Determinants of troponin T and I elevation in old patients without acute coronary syndrome

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Abstract

Cardiac troponins T and I (cTnT and cTnI) are the main markers of acute myocardial cell damage and then of Acute Coronary Syndrome (ACS) if associated with compatible symptoms. Although their cardio-specificity, the cTn may be increased in various clinical conditions but only few recent studies have reported their trends with age. This is a single-center retrospective observational study on two groups of adults consecutive patients, with age ≥65 years, admitted to the Emergency Department of the Sant'Orsola-Malpighi Hospital of Bologna, Italy, with chest pain as chief complaint. In the first group was dosed cTnT (N=617), in the second group cTnI (N=569). The patients with final ACS's diagnosis (N=255) or an incomplete report of blood tests (N=17) were excluded. The definitive database included 471 patients in the first group and 443 in the second one. The observed differences between clinical parameters, patients with cTnT≤14ng/L and those with cTnT>14ng/L (N=207, 44%) are: older age, greater prevalence of diabetes, lower values of Hb e ALT, higher values of white blood cells, INR, glycemia, urea, creatinine, BNP e PCR. In multiple logistics regression (N=333) only 4 variables resulted independently associated to cTnT increase: age (P<0.0001), PCR (P=0.01), creatinine (P=0.02) and urea (P=0.04), R^2=0.30. The differences between patients with cTnI≤40ng/L and those with cTnI>40ng/L (N=46, 10%) are: older age, Hb values equal and higher values of white blood cells, INR, glycemia, urea, creatinine, total bilirubin, AST, BNP e PCR. In multiple logistics regression (N=259) the only 4 variables independently associated to increase of cTnI are age (P<0.0001), glycemia (P=0.004), PCR (P=0.01) and white blood cells (P=0.02), R^2=0.17. Furthermore, the number of patients with high level of cTn significantly increase by age (cTnT: 65-74 years 22.2%, 75-84 years 48.5%, ≥85 years 79.5%; cTnI: 65-74 years 4.3%, 75-84 years 8.1%, ≥85 years 22.5%, P<0.0001). In our study, cTnI showed fewer false positives than cTnT and seems to be less influenced by kidney failure. Furthermore, the acute phase of inflammation was associated with the rise of troponins. High cTn values were found in elderly subjects, without acute coronary syndromes, particularly cTnT. Then the age seems to be the most important factor related to this high-elevated troponin levels.

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Introduction

According to the guidelines of the European Society of Cardiology, troponin dosage is recommended as the first and unique biomarker to be performed in patients with symptoms of myocardial infarction.[1] Therefore, Cardiac Troponin T (cTnT) and I (cTnI) play a key role in the clinical diagnosis of acute coronary syndrome (ACS). A high value of cardiac troponin is indicative of myocardial damage independently to the mechanism of injury; thus, the problem of increase of these values independently from myocardial necrosis is recurrent. Indeed there are some conditions other than ACS and myocardial direct damage which show an increase of cardiac troponin, due to non-ischemic myocardial damage (age, heart failure, diabetes mellitus, kidney failure, coronary heart disease stable) or as anemia and hypertension.

In particular, in literature many studies have shown that troponin may increase with age.[2,3] However few studies have investigated if the correlation between elevation of this marker and age is statistically significant and how troponin increases with age.[2,3]

Not many studies have analyzed the troponin increase in unselected hospitalized patients, and also the diagnostic capacity of troponin I and T has never been compared. This latter may be significant in distinguishing patients with ACS from the ones with other diseases. Furthermore, this evaluation could avoid unnecessary and potentially dangerous diagnostic tools and treatments, together with a possible delay in recognizing and treating the clinical conditions underlying chest pain.

The purposes of this study were: i) to describe significant associations between troponin and other variables detected by blood

tests in two groups of patients whose presented to Emergency Department (ED) for *chest pain*, and come out from hospital with a diagnosis different from ACS; ii) to determine if there is a correlation between the two different troponin T and I and the age.

