High sensitive cardiac troponin T in the management of uncertain chest pain

José A. Giner-Caro [a], Luis Caballero [b], Teresa Casas-Pina [c], Francisco Pastor-Pérez [b], Iris P. Garrido-Bravo [b], Jesús Sanchez-Mas [b], Antonio Lax [b], Mariano Valdés [b], Domingo A. Pascual-Figal [b,*]

[a] Department of Cardiology, Los Arcos del Mar Menor General University Hospital, San Javier, Murcia, Spain
[b] Department of Cardiology, Virgen de la Arrixaca University Hospital and School of Medicine, University of Murcia, Murcia, Spain
[c] Department of Biochemistry, Virgen de la Arrixaca University Hospital, Murcia, Spain

ARTICLE INFO

Article history:
Received 28 April 2013
Accepted 4 May 2013
Available online XX

Keywords:
High-sensitive troponin T
Chest pain
Diagnosis

Chest pain is one of the most frequently reported complaints in emergency departments (EDs) (5–20%) [1] with a complex management that entails significant costs and inadequate therapeutic indications[2,3].

One of the major challenges is that posed by patients with an uncertain diagnosis, normal ECG, undetectable ischemia biochemical markers, and absence of previous heart disease. Conventional cardiac troponins (cTns) have been used as an essential tool, even though 40–60% of the patients with final diagnosis of acute coronary syndrome show undetectable cTn levels upon arrival at the ED [4]. Recently, a new high-sensitive assay to measure troponin T (hsTnT) has been validated and marketed [5]. These new assays have been found to improve performance for the early diagnosis of acute myocardial infarction (MI) [6,7]. The aim of this study was to assess the usefulness of a new hsTnT assay in the detection of coronary artery disease (CAD) in a population with chest pain with uncertain diagnosis.

Included were patients who consecutively presented to the ED, from December 2007 until December 2009 who met the following criteria: 1) chest pain suggestive of coronary origin; 2) normal ECG or non-diagnostic of acute ischemia 3) cardiac troponin T (cTnT) upon arrival under the detection limit (0.01 ng/ml); 4) absence of chronic renal failure; and 5) no known history of heart disease. A serum sample was saved for subsequent analytical determinations of hsTnT, measured by electrochemiluminescence immunoassay (Elecsys Troponin T hs) on an Elecsys 2010 analyzer (Roche Diagnostics GmbH, Germany) [5]. The patients were managed regardless of their hsTnT value, which was blind and obtained in the blood tests run after inclusion. Patients were followed-up for a year after discharge. The study protocol was approved by the local ethics committee and the informed consent was obtained from each patient. The authors certify they comply with the Principles of Ethical Publishing in the International Journal of Cardiology. Patients were classified according to pretest likelihood of CAD in compliance with the criteria for chest pain established by Diamond and Forrester [8], as well as the Geleijnse score.

The endpoint of the study was the objective diagnosis of CAD, defined as MI or unstable angina (UA). The means of continuous variables were compared using the T student test or the Mann–Whitney *U* test as appropriate. The predictive value of hsTnT was studied using the receiver-operating curve analysis (ROC). A multivariate analysis was performed to examine the variables associated with CAD, and the improved diagnosis associated with hsTnT use was studied by the integrated discrimination index (IDI) and the net reclassification index (NRI).

Of the total 103 patients recruited (age 60 ± 12 years; 64.1% males), 21 patients (20.4%) had a final diagnosis of CAD; 9 of them of MI and the other 12 of UA (Table 1). During the one year follow-up, no adverse event was recorded. Patients with CAD presented a higher score both in the Diamond and Forrester method and in Geleijnse score. The concentration of hsTnT on arrival was higher in the group with CAD (median 17 pg/ml vs. 5 pg/ml; $p < 0.001$) and in patients with MI compared with those with UA (mean 30 pg/ml vs. 12 pg/ml; $p = 0.025$).

The ROC analysis revealed an AUC of 0.80 (IC 95% 0.71–0.86) for CAD diagnosis and a higher diagnostic performance represented by the AUC for MI (0.88) than for UA (0.67). ROC analysis identified a hsTnT of 9 pg/ml as the optimal value for CAD diagnosis. However, on the sole basis of MI diagnosis, the optimal value was equal to the p99 of normality (13 pg/ml) (Table 2). The variables independently associated with the presence of CAD in the logistic regression multivariate analysis were a hsTnT >9 pg/ml (OR 11.72; CI 95% 2.91–47.23; $p = 0.001$), Geleijnse score (OR 1.41; CI 95% 1.06–1.88; $p = 0.017$), and diabetes mellitus (OR 3.68; CI 95% 1.04–13.09; $p = 0.044$). The addition of hsTnT to the model based exclusively on clinical parameters was associated with an

Table 1
Baseline characteristics of patients.

