to centrifugation) leading to the formation of fibrin clots are also possible. The optimal time for the complete clotting of the blood sample is approximately 30-60 minutes from the time of blood collection. However, in some cases, laboratory staff, under pressure from clinicians, are forced to reduce the time allotted for clotting a blood sample. This increases the likelihood of fibrin clots and filaments formation in the tubes after centrifugation. Additional factors increasing the risk of fibrin clots are hypocoagulant states (*e.g.* in patients taking anticoagulant drugs). Cases of false positive increases in cardiac troponin concentrations in sera with fibrin clots on Abbott AxSYM [36] and Dade Stratus II immunoanalyzers [37] can be found in the literature. A presumed mechanism underlying false positive troponin tests is the competitive interaction of fibrin clots with diagnostic antibodies (anti-cTn). W Roberts *et al*. in their study identified 2.2% of false positive results due to fibrin clots [37]. Ways to combat fibrin clots are adherence to blood collection and sample preparation guidelines (paying particular attention to the clotting time guidelines), careful visual inspection of the blood sample after centrifugation, and switching to the routine use of whole blood or plasma as biomaterial instead of serum. The latter condition is the most optimal for laboratories involved in the diagnosis of acute conditions, including AMI.

4. HETEROPHILE ANTIBODIES

Heterophile antibodies are immunoglobulins (antibodies) formed by B-lymphocytes against poorly recognized antigens (such as foreign animal proteins). Heterophilic antibodies have a weak but polyvalent activity (avidity) to antigens. The main reasons for the formation of heterophile antibodies in humans are the use of mouse monoclonal sera (antibodies) or incompletely humanized (human) antibodies for the treatment of a number of diseases (for example, systemic connective tissue diseases or oncopathology); frequent contact with microbial antigens, animal antigens (for example, when keeping pets), foreign proteins (for example, in food workers, veterinarians, farmers); vaccination; blood transfusion and long-term persistence of viral agents in the body [38, 39, 51-54]. According to various estimates, the prevalence of heterophile antibodies in the population ranges from <1% to 80%. However, not all patients with heterophile antibodies in the blood have false positive reactions [38, 39]. Unlike a number of pre-laboratory factors (hemolysis, lipemia, fibrin clots) heterophile antibodies cannot be detected by visual inspection of the specimen under examination.

The mechanism of false positive elevation of cardiac troponin concentrations lies in the cross interaction of heterophile antibodies with anti-cTn included in the diagnostic test system (Fig. **3**).

G. Lum *et al*. described an interesting clinical case of a false positive increase in cTnI concentration in a patient without myocardial infarction. A 57-year-old patient admitted to the emergency department had complaints and symptoms similar to AMI. The cTnI concentration measured on

admission with the Beckman Coulter immunoassay was 41.0 ng/mL, significantly higher than normal (0-0.5 ng/mL). However, the levels of total creatine kinase (CK) and creatine kinase-MB isoform (CK-MB) were within the normal range and the electrocardiogram data also did not indicate AMI. After careful examination, other possible causes of elevated cTnI concentration were also excluded. Based on these data, cardiologists suggested the presence of a false-positive result. When cTnI concentrations were repeatedly tested with diagnostic test systems from different manufacturers (Beckman Coulter, Abbot, Bayer, Roche), cTnI levels were positive only with the Beckman Coulter immunoassay, whereas all other immunoassays were negative. Serial dilution of the patient's plasma samples with control plasma (with normal troponin I levels) revealed nonlinear results and led to the assumption of heterophilic antibody interference. To finally confirm this assumption, blood plasma samples were transferred to the research laboratory of Beckman Coulter, where after adding heterophilic antibody blockers to the patient's original blood sample, the cTnI concentration decreased from 41.0 to 1.04 ng/ml [38].

A. Zaidi *et al.* described a clinical case of a false positive increase in cTnI concentration in a 53-year-old female patient admitted to the emergency department with complaints of chest pain. The medical history revealed that the patient had been admitted with similar symptoms three times during the current year. The cTnI concentration at the time of admission (0.37 ng/mL) was 5 times the upper reference limit (0.00-0.069 ng/mL). However, ECG and coronarography data did not reveal signs of ischemia and obstruction of the coronary arteries; so physicians suspected a false positive cTnI increase. The blood sample was sent to another laboratory, where troponin T was measured and was negative. Further analysis revealed the presence of heterophile antibodies in the patient's blood, which led to a false-positive increase in cTnI [55].

