

Clinical Significance of High Troponin T with Normal Creatine Kinase Levels on Ventricular Function in Acute Coronary Syndromes

ALFREDO C. PIOMBO^{MTSAC}, JORGE LAX^{MTSAC}, TOMÁS CIANCIULLI^{MTSAC}, JUAN A. GAGLIARDI^{MTSAC}, ELISABET ULMETE, FRANCISCO GADEA

Received: 11/11/2011

Accepted: 12/15/2011

Address for reprints:

Address for reprints:

Dr. Alfredo C. Piombo
Almirante Brown 240 - 2º Piso
(1155) CABA

e-mail: uco@intramed.net

SUMMARY

Background

The role of elevated troponins to predict changes on ventricular function in patients with high creatine kinase (CK) levels has been well established; yet, little is known about the clinical significance of high troponin levels with normal CK levels.

Objective

To analyze the relation between Troponin T (TnT) levels and global and regional left ventricular function in patients with acute coronary syndromes (ACS) with normal CK and CK-MB levels.

Material and Methods

We included patients admitted to the coronary care unit due to ACS within 48 hours from symptoms onset with elevated TnT levels measured by quantitative determination and normal CK and CK-MB levels. Biomarkers were measured at baseline, 24 and 48 hours. Left ventricular function was analyzed by two-dimensional echocardiography at admission and before discharge, and compared with the highest levels of the biomarkers. Ejection fraction, regional wall motion and global systolic longitudinal strain based on speckle-tracking technique were evaluated.

Results

Thirty patients with ACS were included. The highest median value of TnT was 0.13 µg/L (interquartile range, 0.07-0.25) measured 24 hours after admission. Left ventricular ejection fraction was 62.9% ± 10% at admission and 62.8% ± 10.3% before discharge. Wall motion index was 1.04 ± 0.1 and 1.03 ± 0.1, respectively. Systolic strain at admission was 14.93 ± 3 and improved before discharge 16.51 ± 3.33 (p = 0.0003).

Conclusions

High TnT values in ACS with normal CK levels do not modify global or regional left ventricular function assessed by conventional echocardiography. The evaluation of systolic strain using a more sensitive technique detects transient abnormalities. These findings might question the definition of acute myocardial infarction based on high troponin levels, considering that the classical definition is based on elevated CK values which are associated with changes in ventricular function.

REV ARGENT CARDIOL 2012;80:145-149.

Key words > Acute Coronary Syndrome - Myocardial Infarction - Ventricular Function - Troponin

Abbreviations >	CK Creatine Kinase	WHO World Health Organization
	CK-MB Fraction of Creatine Kinase MB	ACS Acute Coronary Syndrome
	LVEF Left Ventricular Ejection Fraction	TnT Troponin T
	AMI Acute Myocardial Infarction	LV Left Ventricle
	WMI Wall Motion Index	

BACKGROUND

Cardiovascular disease is the leading cause of current death in the world. Within it, acute myocardial infarction (AMI) is, in turn, the most important entity from the epidemiological point of view. Therefore,

the correct definition is the essential starting point for any kind of analysis you want to do about this entity. However, currently there is no single and incontrovertible definition. The classic definition of the World Health Organization (WHO) that dates

back 40 years, based on the known triad of symptoms, electrocardiogram and enzymatic dosage based on creatine kinase level (CK), (1, 2) in the year 2000 it was added a new definition, which the authors called 'universal definition of myocardial infarction,' (3) that even though, it takes into account symptoms, electrocardiogram and images of necrosis makes special emphasis on the presence of biomarkers (sine qua non condition), strongly recommending the use of cardiac troponins above that of CK.

The impact that AMI is defined according to classic criteria on ventricular function, it is an absolutely known fact and beyond dispute, (4, 5) observing different wall motion abnormalities and diverse degrees of decrease in left ventricle ejection fraction (LVEF).

