GENERAL REVIEW

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Biomarkers in aortic dissection, including specific causes of troponin elevation

Biomarkeri u disekciji aorte, uključujući specifične uzroke povišenja troponina

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Ključne reči:
aorta, aneurizma; aneurizma, disekantna; infarkt miokarda; akutni koronarni sindrom; cerebrovaskularni insult; biološki pokazatelji; troponin t; c-reaktivni protein; fibrin fibrinogen, produkti degradacije.

Introduction

Serum/plasma cardiac troponin (cTn) has been recognized as highly sensitive and specific marker of the damage to cardiomyocytes, with no information on the etiopathogenesis of this damage [1]. The expression "false positive cTn" should be reserved for preanalytical and analytic false positives [i.e. when cTn elevation is not really present, but it is due to methodological problem(s)] [2]. cTn is also useful prognosticator in acute myocardial infarction (AMI) [3]. cTn predicts outcome in stable coronary artery disease (CAD), too [4], as well as in many non-ischemic diseases, which increase cTn concentration [5, 6].

Aortic dissection (AoD) is a catastrophic disease of the aorta with the highest mortality rate, which reaches 1% *per* hour in the first 48 h, if left untreated [7]. Initial misdiagnosis of AoD was ≈30% (24% of AoD patients were misdiagnosed as AMI, and 6% as stroke) [8]. Elevated cTn at admission (together with electrocardiography – ECG) sugestive of [acute coronary syndrome (ACS), dyspnea and pleural effusion] may increase time to AoD diagnosis [9]. Indeed, the highest lethality occurs when AoD causes ST segment elevation myocardial infarction (STEMI) and chemical reperfusion (thrombolysis) is used for STEMI, with AoD as the cause being overlooked. Proximal AoD usually arises above right sinus of Valsalva and more likely affects the right coronary artery [10]. If AoD causes AMI, ostium of the right coronary artery is most commonly affected. This is by definition known as right ventricular (RV) AMI. Consequently, in this type of AMI, RV AMI, we should be probably more vigilant to search for AoD as a cause of AMI [11].

Patients who receive thrombolysis (by mistake) for AoD-induced STEMI, have been described even in the cardiologic institutions with very high reputation. It is sometimes "unavoidable" [12], because it is extremely difficult to make in the emergency department differentiation between AMI due to atherothrombosis and due to AoD [13]. In AoD antithrombotic and thrombolytic treatments double hemorrhagic complications and mortality, which approaches 69–100% [14]. Although thrombolytic and anticoagulant agents might temporary improve symptoms and signs of AMI, the mortality rate climbs > 70%, mostly due to hemorrhage into paricardium, which progresses to tamponade [10]. Contemporary expansion of prehospital thrombolysis is rational and life-saving for many STEMI patients. Regrettably, it might enhance the number of thrombolysis in rare cases with AoD-induced STEMI [15].

The motivation for this paper comes from the following: cTn has been increasingly used in the emergency room to im-

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prove detection of the diseases with myocardial necrosis, AMI at the first place. Elevated cTn in a patient with chest pain has been frequently (but erroneously) interpreted as a proof against AoD. It is important for practice that elevated cTn level does not exclude AoD at all. Namely, as much as > 20% of acute ascending AoD patients may have increased cTn values [16]. It could be helpful for practitioners who interpret cTn results to be aware of the following possibilities of elevated cTn in patients with chest pain. Namely, the patient may have AoD and some of the conditions with increased cTn, which could erroneously point toward AMI as the single disease.

CTn can be raised in AoD patients due to various reasons:

When AoD causes AMI

The prevalence of AMI among almost 1,000 AoD patients was 7% [17]. In 1/7 of AoD patients coronary arteries are affected [18]. Up to 1/4 AoD patients have increased cTn concentration, and they have 4-fold higher mortality risk [16]. Additionally, 3% of AoD patients have STEMI, as seen in the large International Registry of Aortic Dissection (IRAD) [19]. Such patients often present with strong retrosternal chest pain, with ST-segment abnormalities, and with increased serum cTn level, all common signs of AMI. It really is AMI, but not usual one, type 1 AMI (due to coronary artery thrombosis), i.e. „classical" STEMI, but caused by AoD [10]. Some quickly performed simple procedures can be life-saving if they help detect AoD as the cause of AMI: comparing pulses and pressures between the arms, discovery of aortic regurgitation murmur, transthoracic echocardiogram in the emergency room or in the coronary care unit. Therefore, high-risk predisposing condition (such as bicuspid aortic valve, aortic aneurysm or manipulation, Marfan syndrome, or positive familly history), high-risk pain characteristics (abrupt, severe, tearing pain), above mentioned high-risk examination features (plus hypotension / focal neurologic deficit) were recognized in the latest European Guidelines as suggestive of AoD.