The largest systematic literature review by G. Lippi *et al*. summarized 16 studies and clinical cases demonstrating the effect of heterophile antibodies on cardiac troponin concentrations. On average, the rate of false positive increases in cardiac troponin levels ranged from 0.1% to 3.0%, and in some studies, it was significantly higher, up to 50%. The effect of heterophile antibodies is an unpredictable phenomenon and can affect both cTnI and cTnT test systems of any manufacturer. According to a systematic literature review, the best way to detect false-positive troponin levels caused by heterophilic antibodies is to pretreat the blood sample with heterophilic antibody blockers. According to most studies, the addition of a blocking reagent led to a dramatic decrease in cardiac troponin concentrations in patients' blood [39]. Some researchers believe that the prevalence of false positive results due to the influence of heterophile antibodies may increase significantly in the future due to the widespread use of immunotherapy for the treatment of many diseases, as well as the use of antibodies in diagnostic immunoscintigraphic studies [56].

Fast detection of false-positive elevation of cardiac troponin levels is important in the emergency diagnosis of AMI. It is possible only with the coordinated interaction of clinicians and laboratory diagnostics specialists. This is due to the fact that laboratory diagnosticians only have access to laboratory results and therefore cannot compare troponin levels with data from other test methods. Clinical laboratory diagnosticians may suspect incorrect (false positive) results if, in addition to cardiac troponins, a patient has been prescribed study of other myocardial damage biomarkers (total CK and its MB isoform (CK-MB), aspartate aminotransferase, myoglobin, lactate dehydrogenase and others). Thus, normal levels of these biomarkers with sharply elevated levels of cardiac troponins should alert laboratory diagnosticians. An equally important role in identifying a possible false positive result of troponin immunoassay is played by clinicians, who have maximum access to the results of all diagnostic methods used in relation to a particular patient. If the laboratory results are inconsistent with the clinical and instrumental data, clinicians should notify the diagnostic laboratory and initiate further investigation. Possible ways to detect false-positive troponin immunoassay results in the laboratory are: 1) testing the sample on another analyzer (if available), or measuring another cardiac marker (another cardiac isoform of troponin, CK-MB, myoglobin, and others); 2) serial dilution of biomaterial with control samples or saline several times and assessment of linearity of the values obtained; 3) pretreating samples with special reagents that block heterophile antibodies (if available) or sending samples to specialized laboratories for these manipulations.

5. ALKALINE PHOSPHATASE

Alkaline phosphatase is a hydrolase enzyme that is widely used to diagnose liver and biliary tract diseases. In addition to its diagnostic value, this enzyme is also used in some immunoassays, including troponin immunoassays, for signal amplification. Some immunoassays using alkaline phosphatase as a component of the immunochemical reaction have been reported to be affected by endogenous (serum) alkaline phosphatase interference [40, 41, 57, 58]. A. Butch *et al*. first established that alkaline phosphatase could have a significant effect on the concentration of a cardiac-specific enzyme CK-MB, measured on a Stratus immunochemical analyzer. The researchers found that in 12 of 23 patients with elevated serum alkaline phosphatase activity, CK-MB levels were falsely elevated [56]. Subsequently, A. Dasgupta *et al*. reported the effect of alkaline phosphatase on cTnI concentration. With alkaline phosphatase activity = 46 U/L, the serum cTnI concentration in the sample was 0.5 ng/ml. Researchers then added alkaline phosphatase solutions to this serum to increase the activity of this enzyme and evaluate its effect on the troponin concentration. With alkaline phosphatase activity = 129 U/L, the cTnI concentration increased to 4.3 ng/ml. A further increase in alkaline phosphatase activity to 222 and 913 U/L also proportionally increased the cTnI concentration to 9.4 ng/ml and 40.1 ng/ml, respectively. Other test systems not using alkaline phosphatase as an immunochemical reaction component are unresponsive to such influence [41].

In a recent research, R. Marinheiro *et al*. also proved that alkaline phosphatase was the cause of the false-positive cTnI result in a patient [57]. According to some authors, immunoassays that do not use this enzyme should be used for serum testing in patients with increased alkaline phosphatase activity [58]. In the absence of such a possibility, the results of patients who have elevated serum/plasma alkaline phosphatase activity should be interpreted with care.