However, the impact of AMI diagnosed by cardiac troponin elevation without concomitant elevation of CK and its MB fraction on ventricular function has been little studied, so that from this point of view it may represent a different event of the traditional AMI, which could have prognostic, epidemiological and, even medical-legal up worthy of consideration, implications.

In this study we have analyzed the impact on global and regional left ventricular function that have the acute coronary syndromes (ACS) with high troponin levels but with dosage of CK and CK-MB levels within normal limits. For this purpose we have used the traditional two-dimensional transthoracic echocardiography, as well as a newly developed method (two-dimensional echocardiographic strain) to measure longitudinal myocardial deformation of left ventricular (LV), high precision for the quantitative measurement of myocardial contractility. (6-8)

MATERIAL AND METHODS

They were included prospectively patients admitted to Coronary Care Unit who fulfilled the following criteria: 1) anginal pain at rest within 24 hours prior to admission, 2) high Troponin T (TnT) levels in the blood sample obtained with a minimum of 8 hours since the last pain (TnT μ 0.03 μ g/L), 3) levels of total CK and CK-MB within normal limits in the same sample.

Patients were excluded if they had any chance of having prior abnormalities of ventricular function or false-positive in the echocardiogram, namely: 1) prior myocardial infarction, 2) a history of CABG, 3) left bundle branch block, 4) atrial fibrillation, 5) cardiomyopathies or valvulopathies, 6) inadequate echocardiographic window and 7) chronic renal insufficiency with creatinine clearance below 30 ml / min (false positive for troponin).

In addition to the baseline samples, biomarkers were dosed (TnT, CK and CK-MB) at 24 and 48 hours of admission. Normal values for our laboratory were: TnT $<$ 0.03 μ / L, total CK $<$ 195 IU / L and CK-MB $<$ 25 IU / L.

A two-dimensional transthoracic echocardiography was carried out at 24-48 hours of admission and another before discharge (5^o to 7^o day). LVEF was measured by the biplane Simpson method, considering left ventricular dysfunction when it was less than 55% and was used a wall motion score ranging from 1 (normal) to 5. The wall motion index

(WMI) was obtained from the sum of scores divided by the 16 myocardial assessed segments.

It was measured the myocardial systolic longitudinal strain of the LV, calculating the speckle tracking from gray scale of the two-dimensional echocardiogram. Three apical views were obtained (2, 3 and 4 apical chambers) and LV was divided into 18 segments. Deformation (%) was defined as the physiological change between the length of end diastolic and end systolic. During this period, the deformation is negative as a result of shortening of myocardial fibers. It was used flow Doppler of LV outflow tract to mark the aortic opening and closing. In each of the apical views, they were placed three points within the endocardial edge: two in the baseline segments along the mitral annulus and one at the LV apex. These three points triggered an automatic process that analyzed the myocardial motion within a myocardial region of interest and measured systolic myocardial deformation in 6 segments in each view. The global systolic longitudinal peak strain was obtained with the mean of the analyzed segments. The result of the deformation of all segments was expressed at a bull's-eye format. Images were obtained with more than 50 pictures per second, adapting to 80% of heart rate.

Statistical Analysis

The description of the categorical variables is presented as numbers and percentages. Continuous variables are expressed as mean and standard deviation or as median and interquartile interval according to their distribution. Categorical variables were compared with contingency tables with chi-square test with Yates or Fisher's correction as it was appropriate. The comparison of continuous variables among groups was carried out using the t test, or nonparametric tests according to their distribution. The intragroup comparison was made with the t test for paired data.

Significance was set at P $<$ 0.05. All analyzes were undertaken using EpiInfo 2000 v3.5.1 and Statistix 7.0 software.

RESULTS

We included 30 patients, 19 men and 11 women, mean age 62.3 ± 10.3 years. Table 1 describes the baseline characteristics of the population. The baseline TnT (median, interquartile range 25% -75%) was 0.10 μ g / L (0.10 to 0.22), corresponding to 24 hours had a value of 0.13 μ g / L (0.07 to 0.25) and to 48 hours was 0.10 μ g / L (0.03 to 0.25) (p = ns).