AoD may cause AMI by compromising coronary artery blood flow directly (mechanically) in 5 ways [15]. Neri recognized 3 main types of lesion: Type A – AoD with disruption of the inner layer, limited to the area of coronary ostium; Type B – AoD with coronary false channel, is a retrograde extension of the AoD into coronary artery wall; Type C – circumferential detachment, with inner cylinder intussuception [20, 21].

Other authors reported somewhat different potential mechanisms of coronary artery obstruction: bulging of dissected false lumen, producing occlusion at the coronary orifice, with possible subsequent distal thrombosis; intimal detachment of coronary orifice and dominant blood flow *via* false lumen; dissection extending into the coronary artery, producing obstruction beyond the coronary orifice; extension of the proximal AoD flap into the right coronary artery; blocking the coronary ostia during diastole, either completely (if the flap reaches the middle portion of the left ventricle) or only partially (if flap is shorter) [10, 21]. Many other mechanisms in AoD can be operative resulting in AMI: stress-induced tachycardia, high blood pressure, etc. It is type 2 AMI [14]. Namely, tachycardia is common in AoD patients, due to excruciating pain and subsequent sympathetic activation. High blood pressure can be expected, too, unless there is, e.g. bleeding or blood leakage from the aorta. All such disturbances cause mismatch between myocardial oxygen consumption and supply, which can lead to ischemic myocardial necrosis (and cTn raise). This scenario occurs typically in AoD patients who also have CAD, but CAD is not *conditio sine qua non*.

When AoD causes the disease, other than AMI (eg, stroke), which can increase cTn concentration

AoD can cease arterial circulation to the brain by obstructing carotid arteries, with resulting ischemic stroke. Of 1,873 patients with type A AoD, enrolled in the large International Registry for Acute Dissection, 4.7% presented with cerebrovascular accident and 2.9% with coma [22]. It is an old clinical rule that we should think of AoD when a patient presents with chest pain and neurologic problems, e.g. syncope. We have to avoid thrombolysis, which is contraindicated if ischemic stroke is caused by AoD (because thrombolysis may increase hemorrhage into the aortic media and promote aortic rupture) [23]. In several studies, cTn concentration was found to correlate significantly positively with the increased volume of the cerebral lesion in ischemic stroke, demonstrated by CT scan. In 15 studies 18.1% [(95% confidence interval (CI) 13.6–22.6)] of 2,901 stroke patients had an increased cTn level [24]. Thus, AoD causes ischemic stroke, which can increase cTn concentration. In addition, approximately half of AoD patients have (acute) aortic insufficiency [13]. This may result in acute heart failure, capable of raising cTn [1, 25].

When the disease increases (cTn) level and contributes to AoD (chronically or acutely)

Renal failure has been known to enhance cTn values, especially of cardiac troponin T (cTnT) [2, 16]. Asymptomatic patients with end-stage renal disease had increased cTnT in 12%–66% and cardiac troponin I (cTnI) in 0.4–38%. Elevated cTnT significantly correlated with all-cause mortality [relative risk (RR) 2.64; 95% CI: 2.17–3.20] and with cardiac death (RR 2.55; 95% CI: 1.93 to 3.37), as demonstrated in a meta-analysis [2, 16]. The exact mechanism is not definitely elucidated, but current explanations for cTn elevations are: asymptomatic necrosis of cardiomyocytes, left vetricle (LV) hypertrophy, LV systolic dysfunction, enhanced cardiac preload accompanied by myocardial stretch, endothelial dysfunction, microvascular derangement, episodes of hypotension during dialysis or myocardial lesion due to calcium and oxalate deposition [26]. Diminished renal clearance of cTn and its particles may also contribute. Increased cTnT could come from skeletal muscles (skeletal isoform) [26].