Materials and Methods

Patients

In this retrospective study all patients with age ≥65 years admitted to the ED of the S. Orsola-Malpighi Hospital of Bologna, Italy, with *chest pain*/*epigastralgia*/*angor*/*toracalgia* chief complaint, were enrolled. In this cohort two groups were identified on basis of type of dosed troponin (T or I). The first group included 617 patients admitted to ED from 1 January 2014 to 30 June 2014. In this one cTnT was dosed. 134 of these were excluded because of their final diagnosis was ACS; 12 were excluded for incomplete blood tests report performed in ED. Finally this group included 471 patients with a final diagnosis at discharge from Emergency Department or Hospital other than ACS. The second group included 569 patients from 1 January 2016 to 30 June 2016, for which cTnI was dosed. 121 patients of this second group were excluded, because they were discharged with final diagnosis of ACS; 5 were excluded due to incompleteness blood tests report performed in ED. Therefore, this second group finally included 443 patients with a final diagnosis at discharge from Emergency Department or Hospital different from ACS.

Variables of the study

The anamnestic and laboratory data have been collected by the archive of ED records. All patients with ACS as diagnosis of resignation from ED were excluded from the cohort.

Laboratory analyses

According with Casagranda *et al*.,[4] cTnT is measured by the only analytical procedure available in Italy. This feature allows having a single reference value as cut-off even if used on different platforms.The assay is the *Troponin T hs Elecsys*, which employs two monoclonal antibodies specifically directed against human cardiac troponin. The antibodies recognize two epitopes (amino acid positions 125-131 and 136-147), located in the central part of the troponin T cardiac protein, which is made up of 288 amino acids. This test is also used in the Central Laboratory of Sant'Orsola-Malpighi Hospital. The cTnI, on the other hand, can be measured by different analytical procedures and this leads to several cut-offs among themselves. Particularly, in the Central Laboratory of the Sant'Orsola-Malpighi University Hospital, is used the *Access AccuTnI Beckman-Coulter*. This is a chemiluminescence immunoassay using paramagnetic particles for the quantitative determination of contemporary sensitivity of serum and plasma human troponin I. The cut off used for both methods are the 99 percentile.

Statistical analysis

Variables were expressed as mean ± SEM or median/range as appropriate, according to their distribution. As previously described, the cohort was divided in two groups depending on the dosed troponin. In both groups were examined the patients with normal troponins (cTnT<14 ng/L and cTnI<40 ng/L) and those with high troponins in absence of Acute Coronary Syndrome (cTnT>14 ng/L and cTnI> 40 ng/L). Differences between groups were evaluated by unpaired or paired Student's t-test for unmatched data or with Mann-Whitney's tests as appropriate. The differences between percentages were tested with the chi square. To detect the independent association between the increase of troponin and the absence of acute coronary heart disease, a multiple logistic regression and back elimination procedure were used. A P-value<0.05 was considered statistically significant.

Results

Table 1 illustrates the factors considered in the group of

Table 1. Factors associated with Troponin T elevation.

	N	Normal (≤14 ng/L)	N	High (>14 ng/L)	P
Total Patients	264		207		
Age	264	74.1 ± 6.5	207	80.9 ± 7.2	<0.0001
Male	121	45.80 %	104	50.20 %	0.34
Diabetes	38	14.40 %	48	23.20 %	0.01
WBC (109/L)	263	7.09 [5.93-8.51]	206	7.63 [6.05-9.50]	0.05
Haemoglobin (g/dL)	263	13.6 ± 1.6	206	12.5 ± 2.0	<0.0001
MCV (fL)	263	89.4 [86.6-92.3]	206	90.5 [87.0-93.4]	0.08
Platelet (10^9/L)	259	210 [180-255]	202	220 [183-254]	0.38
MPV (fL)	259	7.7 [7.2-8.2]	202	7.7 [7.3-8.2]	0.16
INR	247	1.07 [1.02-1.12]	198	1.12 [1.05-1.39]	<0.0001
Glucose (mg/dL)	246	105 [94-127]	192	114 [101-146]	0.0001
Urea (mg/dL)	252	40 [34-48]	201	51 [39-71]	<0.0001
Creatinine (mg/dL)	256	0.91 [0.76-1.07]	205	1.11 [0.92-1.49]	<0.0001
Total Bilirubin (mg/dL)	194	0.41 [0.31-0.60]	160	0.46 [0.34-0.67]	0.07
AST (U/L)	248	20 [17-25]	194	19 [16-26]	0.53
ALT (U/L)	240	18 [14-23]	197	15 [11-21]	0.0001
CK (U/L)	93	79 [60-110]	83	74 [57-117]	0.37
BNP (pg/mL)	41	310 [130-598]	45	1387 [573-4182]	<0.0001
PCR (mg/dL)	218	0.23 [0.10-0.68]	176	0.43 [0.13-1.45]	<0.0004

N, number of patients; WBC, white blood cells; MCV, mean corpuscolar volume; MPV, mean platelet volume; INR, international normal ratio; AST, Aspartate aminotrasferase; ALT, Alanine aminotransferase; CK, creatinine kinase; BNP, brain natriuretic peptide; PCR, Protein c reactive.

patients with normal cTnT (≤14 ng/L) and in patients with high cTnT (>14 ng/L) in the absence of Acute Coronary Syndrome.