6. RHEUMATOID FACTOR

Rheumatoid factor - autoantibodies (immunoglobulins) that are directed against their own IgG. Elevated levels of rheumatoid factor are not only of diagnostic value but can also have a significant impact on the results of laboratory tests performed on immunochemical analyzers [42, 59-64]. In patients with autoimmune diseases (rheumatoid arthritis, systemic lupus erythematosus, *etc*.) the main cause of falsely elevated troponins is the rheumatoid factor [61-63]. According to A. Al-Awadhi *et al*., 5 of 50 patients with seropositive rheumatoid arthritis had cTnI concentrations > 0.1 ng/ml (diagnostic threshold for AMI), while none of the patients with seronegative rheumatoid arthritis had cTnI concentrations above the reference limit. One-factor regression analysis showed a positive correlation between cTnI and rheumatoid factor concentrations ($r=0.35$; $p<0.02$) [63]. A Dasgupta *et al*. in their research, found false-positive cTnI concentrations in 4 of 12 patients with elevated rheumatoid factor levels. To eliminate the interference, the researchers used polyclonal antisera against rheumatoid factor, which resulted in a normalization of cTnI levels [61].

A large multi-center study of analytical interferences on laboratory results concentration examined the prevalence of false positives. This study included patients with autoimmune diseases associated with elevated rheumatoid factor concentrations. In general, about 8.7% of the 3.445 results were false positive. However, only a small fraction (21% of all false positives) of the results were corrected with a blocking reagent, whereas 49% of the false positives were not corrected with blocking reagents and would potentially mislead clinicians in making the diagnosis [64]. Thus, clinicians should be very careful when interpreting laboratory immunochemical studies in patients with autoimmune diseases and elevated serum rheumatoid factor levels.

7. CROSS-REACTIONS OF DIAGNOSTIC (ANTI-CTN) ANTIBODIES WITH TROPONIN MOLECULES RELEASED FROM SKELETAL MUSCLE

Damage to striated skeletal muscle in congenital and acquired diseases (myopathies, rhabdomyolysis) can lead to a false positive increase in cardiac troponin levels due to the cross-reactions of anti-cTnI and anti-cTnT antibodies with skeletal troponin molecules. Most often, such false positive reactions occurred with first and second generation troponin immunoassays with weakly specific antibodies that could interact with skeletal troponin molecules [65-67] However, subsequently, a considerable number of cases of false positive increases in cardiac troponins were registered when using more specific third and fourth generation troponin immunoassays [43-46]. The specific cause and mechanism of increase in cardiac troponins in patients with skeletal myopathies have not been unraveled yet, and cases of false positive increases in cardiac troponins have been described even with the use of modern highly sensitive immunoassays [67]. There are two possible mechanisms for the increase in the levels of cardiac troponins in diseases and injuries of skeletal muscles: 1) re-expression of cardiac troponin molecules in skeletal muscles after injury and the release of these molecules into the bloodstream from skeletal muscle fibers [68-70], 2) cross-reactions of diagnostic antibodies (anti-cTnI and anti-cTnT) with skeletal troponin molecules released into the bloodstream during skeletal muscle injury [67, 71]. Discussions on these mechanisms are still ongoing [72, 73].

A number of studies have reported elevated serum cardiac troponin levels in many patients with skeletal myopathies, even in the absence of ischemia and myocardial injury. G. Punucollu *et al*. reported elevated serum cTnT concentrations in 19 of 91 patients with rhabdomyolysis with no signs of coronary artery damage [44]. G. Egholm *et al*. described a clinical case of a significant increase in hs-TnT (471 ng/L, 99th percentile <14 ng/L) in a 48-year-old patient with drug-induced rhabdomyolysis. The concentrations of myoglobin (29120 μg/L), total creatine kinase (30750 U/L) and its MB isoform (162 μg/L) were also significantly increased [45].

Rheumatologists revealed elevated cardiac troponin T concentrations in many patients with idiopathic inflammatory myopathies (polymyositis, dermatomyositis, myositis associated with systemic connective tissue disease). Eighteen of 23 patients with myopathies had elevated levels of creatine kinase and cTnT, while the remaining 5 patients had normal creatine kinase and cTnT levels. Only 1 patient with myopathy had elevated cTnI level. Researchers also noted that creatine kinase levels correlated closely with cTnT levels ($r=0.62$; $p=0.001$) [65]. The most likely mechanism for the elevation of troponin T in this study is the cross-reaction of anti-cTnT with skeletal troponin T molecules. This is evidenced by the close correlation of cTnT with another skeletal muscle damage marker (creatine kinase) and the absence of a significant increase in cTnI. Thus, cTnT and cTnI have almost the same diagnostic value, and in case of cardiomyocyte damage, the concentration of cTnT and cTnI in serum would increase proportionally. A significant increase in only one cardiac troponin isoform (cTnT or cTnI), however, would be more indicative of analytical problems, particularly, cross-reactivity of the diagnostic antibodies included in the corresponding troponin immunoassay.