In 3,243 patients of Chronic Renal Insufficiency Cohort (CRIC), cTnT concentrations were mainly an indicator of

LV hypertrophy [27]. The great majority of renal failure patients have arterial hypertension (AHT), which is commonly difficult-to-treat and uncontrolled, representing chronic risk factor for AoD. Hypertensive crisis was listed as condition which can acutely raise cTn [2, 16]. It is due to LV pressure overload and tachycardia (with consequent increase in myocardial oxygen consumption), as well as to sympathetic and catecholaminergic enhancement of the tone of coronary arteries (with resultant decrease in coronary flow), etc. At the same time, hypertensive crisis can cause/contribute to AoD [17].

When other factor induce cTn elevation independently from AoD

AoD can occur in patients who already have raised cTn level. A list of conditions, characterized by cTn elevation is very long [2, 16, 17] and obviously not finished. Its simplification was published to make it easier for learning [1]. Moreover, it is important to recognize that diseases from each system of organs can raise cTn value. cTn and/or hs-cTn is solid prognosticator in many non-infarction causes of elevated cTn concentrations: congestive heart failure, pulmonary embolism, chronic obstructive pulmonary disease, sepsis, renal failure, critical illness and the perioperative period [6].

When cTn elevation is the result of analytical (laboratory) error (false positive cTn elevation)

False positive increases of cTn concentration are less frequently found now - with new, improved essays [2, 6, 16]. In order to diminish any potential of false positive cTn elevation (which is the result of the imprecision in the low concentration range), the aim is to have all cTn assays attain a 10% coefficient of variation (CV) at the 99th percentile reference limit [28]. Taken together, raised cTn concentration in chest pain patients should not automatically lead to the conclusion that it is AMI and to the administration of antithrombotic therapy. It may actually be AoD patient with any of the aforementioned 5 conditions.

Some obvious implications for practice and research

In patients with diagnosed AoD, high cTn should be interpreted having in mind the possibilities numbered in this paper. For example, angiotensin-converting enzyme (ACE) inhibitor may be administered in AoD if elevated cTn is a result of AoD-induced AMI, but not if cTn increase comes from acute kidney injury.

AoD may cause stroke. In patients with ischemic stroke, elevated cTn concentration is important for prognosis and imposes the need for cardiologic examination, including probably echocardiogram with focus also on aorta.

It should be investigated which of the etiopathogenic mechanisms of cTn raise in AoD are common and clinically relevant.

In patients with the diagnosed AoD, high cTn is believed to have prognostic value. Moreover, it is highly probable that various causes of elevated cTn in AoD are not equally good prognosticators; some (e.g., AMI–induced) may be valid, but others (e.g., false-positive) are certainly not.

In which of the etiopathogenic type of cTn increase in AoD (e.g. within AMI-induced cTn elevation), is cTn quantitatively related to bad prognosis (i.e. is there a threshold for cTn as a prognosticator)?

Important biomarkers in AoD: D dimer (DD)

Since early laboratory investigations in AoD, e.g. serum transaminase and lactic acid dehydrogenase, by Mold [29] in 1964 , many of biomarkers have been studied, including DD, C reactive protein (CRP), smooth muscle myosin heavy chain, calponin, soluble elastin fragments (sELAF), matrix metalloproteinases (MMPs), tenascin, transforming growth factor beta (TGF-b), N-terminal pro-brain natriuretic peptide (NT-proBNP), big endothelin-1 (Big ET-1), creatine kinase-BB isozyme, Notch signaling pathway, and genetic markers [30–33].

DD is now the most widely available and reliable biomarker for AoD, the only biomarker for AoD tending to become a gold standard [33, 34]. DD is the consequence of the fibrinolysis, it circulates in the blood several days after intravascular thrombus formation (the half-life is ≈ 8 hours) [35]. AoD activates inflammatory, coagulation and fibrinolytic cascades [36]. In AoD low admission platelet count is a sign of their massive consumption, possibly with similar consumption of fibrinogen and other coagulation factors [37].

Diagnostic potential of DD in AoD

Probably, the first paper about usefulness of DD in AoD was the one published by Weber et al. [38] in 2003. They analyzed 24 AoD patients: 12 with type A and 12 patients with type B. DD concentration was abnormal (> 500 ng/mL in all of them, with the average result of 9,400 ng/mL. In a meta-analysis, plasma DD for AoD has the high sensitivity (0.97; 95% CI, 0.94–0.99), but low specificity (0.56; 95% CI, 0.51–0.60) [39]. In a large cohort of patients with suspected AoD, ADD risk score 0 or 1 plus a negative DD accurately and efficiently ruled out AoD [40]. DD is better in the detection of AoD compared to the smooth myosin heavy chain and soluble elastin fragments, because of its longer half-life and higher sensitivity [30].