Baseline CK was 121 IU / L (83-189), that of 24 hours was 128 IU / L (85-156) and that of 48 hours was 81 IU / L (58-105) (p = 0.001 .) As to the values of the MB fraction were: baseline of 18 IU / L (14-34), at 24 hours, 15 IU / L (11-22) and 48 hours, 15 IU / L (11-23) (p = ns).

The results are summarized in Table 2. The LVEF in the first echocardiogram was $62.9\% \pm 10\%$ and the predischage study was similar ($62.8\% \pm 10.3\%$) (p = ns). No patient had global LV systolic dysfunction. In a contemporary series of 30 patients admitted to our Coronary Unit with AMI diagnosed by high CK / CK-MB levels compared by sex and age, LVEF assessed by the same method was $43.4\% \pm 8\%$ (p $<$ 0.0001 between the two samples).

The WMI in the first echocardiogram was 1.04 ± 0.1 , with no reported changes in the second study (1.03 ± 0.1) ($p = ns$).

For its part, the global systolic longitudinal strain of LV at admission was 14.93 ± 3 and the predischarge echography was -16.51 ± 3.3 (Figure 1 shows the study in a patient.) A statistically significant improvement was perceived between both measurements ($p = 0.0003$).

During the hospital course, 7 patients developed recurrent angina, 6 were revascularized with coronary angioplasty and AMI or deaths were not registered (according to standard definition).

DISCUSSION

The AMI is a nosological entity of high worldwide prevalence and of a huge and indisputable epidemiological importance, becoming the leading cause of cardiovascular death in almost all regions of the world, regardless of level of development. However, it is a remarkable fact that its definition has varied in different historical moments and in the present two definitions coexist without either of them have been clearly imposed in medical practice.

In 2000, a board composed of the European Society of Cardiology and the American College of Cardiology proposed a new definition which was called ‘universal definition of myocardial infarction’ in order to replace the historic definition of WHO. (3) The new definition has as fundamental difference that it based its diagnosis on a sine qua non condition: the serum elevation of markers of necrosis and, even though accepting the use of CK / CK-MB for this purpose,

strongly recommend dosage of cardiac troponins for accurate diagnosis of AMI.

This is based on the fact that the troponins are undoubtedly more sensitive markers of necrosis of myocyte than CK. Thus, it is equaled the concept of myocardial infarction with necrosis regardless of the magnitude of this. Considering myocardial infarctions small amounts of necrosis, the result has been an increase in the number of diagnosed cases and a decreasing of its severity, expressed mainly in its mortality.

Thus, according to the adopted definition, there will be different prevalences, incidences, evolutions and even clinical intervention studies have different results according to the classical or new definition is applied. This has led, for example, to the high prevalence of clinical studies that demonstrate reduced incidence of heart attacks with different therapeutic interventions without a concomitant decrease in mortality. According to a data-base, more than half of patients present disagreements between the two definitions of AMI. Most of them only kept up the criteria of the new definition and 36% of these did

Table 1. Baseline characteristics of the population

Age (years)	62,3 ± 10,3
Sex male/female	19/11
Tobaccoism (%)	40
Hypertension (%)	86
Diabetes mellitus (%)	13
Dyslipidemia (%)	57
Obesity (%)	46
Prior aspirin (%)	50
Acute ECG changes (%)	90
ST segment elevation(%)	43
Isolated changes of the T wave (%)	47

Table 2. Measurements of ventricular function in the two echocardiographic studies

	LVEF	WMI	Strain
Eco 1	62,9 ± 10%	1,04 ± 0,1	14,93 ± 3
Eco 2	62,8 ± 10,3%	1,03 ± 0,1	16,51 ± 3,3
p	ns	ns	0,0003

LVEF: Left Ventricular Ejection Fraction. WMI:Wall Motion Index.