As showed in Table 1, several factors are significantly associated with cTnT elevation: age, white blood cells, INR, glucose, diabetes prevalence, urea, creatinine, BNP and PCR were higher than in normal level cTnT group; moreover, ALT and hemoglobin were lower in the group with high level of cTnT. Sex, platelet count and their average volume are not statistically different between two groups. A series of multiple logistic regressions with the back-elimination procedure of non-significant variables was performed to identify which of the considered factors were independently associated to the elevation of cTnT. The initial model included the 10 variables significantly associated with elevation of cTnT, as indicated in Table 1. BNP has been excluded in multivariate analysis, although significantly correlated, because it was available only in a few cases. Only the patients where all ten variables were available (N=333) contributed to the model.

Table 2 lists the variables resulted significantly associated to cTnT elevation *i.e.* age, PCR, creatinine and urea. This model explains 30% of the cTnT increase (R^2=0.30, P<0.0001) and correctly identifies 77% of the values.

Table 3 illustrates factors considered in normal (≤40 ng/L) and high (>40 ng/L) patients without ACS: some of these are significantly associated with the elevation of the biomarker. As indicated, several factors are significantly associated to the increase of cTnI: age, white blood cells, INR, glucose, urea, creatinine, AST; total bilirubin, BNP and PCR was higher than in the group with normal cTnI level; moreover hemoglobin was statistically lower in the group with high level of cTnI. Sex, platelet count and their average volume are statistically not different between the two groups. A series of multiple logistic regressions with the back-elimination procedure of non-significant variables was performed to identify which of the considered factors was independently associated to the increase of cTnI. The initial model included the 10 variables in Table 3 associated to elevation of cTnI. BNP was excluded from the multivariate analysis, although significantly correlated, because it was available only in a few case than other variables. Only the patients where all variables were available (N=259) contributed to the model.

Table 4 lists the variables that were significantly associated with elevation of troponin I at the end of the procedure: age, blood glucose, PCR, and white blood cells. This model explains 17% of the elevation of troponin I (R^2=0.17, P<0.0001) and also allows to correctly identify 92% of the values.

Table 5 shows the comparison between the group (N=471) where the troponin T was dosed and the group (N=443) where troponin I was dosed. The comparison was used to determine the trend of the two troponin in correlation with the age of the patients.

Both groups were divided into three subgroups according to patients' age: i) 65-74 years old; ii) 75-84 years old; iii) over 85 years old. As indicated, in the three age subgroups of both populations there is a statistically significant increase of troponin (not due to Acute Coronary Syndrome). Lastly, the diagnosis of discharge from emergency unit of patients with chest pain enrolled in this study are: thoracic not-specific pain (46%), arrhythmias (7%), heart failure (5%), hypertensive crisis (4%), acute pulmonary embolism (3%), stable angina (2%), palpitations (2%), anemia (2%), respiratory failure (2%), aortic dissection (0.6%), BPCO exacerbations (0.4%), and other unknown causes (26%).

Table 2. Indipendent factors association with Troponin T elevation.

Variables	B coefficient	Standard error	P
Age	0.144	0.021	<0.0001
PCR	0.178	0.072	0.01
Creatinine	1.341	0.580	0.02
Urea	0.021	0.010	0.04
Interception	-13.946	1.736	<0.0001

Table 3. Factors associated with Troponin I elevation.