AoD patients with stroke had a significantly higher DD as compared with any other stroke subtypes and their B-type natriuretic peptide (BNP) concentrations were significantly lower in comparison to patients with cardioembolic stroke. Moreover, DD:BNP ratio was significantly higher in AoD patients with stroke than in patients with any other stroke subtypes (within 6 h of onset, sensitivity was 81.8% and specificity 96.4%) [41]. In a study using DD as a screening tool in patients not highly suspected of having AoD, the clinical picture and physician's judgment remained principal, despite a well-known high sensitivity of DD for AoD [42]. Although DD by itself is not able to discriminate AoD from PTE, if DD is very high, it may demand an urgent CT, aiming to detect AoD or PTE [34]. In general, raised DD concentrations, caused by tissue injury, show a trend for gradual decline within the first few days following the event [38].

Cut-off values of DD for AoD

Different DD cut-offs were used as upper normal limit in the medical literature (100–900 ng/mL) [39]. The lower the cut-off, the higher the sensitivity and the lower the specificity, but even with the cut-off concentration of 400 ng/mL, the sensitivity of DD for aortic intramural hematoma (IMH) was only 90% and insufficient to rule out the diagnosis of acute aortic syndrome (AAS), particularly if there is high clinical suspicion [43]. IRAD-Bio published 96.6% sensitivity and 46.6% specificity using a 500 ng/ml DD cut-off during the first day of symptom onset [34]. The specificity increased to 73% when the cutoff value was 626 ng/mL [30]. The largest study on the use of DD in AoD showed its marked elevation within 6 hours of the clinical event: 3,213 ± 1,465 ng/mL in type A and 3,574 ± 1,430 ng/mL in type B versus 2,452 ± 1,891 ng/mL in pulmonary thromboendarterectomy (PTE) patients, 1,459 ± 1,650 ng/mL in patients with myocardial infarction, and 760 ± 974 ng/mL in patients with angina pectoris. With the cut-off level of 500 ng/mL, within the first 6 h, sensitivity was 95.7% and specificity 61.3%. Importantly, AoD can be ruled in if DD concentration is > 1,600 ng/mL during the initial 6 hours [32].

The same 500 ng/mL DD cut-off value is also used for PTE, which is beneficial for simplicity and cost-effectiveness: with a single blood test, one can rule out AoD and PTE in patients at low risk [33]. DD is useful in AoD up to 10 days after the onset (with a cut-off of 1,600 ng/ml sensitivity was 95.3%). It is important that DD concentrations may be measured in 2 different units: DD unit (DDU) or fibrinogen equivalent unit (FEU). One DDU is equivalent to 2 FEU [44, 45]. Therefore, DD units should be reported in publications and different units (DDU or FEU) can not be used interchangeably.

False negatives DD in AoD

False negative results (when DD is normal in an AoD patient) were most likely in patients: 1) under 70 years old, with intromural hemorrhage (IMH), with thrombosed false lumen, and with shorter dissections (in length) [40, 44, 46, 47]. DD concentration may be within the normal limits in young patients with short dissection and a thrombosed false lumen, without penetrating atherosclerotic ulcer (PAU) [30]. The DD concentration < 100 ng/mL can exclude AoD, but not IMH or PAU [48, 49].

Prognostic potential and correlations of DD in AoD

In the study of Weber et al. [38] DD was not higher in AoD patients who died in hospital. To the contrary, in the study of Ohlmann et al. [43], the independent markers of in-hospital mortality were: pericardial effusion [odds ratio (OR), 6.80; CI, 1.87–27.60), DD > 5,200 ng/mL (OR, 5.38; CI, 1.27–30.87), and female gender (OR, 4.96; CI, 1.39–19.95) [43]. Serum DD ≥ 10,000 ng/mL resulted in the sensitivity of 61.5% and specificity of 84.1% for the prediction of in-hospital death [50]. DD was higher in patients with in-hospital death [51]. This is a consequence at least in a part of a positive correlation between the extent of AoD and DD concentration [30, 51, 52]. The average DD increased from DeBakey class II AoD, over class III, to class I AoD ($r = 0.63$; $p < 0.01$) [51]. DD decreased with longer duration from the onset of symptoms, allowing the differentiation of acute from chronic AoD [30, 52, 53].