In another study, cTnT or cTnI levels were measured in 78 patients with skeletal myopathies including muscular dystrophies, myotonic dystrophies, inflammatory myopathies, myotonia, and neurogenic muscle pathologies. cTnT was increased in 56 patients (72.8%) and troponin I in only 2 (2.6%). When grouping patients with elevated cTnT levels by nosology, it turned out that cTnT was elevated in all patients (100%) with neurogenic muscle pathologies, in 87% of patients with muscular dystrophy, in 75% of patients with inflammatory myopathies, in 72% of patients with myotonic dystrophy and in none of the patients with myotonia (0%). Studies of skeletal muscle biopsy specimen using western blotting and mass spectrometry revealed no cardiac troponins [71], which indicates the absence of cardiac troponins expression in skeletal muscle. Based on these results, the most likely mechanism for the troponins elevation in this study is the cross-reactions (false positive) of diagnostic antibodies with skeletal troponin molecules that are released from damaged muscle fibers.

J. Schmid *et al*. used highly sensitive assays to measure cTnI and cTnT during the examination of 74 patients with hereditary and acquired skeletal myopathies. Hs-TnT levels were elevated in a much larger number of patients (> 14 ng/L; 68.9%) compared with hs-cTnI levels (> 26 ng/L;

Table 2. Summary table on the mechanisms of false increase in cardiac troponin levels.

The Main Interfering Factors (Substances)	Reason of Interference	References
Fibrin clots	Competitive interaction of fibrin clots with diagnostic antibodies	[7, 10, 35-38, 49, 50]
Heterophile antibodies	Cross interaction of heterophile antibodies with anti-cTn included in the diagnostic test system	[11, 38, 39, 51-55]
Alkaline phosphatase	Endogenous alkaline phosphatase can catalyze the enzymatic reaction in immunoassay and thereby amplify the signal, which is proportional to the concentration of cardiac troponins in the sample	[40-42, 56-58]
Rheumatoid factor	Non-specific interaction of rheumatoid factor (autoantibodies) with diagnostic antibodies	[1-3, 59-63]
Cross-reactions of diagnostic (anti-cTn) antibodies with troponin molecules released from skeletal muscle	Cross-reactions of diagnostic antibodies with skeletal troponin molecules released into the bloodstream during skeletal muscle injury / Re-expression of cardiac troponin molecules in skeletal muscles after injury and the release of these molecules into the bloodstream from skeletal muscle fibers	[65-73]

4.1%). There was a close correlation of hs-cTnT with creatine kinase (r=0.679) and even closer one with myoglobin (r=0.786). Serial measurements of hs-cTnT concentrations revealed a chronic elevation of hs-cTnT in most patients. The study of skeletal muscle biopsy specimens showed no expression of cardiac troponin isoforms in them, leading the researchers to a conclusion that there is no re-expression of cardiac troponin molecules in skeletal muscle. According to the researchers, the most likely reason for the increase in serum hs-cTnT and hs-cTnI levels was the false positive (cross) reactions of anti-hs-cTnT and anti-hs-cTnI with skeletal troponin isoforms [67]. However, several other studies have revealed the expression of cardiac troponin molecules in skeletal muscle in skeletal myopathies, which may indicate the possibility of increasing the serum cardiac troponins concentration through the release of cardiac troponin molecules from skeletal muscle fibers into the bloodstream [68, 69]. A recent cohort study has also detected messenger RNA and peptide fragments of cTnT using mass spectrometry in patients with Pompe disease, an inherited glycogen storage disease predominantly damaging nerve and muscle cells throughout the body [67]. Thus, the data regarding the source and mechanism of positive troponin tests results in skeletal myopathies are inconsistent and need further clarification.

CONCLUSION

Physicians and researchers should also keep in mind that there are a significant number of factors (fibrin clots, heterophilic antibodies, rheumatoid factor, alkaline phosphatase, cross-reactions of diagnostic antibodies (anti-cTn) with skeletal troponin molecules) that cause false positive elevations in cardiac troponins, as well as ways to detect false positive results and counteract them (Table **2**). Understanding these causes and mechanisms of a false positive increase in cardiac troponins in blood serum will help practitioners and researchers improve the diagnosis of cardiovascular diseases, in particular myocardial infarction, and reduce the risk of misdiagnoses.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The author declares no conflict of interest, financial or otherwise.

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