	N	Normal (≤40 ng/L)	N	High (>40 ng/L)	P
Total Patients	397		46		
Age	397	77.7 ± 8.0	46	83.6± 8.1	<0.0001
Male	200	50.30 %	28	60.90 %	0.18
Diabetes	62	15.60 %	8	17.30 %	0.75
WBC (109/L)	397	7.37 [6.05-8.86]	46	9.16 [7.55-11.79]	<0.0001
Haemoglobin (g/dL)	397	12.9± 2.0	46	12.1 ± 2.1	0.006
MCV (fL)	397	90.0 [86.0-93.0]	46	90.9 [86.0-93.0]	0.67
Platelet (10^9/L)	375	218 [177-268]	45	237 [155-302]	0.53
MPV (fL)	369	10.6 [9.7-11.5]	42	10.9 [9.6-11.8]	0.54
INR	371	1.10 [1.04-1.21]	41	1.18 [1.10-1.37]	0.002
Glucose (mg/dL)	367	110 [98-132]	42	132 [25-157]	0.01
Urea (mg/dL)	379	43 [34-56]	45	65 [44-98]	<0.0001
Creatinine (mg/dL)	387	0.96 [0.80-1.21]	46	1.14 [0.97-1.79]	0.0001
Total Bilirubin (mg/dL)	307	0.59[0.44-0.88]	36	0.77 [0.59-1.03]	0.005
AST (U/L)	382	21 [17-27]	44	24 [19-31]	0.04
ALT (U/L)	376	16 [11-21]	42	16 [12-24]	0.49
CK (U/L)	135	83 [57-112]	17	67 [47-111]	0.37
BNP (pg/mL)	69	179 [81-396]	17	674 [450-1393]	<0.0001
PCR (mg/dL)	330	0.33 [0.14-0.82]	37	2.01 [0.74-4.31]	<0.0001

Discussion

This study shows that elevation of troponin in patients without ACS is associated with clinical conditions in a statistically significant wise: these are age, PCR, creatinine and urea (cTnT); age, blood glucose, PCR, and white blood cells (cTnI). Thus, elevation of both troponins is highly related to age and to inflammation factors.

Inflammation factors

In clinical conditions with severe systemic inflammatory processes, such as sepsis, it can be there a decrease of systemic perfusion involving also myocardial (a shock state) resulting in cTn release.[5] However, myocardial injury can occur even in less serious inflammatory conditions.

Indeed, despite a certain causal relationship has not yet been established, it has been suggested that some inflammatory chemical mediators, in particular some cytokines such as α tumor necrosis factor (TNFα) and interleukin 6 (IL6), may have a toxic effects on myocardium.[6,7] It has also been suggested that these mediators cause an *in situ* cTn fragmentation and an increase in permeability of the cell membranes: cTn fragments would be easily released in circles.[8] In our retrospective study, troponin is significantly associated not only with PCR but also with other variables influenced by inflammatory processes: urea, blood glucose and white blood cells.

Considering the crucial role played by inflammatory processes in determining plaque stability, some studies have focused on the fact that plasma inflammatory markers, in particular PCR, may contribute to identify necrotic damage during myocardial infarction. Thereby the detection of PCR may improve the risk stratification identifying the groups of patients who may benefit from rapid treatment.[9-13]

Chronic renal failure

Other studies had shown that persistent high levels of cTn are found in patients with chronic renal failure.[14-16] This data does not seem likely to depend from kidney excretion deficiency; rather, this increase is associated with the presence in these patients of small areas of clinically silent myocardial necrosis.[6] In our study, creatinine is associated only with elevation of troponin T, while there are not associations with troponin I.

This data, previous known in the literature,[14] was also reported in the study of Vestergaard *et al*.[17] Therefore, a higher specificity of troponin I for the diagnosis of ACS also occurs in the presence of chronic renal failure. However, this evidence should be confirmed by further studies.

Age

A greater sensitivity of the test necessarily associates with a lower specificity for acute myocardial infarction.

Contemporary sensitive assay for cTn, for example, may be above 99% in many pathological states other than acute myocardial infarction. This result appears larger than in non-ultrasensitive tests. In this regard, a problem that we detected was to define the reference *healthy population*. In fact, the cut-off of the 99th percentile varies according to the demographic characteristics of the population and for the exclusion of subjects with heart disease.

The European Society of Cardiology Cardiac Study Group has specified that the reference population should be made up of at least 300 apparently healthy people, of both sexes, and distributed according to age classes.[18] Additionally, these subjects should be negative to a maximum stress test and have a cardiac function within the limits of the standard, evaluated by a cardiac imaging test. Unfortunately, these recommendations are difficult to apply mainly due to the high number of required sample.