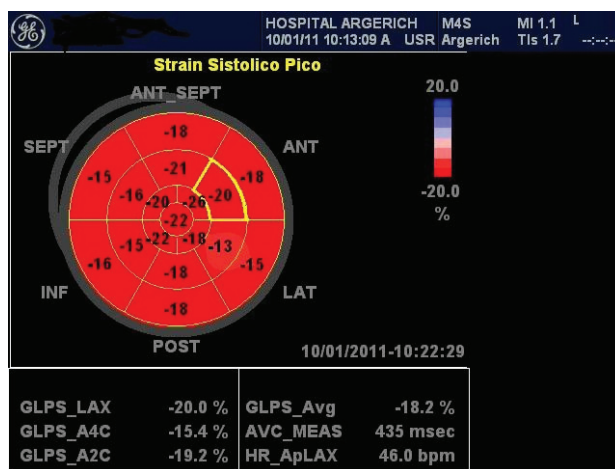
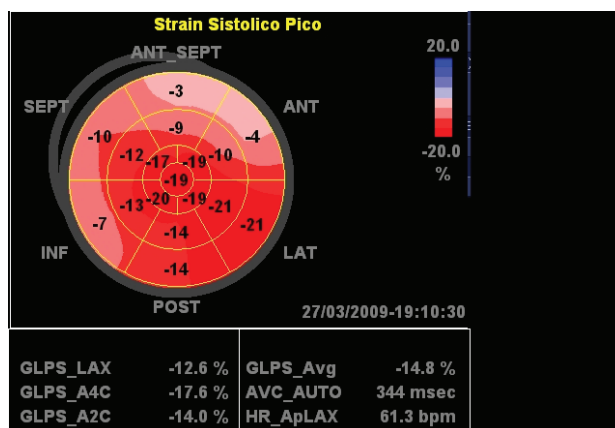


Fig. 1. Example of global systolic longitudinal strain in a patient. In the image above (first study) the value is -14.8%. In the lower one (second study) the value is 18.2%

not keep up any of the three classic criteria. (9)

The AMI has classically been characterized as an entity that has an impact, to varying degrees, on left ventricular function both regionally and globally. For example, in a study that measured ejection fraction by radionuclides within 5 days of the event, the mean was $52\% \pm 0.05\%$ in patients with uncomplicated infarction. In those with mild to moderate pump failure was $40\% \pm 0.05\%$, and in those who suffered pulmonary edema was $33\% \pm 0.07\%$. (4) In another study was observed that 95% of patients with diagnosed infarct by classic criteria had at least one area of akinesia in the left ventricular wall. (5)

This paper seeks to clarify what impact has on LV function the development of a defined AMI according to the 'universal definition' when there is no abnormal elevation of CK / CK-MB levels. In a work that nuclear magnetic resonance imaging was used with gadolinium injection, it was observed that the value of cardiac TnT at 96 hours of an AMI presents well correlation with infarct size, mainly when it evolves with supra slope of ST segment, (10) but CK / CK-MB levels were not measured, which have probably been increased taking into account that reported TnT values are markedly higher than those we have reported in patients without high CK levels.

In our population myocardial deformation values measured by echocardiographic strain are within a pathological range. One study that included 250 healthy volunteers found a value of systolic longitudinal strain of LV of $-18.6 \pm 0.1\%$. (11) Our measurements determine a reduced value of ventricular strain, although not reaching normal, significantly enhances days later, which may be interpreted as an improvement in contractility produced after acute myocardial ischemia. It is likely that the amount of necrosis was not large enough to show an impact on ventricular function estimated by conventional echocardiography, but by a more sensitive method such as speckle tracking.

Ryczek et.al observed a strong correlation between global and regional systolic longitudinal strain values with ejection fraction and left ventricular WMI. (12) However, ventricular function values reported in his work are much lower than ours (LVEF $43.1\% \pm 12\%$; WMI 1.68 ± 0.5). Further studies are necessary to understand better this relationship.

Although today is a known fact that there may be cardiac troponin elevation without the existence of necrosis, as for example in the extreme physical exercise (13, 14), the fact that are detected alterations of myocardial deformation with the used method seems to indicate that in our patients existed some degree of necrosis, probably small amount.