	Total	Coronary artery disease		
	(n = 103)	No (n = 82)	Yes (n = 21)	p
Age	60 ± 12	59 ± 12	62 ± 11	0.268
Sex (% male)	66 (64.1%)	49 (60%)	17 (81%)	0.071
Diabetes	33 (32%)	21 (26%)	12 (57%)	0.006
Hypertension	58 (56%)	41 (50%)	17 (81%)	0.019
Dyslipidemia	42 (41%)	30 (36%)	12 (57%)	0.124
Smoking	48 (47%)	36 (44%)	12 (57%)	0.278
Systolic blood pressure	143 ± 24	141 ± 23	153 ± 27	0.036
Diastolic blood pressure	82 ± 17	81 ± 18	83 ± 17	0.745
Heart rate (bpm)	75 ± 12	74 ± 12	78 ± 16	0.258
Effort-related chest pain	32 (31%)	22 (27%)	10 (48%)	0.076
Intensity				
Mild (1–3/10)	15 (15%)	14 (17%)	1 (5%)	0.044
Moderate(4–7/10)	68 (66%)	56 (68%)	12 (57%)	
Severe (8–10/10)	20 (19%)	12 (15%)	8 (38%)	
Duration (minutes)	73 ± 103	65 ± 97	100 ± 123	0.185
Response to NTG	22 (21%)	13 (16%)	9 (43%)	0.027
Diamond criteria				
0 (Non-anginal CP)	10 (10%)	10 (12%)	0 (0%)	
1 (Non-anginal CP)	31 (30%)	26 (32%)	5 (24%)	
2 (Atypical angina)	54 (52%)	43 (52%)	11 (52%)	0.009
3 (Typical angina)	8 (8%)	3 (4%)	5 (24%)	
Geleijnse score	9 ± 3	8 ± 3.	11 ± 3	0.001
Time from pain onset (minutes)	405 [190–543]	470 [199–552]	280 [163–532]	0.208
Creatinine (mg/dl)	0.9 ± 0.2	0.9 ± 0.2	1.0 ± 0.3	0.018
Hemoglobin (g/dl)	14. 4 ± 1.6	14.4 ± 1.5	14.3 ± 2.1	0.642
CK (U/l)	109 [72.50–151.25]	104 [53.40–147]	124 [38.40–192]	0.070
CKMB (U/l)	3.40 [2.50–4.53]	3.10 [2.42–4.30]	3.80 [2.04–6.07]	0.021
hsTnT (pg/ml)	6 [4–14]	5[3–9]	17 [10.50–42.50]	0.001
NT-proBNP (ng/l)	103 [35–197]	75 [35–192]	138 [37–271]	0.351

CK: creatine phosphate kinase; CKMB: creatine phosphate kinase MB fraction; NTG: Nitroglycerin; hsTnT: High-sensitive troponin T.

* Corresponding author at: Department of Cardiology, Virgen de la Arrixaca University Hospital and School of Medicine, University of Murcia, Ctra. Madrid-Cartagena s/n, 30120 Murcia, Spain. Tel./fax: +34 968 369662.
E-mail address: dpascual@um.es (D.A. Pascual-Figal).

Table 2
Area under the receiver-operating-characteristic curve (AUC), Sensitivity (Sn), specificity (Sp), negative (NPV) and positive (PPV) predictive values for hs-TnT cutoff points 9 pg/ml and 13 pg/ml in the diagnosis of coronary artery disease (CAD).

	AUC	Sn	Sp	NPV	PPV
Coronary artery disease (n = 21)	0.80 (0.71–0.86)				
9 pg/ml[a]		81 (58–95)	80 (70–88)	94 (86–98)	52 (33–70)
13 pg/ml		62 (38–82)	84(74–91)	90 (81–95)	50 (30–70)
Infarction (n = 9)	0.88 (0.80–0.94)				
9 pg/ml		89 (52–100)	73 (63–82)	99 (92–100)	24 (11–43)
13 pg/ml[a]		89 (52–100)	81 (71–88)	99 (93–100)	31 (14–52)
Unstable angina (n = 12)	0.67 (0.57–0.76)				
9 pg/ml[a]		75 (43–95)	74 (63–82)	96 (88–99)	27 (13–46)
>13 pg/ml		42 (15–72)	77 (67–85)	91 (82–96)	19 (6–40)

[a] Indicates the optimal cutoff value for the diagnosis of each event.