In literature is widely demonstrated that the cTn concentrations are higher in males than females and that progressively increase with age.[19,20]

The PIVUS (Perspective Study of the Vasculature in Uppsala Seniors) study, applying more stringent criteria to select the healthy population and exclude cardiopathic patients (*i.e*. absence of left ventricular hypertrophy, electrocardiogram alteration or increased proBNP values) reduced the cut-off (99th percentile) of hs-cTnI from 44 ng/L to 28 ng/L.[20]

Other some literature data, however, suggest that the 99th percentile should be subdivided into subgroups, for example, for sex or age.[20] Some studies on the general population, with no considered cardiovascular disease, had shown an elevation of high-sensitivity troponin in a higher percentage in elderly subjects.[21,22] Our study has shown that elevation of troponins is strongly and significantly influenced by the age of patients. In fact, as the age increases, the percentage of patients with high troponin in the absence of ACS is increased.

In particular, troponin T was elevated (>14 ng/L) in approximately 80% of patients over 85 years of age.

The study of Mueller-Hennessen *et al*.[23] has also highlighted this trend of troponin T. The authors proposed a higher cut-off rate (28 ng/L) for patients >65 years of age, which reduced the percentage of patients with final ACS diagnosis. In addition, the new cut-off has allowed to reclassify the risk of death at 1 month and 3 months. This study also showed that sex does not influence the cut-

Table 4. Indipendent factors association with the positivity of Troponin I.

Variables	B coefficient	Standard error	P
Age	0.140	0.036	0.0001
Glucose	0.012	0.004	0.004
PCR	0.128	0.051	0.01
WBC	0.167	0.072	0.02
Interception	-17.024	3.283	<0.0001

Table 5. Comparison of elevation of Troponin T and I in subgroups divided according to patients' age.

Age	N	cTnT>14 ng/L	%	P	N	cTnI>40 ng/L	%	P
65-74	185	41	22.2		161	7	4.3	
75-84	198	96	48.5		171	14	8.1	
>85	88	70	79.5		111	25	22.5	
				<0.0001				<0.0001

cTnT, Troponin T; cTnI, Troponin I.

off of troponin sensitivity, as confirmed by our study. Instead other recently published papers showed difference gender related in cTn normal level, though real clinical implication of these data are also under investigation.[24] Moreover, in our study the troponin I is less influenced by age than cTnT, and it proves more specific. In fact, cTnI was elevated (>40 ng/L) in approximately 22% of patients over 85 years of age.

Limitations

This is a retrospective study and, like all retrospective studies, may have a bias selection. For example, since the main focus was on troponin alterations in patients over sixty-five, we did not consider the entire population of patients in ED for chest pain, but we only selected the patients in the age range of our interest. Actually, the gold standard for the identification of ACS is the identification of risk-prone at the triage of ED, the execution of an ECG and the troponin dosage.

In addition, not all patients over sixty-five years who came to ED for chest pain have not been enrolled, due to absence of troponin testing. A further limitation arises from the non-complete collection of patients' anamnestic data: in fact, not always we obtained reliable data on the presence or absence of pathologies such as hypertension and tobacco habit. Moreover, the methods used for the measurement of cTnI are not high-sensitivity immunoassay as suggested by the most recent international guidelines:[25] this could be performed in further studies.

Finally, the available data allowed us to identify some determinants of not specific increase for both troponins, but obviously other determinants, that have not been actively sought and recorded, are possible (as reported in previous studies).

Conclusions

This comparison study between cTnT and cTnI in non-ACS patients with chest pain has shown the following: i) cTnI was confirmed more specific than cTnT. This observation justified the current trend to replace cTnT with cTnI in the diagnosis of myocardial damage; ii) This more specificity is largely supported by the fact that cTnI, unlike cTnT, seems to be lesser or no affected by kidney failure; iii) Inflammation, and more generally its acute phase, are conditions that contribute to the elevation of both troponin; iv) Finally, age in itself is an important determinant of the values of both troponin. Relatively high values can be found in very old subjects, regardless of the presence of acute coronary heart disease. Perhaps, this is the most important factor to keep in mind when attempting to evaluate individual elevated levels of troponin; although the diagnosis of myocardial infarction does not depend on the absolute value of troponin, but its variation over time. More largest and prospective studies are needed to clarify every conclusion.

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