DD values are lower in AoD patients with thrombosed false lumen in comparison to patients with partially thrombosed one (which predicts poor outcome) [30, 33, 34, 54]. Ohlmann et al. [43] suggested that DD increased proportionally to the surface of contact between the bloodstream and thrombogenic components of the patent false lumen, which triggers the coagulation cascade and thereby raises DD level. DD concentration can be normal in patients with IMH [30, 33, 43]. Re-elevation of DD is unfavorable. During in-hospital treatment of AoD, the coagulation cascade could be activated by aortic injury, prolonged bed rest, and hemoconcentration, due to increased vascular permeability, as the result of inflammatory response. Serial measurements of DD can be used for early detection of re-AoD or venous thromboembolism (VTE) during in-hospital management of Stanford type B AoD [53].

Final remarks on DD in AoD

DD may be used in the same fashion in AoD as in PTE: negative result renders the presence of the disease very unlikely [38]. DD to rule out AoD is most likely to be useful in individuals with low to moderate risk of AoD. Excluding patients from definitive imaging studies due to normal plasma DD may be unwise, especially in high-risk patients (those with Marfan syndrome or uncontrolled AHT) [39]. Current evidence supports routine measurement of DD for the suspected acute AoD: if DD is < 100 ng/mL, this excludes acute AoD in all cases with a low likelihood of disease [55].

DD < 500 ng/mL (this cut-off has been used to rule out PTE in patients with low likelihood), can almost exclude AoD during the first day of presentation (negative likelihood ratio of 0.07). At higher levels in patients presenting within 6 h of symptoms onset, DD may be used to rule in AoD [34]. Neema [56] suggested that the absence of both increased DD and ECG changes is considered specific to rule out AoD.

CRP in AoD

CRP is mostly synthesized in the liver by stimulation of many cytokines, particularly by interleukin (IL)-6 [30]. In acute inflammation (due to infection, trauma, etc.), CRP levels increase promptly within 4–6 h, and reaches its maximum concentration at 36–50 h, and then diminish as the inflammation response decreases [33, 57]. CRP levels are significantly higher in both acute AoD and chronic aortic aneurysm.

Mechanisms of CRP elevation in AoD

Increased levels of inflammatory markers [IL-6, CRP, tumor necrosis factor alpha (TNF-α) in plasma] and changes in MMP-9 are significantly associated with AoD, suggesting

the role for inflammatory process in the AoD pathogenesis [57]. CRP rise is believed to originate from systemic stress with systemic acute-phase response, and local aortic inflammatory processes [52, 58, 59]. CRP levels depend greatly on the time elapsed from the onset of symptoms. Plasma CRP concentrations are higher in patients with aortic aneurysms in comparison with controls, but the average CRP levels were similar in patients with AoD and chronic aortic aneurysms. On the other hand, the white blood cell (WBC) count was only elevated in AoD in at least two studies [52]. CRP concentrations are increased in patients with asymptomatic abdominal aortic aneurysm (AAA), and they correlate with the size of AAA.

Diagnostic potential of CRP in AoD

CRP level is seldom prominent within the first hours after AoD onset. Therefore, CRP is not useful to diagnose acute AoD. Moreover, CRP is not appropriate for the discrimination between acute AoD and chronic aneurysm, because in some studies CRP levels were found to similarly increase in both diseases [30]. Newer data demonstrate increased CRP values in acute AoD compared with chronic AoD and AHT, as well as with healthy subjects (13.48 ± 3.74 mg/L *vs* 4.12 ± 2.99 mg/L, *vs* 1.62 ± 0.65 mg/L, and 1.12 ± 0.35 mg/L, respectively; $p < 0.001$) [57].

Prognostic potential of CRP in AoD

In a study of Schillinger et al. [58] higher CRP concentrations predict higher mortality. Mortality hazard ratios in AoD patients with CRP levels from 2nd to 4th quartiles *versus* the first quartile were 0.7, 1.8, and 2.6, respectively. CRP concentration > 63.0 mg/L predicted high short-term mortality. The admission CRP > 68.0 mg/L in AoD and/or aortic aneurysm predicted a higher mortality rate both in operated and conservatively treated patients [60]. In type III AoD, a peak CRP value over 150 mg/L was a marker of a high risk for oxygenation impairment and adverse outcome [61]. Higher maximal CRP concentrations were found in AoD patients with adverse outcome (251 ± 123 mg/L), as compared to patients without them (161 ± 74 mg/L, $p = 0.010$) [61]. The highest quartile of the peak CRP level is associated with higher incidence of adverse long-term events in type B AoD. Since CRP is a nonspecific marker of inflammation, it reveals not only AoD itself, but complications (e.g., pneumonia), too [32, 62, 63].