Our work is not intended to examine the prognostic value of isolated elevation of TnT in patients with ACS, but the results do not support the fact that this significantly affects ventricular function as typically occurs with high CK / CK-MB levels . Moreover,

the LVEF is undoubtedly one of the most powerful prognostic factors that have been described in patients with AMI. Consideration of small necrotic events such as AMI may be discussed and, in fact, the definition of AMI through the dosage of troponin is not universally accepted, which is associated with an overdiagnosis of heart attacks. (15) It has been reported that patients whose diagnosis is based solely on troponin elevation have better survival than those who keep up the traditional criteria. (16) Our study does not have statistical power to analyze the incidence of events, so these refer to information only.

Although the size of the included population is small and involves a limitation of the study, the strong consistency of the results seems unlikely to be different with the inclusion of more patients. By excluding all possible causes of impaired ventricular function different from the acute ischemic event, a population of high purity was studied in order to analyze the consequences of myocardial release of troponin.

CONCLUSIONS

We observed that patients with ACS evolving elevation in troponin T levels but normal CK / CK-MB levels, present a normal ventricular function, both from regional and global point of view, assessed by two-dimensional transthoracic echocardiographic. The use of more sophisticated and sensitive technology, such as echo-strain, allow us to identify that this group of patients often present alterations of myocardial deformation of LV that go unnoticed in conventional two-dimensional echocardiogram. The impact that this finding may have from the standpoint of prognosis is unknown, although it is observed in patients with preserved ventricular function seems reasonable that its prognostic value is relatively low. It will be necessary to conduct larger studies to clarify this issue.

RESUMEN

Repercusión de la elevación de troponina T con valores normales de creatinina sobre la función ventricular en los síndromes coronarios agudos

Introducción

La repercusión de la elevación de troponinas sobre la función ventricular izquierda en pacientes que no presentan aumento de creatinina (CK) por sobre el valor normal se conoce poco, a diferencia de lo que ocurre con los que presentan elevación de CK.

Objetivo

Analizar la relación entre los valores de troponina T (TnT) y la función ventricular izquierda global y regional en pacientes con síndromes coronarios agudos (SCA) sin elevación de CK total ni de CK-MB.

Material y métodos

Se estudiaron pacientes ingresados a Unidad Coronaria con SCA que durante las primeras 48 horas de evolución presentaron elevación de TnT medida cuantitativamente

con valores normales de CK y CK-MB. Se dosaron los biomarcadores en forma basal, a las 24 y a las 48 horas. Los valores más elevados se utilizaron para compararlos con la función ventricular izquierda medida con ecocardiografía bidimensional transtorácica efectuada al ingreso y antes del alta hospitalaria. Se evaluaron la fracción de eyección, la motilidad parietal regional y la deformación sistólica longitudinal global del ventrículo izquierdo, esta última mediante la técnica de speckle tracking.

Resultados

Se incluyeron 30 pacientes con SCA. La TnT más elevada (mediana, rango intercuartil) fue de 0,13 µg/L (0,07-0,25) correspondiente a las 24 horas del ingreso. La fracción de eyección ventricular izquierda en el primer ecocardiograma fue del 62,9% ± 10% y en el segundo, del 62,8% ± 10,3%. El índice de motilidad parietal fue de 1,04 ± 0,1 y de 1,03 ± 0,1. La deformación sistólica tuvo un valor de 14,93 ± 3 al ingreso, que mejoró antes del alta con un valor de 16,51 ± 3,33 (p = 0,0003).

Conclusión

La elevación de TnT en los SCA sin elevación concomitante de CK no altera la función ventricular global ni regional medida con metodologías convencionales. Utilizando un método más sensible que mide la deformación sistólica ventricular se detectan alteraciones transitorias. Esto podría cuestionar la definición de infarto agudo de miocardio basada en la elevación de troponinas, teniendo en cuenta que la definición clásica basada en la CK suele repercutir, en mayor o en menor grado, sobre la función ventricular.