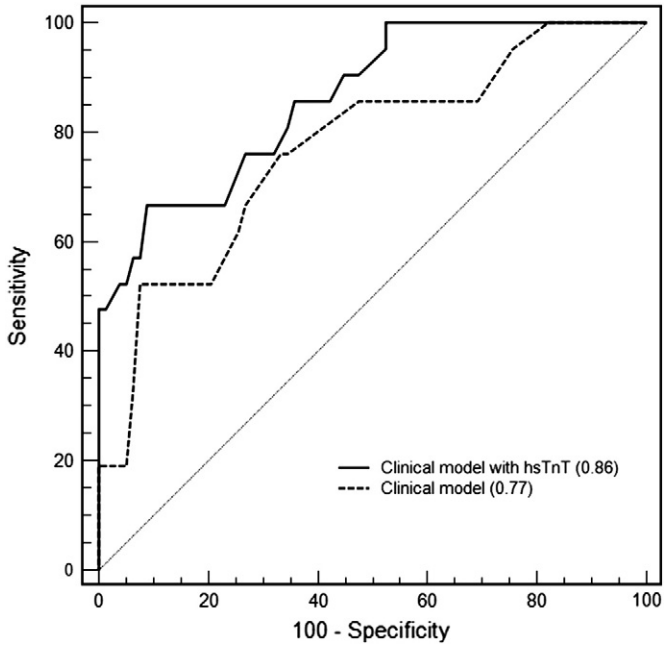

Fig. 1. Analysis of the receiver-operating-characteristics curves and C-indexes for the diagnosis of coronary artery disease based on a clinical model and after adding the value of high-sensitive troponin T.hsTnT = High-sensitive troponin T.

increase in the C-index an improved CAD discrimination (0.77 vs. 0.86; $p = 0.020$) (Fig. 1). This rise was validated by bootstrap analysis (Δ C-index of 0.12 ± 0.05, $p = 0.025$). Likewise, the addition of hsTnT led to a relative improvement of +92% ($p < 0.001$) in the IDI, and to a significant increase of 74% ($p < 0.001$) in the NRI, both for improving the classification of patients with CAD (+43%, $p = 0.007$) and without it (+32%, $p < 0.001$).

Our study shows, in the first place, that up to a 20% of patients from this apparently low-risk population upon arrival to the ED, present CAD. Less than half of this 20% would correspond to necrosis detectable with conventional methods of measuring cTnT in the serial samples, while the rest represent patients with UA or CAD without myocardial necrosis, an event less described in clinical studies but diagnostically challenging in the routine practice [6,9].

The independent value reached with the presence of diabetes mellitus and the clinical Geleijnse score confirms the relevance of pretest likelihood, clinical evaluation, and anamnesis. However, measuring troponin concentration with a new high-sensitive assay also enhanced significantly the discrimination capability of CAD, as evidenced by C-index increase and the improvement of discrimination and reclassification indexes. The importance of these findings related to the integration between hsTnT and the clinical profile of chest pain lies in the fact that they reflect routine clinical practice and have never been evaluated before. Even if previous studies have shown the superiority of high-sensitivity assays over conventional ones [6,9,10], they have not addressed anamnesis and the characteristics of chest pain. This is essential for every analysis on the real additional value of troponins in the initial evaluation of the patients.

Apart from being consistent with the main studies published [6,9] our research confirms that determining hsTnT upon arrival to the ED identifies not only patients with MI, but also those with CAD with minimal necrosis not detectable with cTn. Our analysis identifies the 99th percentile as optimal for MI diagnosis, but a lower value (9 pg/ml) as the best cut-off value to identify CAD, suggesting that lower values (between 9 and 13 pg/ml) must be contemplated for the diagnostic suspicion of CAD.

References

[1] Bayon FJ, Alegria EE, Bosch GX, et al. Chest pain units. Organization and protocol for the diagnosis of acute coronary syndromes. Rev Esp Cardiol 2002;55(2):143–54.
[2] Bardají A, Martínez-Sellés M, García-Moll X, Bueno H. Examples of interventions that improve quality of care in non-ST-elevation acute coronary syndrome. Rev Esp Cardiol 2005;5:47–52 [Supl.C].
[3] Bueno H, Bardaji A, Fernandez-Ortiz A, Marrugat J, Marti H, Heras M. Management of non-ST-segment-elevation acute coronary syndromes in Spain. The DESCARTES (Descripcion del Estado de los Sindromes Coronarios Agudos en un Registro Temporal ESpanol) study. Rev Esp Cardiol 2005;58(3):244–52.
[4] Hamm CW, Goldmann BU, Heeschen C, Kreymann G, Berger J, Meinertz T. Emergency room triage of patients with acute chest pain by means of rapid testing for cardiac troponin T or troponin I. N Engl J Med 1997;337(23):1648–53.
[5] Giannitsis E, Kurz K, Hallermayer K, Jarausch J, Jaffe AS, Katus HA. Analytical validation of a high-sensitivity cardiac troponin T assay. Clin Chem 2010;56(2):254–61.
[6] Reichlin T, Hochholzer W, Bassetti S, et al. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. N Engl J Med 2009;361(9):858–67.
[7] Reichlin T, Irfan A, Twerenbold R, et al. Utility of absolute and relative changes in cardiac troponin concentrations in the early diagnosis of acute myocardial infarction. Circulation 2011;124(2):136–45.
[8] Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease. N Engl J Med 1979;300(24):1350–8.
[9] Keller T, Zeller T, Peetz D, et al. Sensitive troponin I assay in early diagnosis of acute myocardial infarction. N Engl J Med 2009;361(9):868–77.
[10] Keller T, Zeller T, Ojeda F, et al. Serial changes in highly sensitive troponin I assay and early diagnosis of myocardial infarction. JAMA 2011;306(24):2684–93.

0167-5273/$ – see front matter
http://XX