Okina et al. [63] studied 240 AoD patients and found that CRP values at admission most often were negative (< 5.0 mg/L) in the uneventful subgroup. In the event-free subgroup, CRP demonstrated the peak on the 4th day after AoD onset (4.2 ± 3.9 days, the average CRP value 137 mg/L), then gradually decreased to the average of 46 mg/L 4 weeks later. On the other hand, in the subgroup with clinical events, there was prolonged CRP elevation and/or re-elevation, peak CRP was significantly delayed (time to the maximum CRP: 8.1 ± 5.1 days, $p < 0.05$ in comparison with the event-free subgroup). Namely, CRP continued to raise after the 4th day, and subsequently adverse cardiac events occurred in these patients. Thus, persistently elevated CRP may be a sign of inflammation and AoD progression, imposing the need for (repeated) application of magnetic resonance imaging (MRI) or computed tomography (CT), improved blood pressure (BP) control and/or an early cardiosurgery [63].

In analysis of 180 patients with aortic IMH, the maximal CRP was found 4 days after the onset of symptoms (124 ± 63 mg/L). Those with raised CRP concentration (≥ 72 mg/L) at 2 weeks had significantly more adverse aortic events ($p < 0.001$) [64]. Suzuki et al. [32] suggest that maximal CRP concentration reflects the degree of inflammatory reaction and the damage of the aortic wall [32]. One study in acute AoD showed higher CRP in patients with longer hospitalization, due to complications [57]. In chronic type B AoD increased CRP concentration pointed to adverse outcome, particularly in patients on conservative treatment in comparison with the operated ones [58]. CRP was suggested for possible monitoring of the course of false lumen thrombosis [32, 65] (Table 1).

Correlations of CRP in AoD

Plasma CRP levels decrease significantly when the time from the onset of acute AoD to hospitalization increase ($p = 0.013$) [57]. CRP value is usually a low level within 24 h from the first symptoms. The peak of CRP level in the study of

Table 1

Some of contemporary biomarkers for aortic dissection (AoD) patients

Biomarker	Origin of biomarker increase	Main purpose in AoD currently	Relevant references
DD	High DD is a consequence of fibrinolysis of hematoma in the aortic media	To help excluding AoD in low risk patients	34, 38–41, 66
CRP	CRP rise results from systemic stress and local aortic inflammatory processes	Prognostication	32, 57, 58, 61, 63–65
cTn	Elevated cTn concentration is due to acute myocardial infarction type II of type one, or due to renal failure, stroke, etc.	Indicator of possible coronary artery affection by AoD	9, 16, 21, 67

DD – D dimer; CRP-C – reactive protein; cTn – cardiac troponin.

Sugano et al. [61] was observed at 3 ± 1 days. In AoD, the injury of the vessel wall induces inflammatory response, including numerous humoral factors, capable of activating not only endothelium in lungs, but extensive resident neutrophil pool, as well. In AoD patients, maximal CRP concentration ≥ 150 mg/L was an independent predictor of forthcoming lung injury (relative risk = 12.6, $p = 0.001$) [61].

Final remarks on CRP in AoD

CRP does not increase within the first day from the AoD symptoms onset, and therefore CRP is not a valuable biomarker for diagnostic purposes. Markedly elevated CRP during in-hospital stay results probably either from extensive aortic damage or from significant comorbidity, making CRP suitable candidate for valid prognostic marker in AoD.

Conclusion

Elevated troponin concentration does not exclude AoD. Five categories of diseases/clinical situations are probable causes of troponin raise in patients with AoD. Laboratories made a tremendous progress in troponin estimation, many scientists proved its usefulness for diagnostic purposes and prognostication, and it is time for all of us to optimize troponin interpretation in everyday work.

DD is now the most widely available and reliable biomarker for AoD, the only biomarker for AoD tending to become the gold standard. DD may be used in the same fashion in AoD as in PTE: negative result renders the presence of the disease very unlikely.

CRP is not useful for the AoD diagnosis, but has a potential as a prognostic marker. More investigation is needed to confirm this and to find optimal cut-off concentration and adequate time for the measurement, since CRP concentration depends a lot on time (in days) from the AoD onset.

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