Palabras clave > Síndrome coronario agudo - Infarto del miocardio - Función ventricular - Troponina

BIBLIOGRAPHY

- World Health Organization. WGoTEoIHDR. Report of the Fifth Working Group, Copenhagen. Report no. Eur 1971;(5):8201.
- World Health Organization, WHO MONICA Project. 1998-1999.
- Alpert JS, Thygesen K, Antman E, Bassand JP. The Joint European Society of Cardiology/American College of Cardiology Committee. Myocardial Infarction Redefined - A Consensus Document of The Joint European Society of Cardiology/American College of Cardiology Committee for the Redefinition of Myocardial Infarction. *J Am Coll Cardiol* 2000;36:959-69.
- Schelbert H, Henning H, Ashburn W, Verba J, Karliner J, O'Rourke R. Serial measurements of left ventricular ejection fraction by radionuclide angiography early and late after myocardial infarction. *Am J Cardiol* 1976;38:407-15.
- Rigo P, Murray M, Strauss H, Taylor D, Kelly D, Weisfeldt M, et al. Left ventricular function in acute myocardial infarction evaluated by gated scintigraphy. *Circulation* 1974;50:678-84.
- Leitman M, Lysiansky P, Sidenko S, Shir V, Peleg E, Binenbaum M, et al. Two-dimensional strain - a novel software for real-time quantitative echocardiographic assessment of myocardial function. *J Am Soc Echocardiogr* 2004;17:1021-9.
- Becker M, Bilke E, Kuhl H, Katoh M, Kramann R, Franke A, et al. Analysis of myocardial deformation based on pixel tracking in two dimensional echocardiographic images enables quantitative assessment of regional left ventricular function. *Heart* 2006;92:1102-8.
- Leitman M, Lysiansky M, Lysiansky P, Friedman Z, Tyomkin V, Fuchs T, et al. Circumferential and longitudinal strain in 3 myocardial layers in normal subjects and in patients with regional left ventricular dysfunction. *J Am Soc Echocardiogr* 2010;23:64-70.
- Nagurney J, Huang C, Heredia O, Sane S, Lewis S, Chang Y, et al. The new and old definitions of acute myocardial infarction: a data-based comparison. *Am J Emerg Med* 2008;26:523-31.
- Steen H, Giannitsis E, Futterer S, Merten C, Juenger C, Katus H. Cardiac troponin T at 96 hours after acute myocardial infarction correlates with infarct size and cardiac function. *J Am Coll Cardiol* 2006;48:2192-4.
- Marwick T, Leano R, Brown J, Sun J, Hoffmann R, Lysiansky P, et al. Myocardial strain measurement with 2-dimensional speckle-tracking echocardiography. Definition of normal range. *J Am Coll Cardiol* 2009;2:80-4.
- Ryzek R, Krzesinski P, Krzywicki P, Smurzynski P, Cwetsch A. Two-dimensional longitudinal strain for the assessment of the left ventricular systolic function as compared with conventional echocardiographic methods in patients with acute coronary syndromes. *Kardiologia Pol* 2011;69:357-62.
- Shave R, Baggish A, George K, Wood M, Scharhag J, Whyte G, et al. Exercise-induced cardiac troponin elevation. Evidence, mechanisms, and implications. *J Am Coll Cardiol* 2010;56:169-76.
- Turer A, Addo T, Martin J, Sabatine M, Lewis G, Gerszten R, et al. Myocardial ischemia induced by rapid atrial pacing causes troponin T release detectable by a highly sensitive assay. Insights from a coronary sinus sampling study. *J Am Coll Cardiol* 2011;57:2398-405.
- White H. Evolution of the definition of myocardial infarction: what are the implications of a new universal definition? *Heart* 2008;94:679-84.
- Roger V, Killian J, Weston S, Jaffe A, Kors J, Santrach P, et al. Redefinition of myocardial infarction. Prospective evaluation in the community. *Circulation* 2006;114:790-7.