Determination of cardiac troponin-I in patients with chronic renal failure

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SUMMARY

Objective: *The aim of the study was evaluate cardiac troponin I (cTnI) determination in patients with chronic renal failure (CRF) and compare with creatine kinase-MB isoenzyme (CK-MB and CK-MB/CK).*

Methods: *We performed a retrospective study on patients with CRF with MDRD (modification of diet in renal disease study group) < 60 mL/min admitted with suspected myocardial injury by history, physical examination and electrocardiography. cTnI measurement was assessed at admission with the ACCESS® analyzer (Beckman).*

Results: *Acute myocardial injury (AMI) was diagnosed in 10% (47/467) patients with cTnI determination > 0.05 ng/mL, while the diagnostic was angina in 9% (41/467) and in 81% (379/467) we finded other diagnostics. In the AMI group, 49% had chest discomfort, 43% diabetes and the mortality was 45%, while in the angina group were 41%, 32% and 7%, respectively. The sensitivity for cTnI with cut-off value > 0.5 ng/mL was 70% and specificity 92%. The number of false positives was 31% (20 patients).*

Discussion: *cTnI is the preferred biomarker for myocardial damage in patients with CRF. Other cut-off value could enhance the sensitivity for AMI.*

Key words: ***Cardiac troponin I. Creatine kinase MB. Chronic renal failure.***

DETERMINACIÓN DE TROPONINA I CARDÍACA EN PACIENTES CON INSUFICIENCIA RENAL CRÓNICA

RESUMEN

Objetivo: *Evaluar los resultados de troponina I cardíaca (TnIc) en pacientes con insuficiencia renal crónica (IRC) y comparar con los marcadores clásicos (CK-MB y CK-MB/CK).*

Métodos: *Realizamos un estudio retrospectivo en pacientes con IRC con filtrado glomerular estimado por MDRD (modificación de la dieta en el grupo de estudio de la enfermedad renal) < 60 mL/min ingresados por sospecha de daño miocárdico según la historia clínica, el examen físico y el electrocardiograma (ECG). Sólo se evaluó la concentración de TnIc al ingreso la cual fue medida con el analizador ACCESS® (Beckman).*

Resultados: *Se identificó Infarto agudo del miocardio (IAM) en el 10% de los pacientes (47/467) con una concentración de TnIc > 0,05 ng/mL, mientras que el diagnóstico fue angina en el 9% de los pacientes (41/467) y en el 81% (379/467) se encontraron otros diagnósticos. En el grupo con IAM el 49% presentó dolor torácico, el 43% diabetes mellitus y la mortalidad fue de 45%, mientras que en el grupo con angina los valores fueron 41%, 32% y 7%, respectiva-*

mente. La sensibilidad para la TnIc con un valor de corte > 0,5 ng/mL fue de 70% y la especificidad de 92%. El número de falsos positivos fue de 31% (20 pacientes)

Discusión: *La TnIc es el marcador de elección para diagnosticar daño miocárdico en pacientes con IRC. La aplicación de un valor de corte diferente puede incrementar la sensibilidad en la detección de IAM.*

Palabras clave: ***Troponina I cardíaca. Creatina cinasa MB. Insuficiencia renal crónica.***

INTRODUCTION

Chronic renal failure (CRF) has high morbid-mortality rate worldwide due to increasing population aging, associated cardiovascular pathology (mainly systemic arterial hypertension), diabetes mellitus, and patients' clinical status at the beginning of renal replacement therapy.[1,2]

Cardiovascular complications represent the main mortality cause of patients with end-stage renal failure (higher than 40%). CRF patients have an increased risk for silent ischemia or atypical clinical symptoms during an acute coronary syndrome. Similarly, EKG data may be unspecific since changes of the ST segment are difficult to interpret because of left ventricular hypertrophy, water and electrolytic changes, conduction abnormalities, or medicines. The diagnosis of myocardial damage in CRF patients is often difficult since heart markers may be elevated in the absence of an acute coronary syndrome; in their study, Choy et al.[3] describe a raise in TnTc values in 42% of the patients, in TnIc in 15%, and in CK-MB in 4%. It is suggested that unspecific elevation of these markers[3-6] may indicate minor myocardial damage, an inflammatory response, or a state of chronic volume overload.

In the year 2000, a re-definition of acute myocardial infarction (AMI) was published by the European Society of Cardiology and by the American College of Cardiology, where they point out the criteria for diagnosing a recent or established AMI.[6] The consequences of this new definition will imply increased sensibility and specificity for AMI cases. Besides, in hospital laboratories the old biochemical markers (myoglobin, AST, CK) will have to be replaced by the new ones (troponin-I or troponin-T and CK-MB).

The aim of this study was to assess the results of cardiac troponin-I (TnIc) in CRF patients in a clinical routine status, and compare the diagnostic performance with that of classical markers (CK-MB and CK-MB/CK).

MATERIAL AND METHODS

Patients

A retrospective study was done that included CRF patients (MDRD < 60 mL/min)[1,7,8] that came for a routine visit at the Hospital Complex of Orense between January and July of 2004, and in whom TnIc was done (in some CK and mass CK-MB were also measured). Exclusion criteria were: 1) CRF patients transferred to another hospital, and 2) lack of data on the discharge report.

Patients were assessed at the department were they asked for their consultation, by means of clinical history, physical examination and 12-lead EKG.

Variables included in the study and recorded on the discharge report (either the emergency room report or the department where they were admitted) were: age, gender, smoking history, diabetes mellitus, systemic arterial hypertension, chest pain, dyspnea, 12-lead EKG at admission, main diagnosis, reason for discharge, determination of serum TnIc, CK and CK-MB (not all cases included these to last laboratory determinations).

Patients were divided into three groups according to main diagnosis on the discharge report: 1) patients with acute myocardial infarction (AMI) based on the 2001 re-definition, 2) patients with angina (stable or unstable), and 3) patients with other diagnoses (not included in the previous two groups).

Biochemical markers

Venous blood samples were collected in Vacutainer® tubes with separator gel, with no preservatives. After a waiting time of 20 minutes, the samples were centrifuged at 1400 g for 10 minutes, and determination of serum TnIc, CK, CK-MB, and creatinine was done by technicians unaware of patients' clinical characteristics.

Cardiac troponin-I (TnIc) was measured with the Access AccuTnI® assay (Beckman Coulter Inc), which is a chemiluminescent immunoenzyme method with two antibodies (sandwich type). The population reference value is less than 0.05 mg/mL, so that the cut-off point considered for diagnosing AMI was the 0.5 ng/mL value (which is the usual cut-off point of our laboratory); the gray zone includes the TnIc results between 0.05 and 0.5 ng/mL.

The mass concentration of Creatin Kinase MB (CK-MB) was measured by the Access CK-MB® assay (Beckman Coulter Inc.), which uses a chemiluminescent immunoenzyme method with two antibodies (sandwich type). The reference value used was higher than 6.3 ng(mL (4.8% of the ratio CK-MB/total CK), and the declared detection limit is 0.1 ng/mL. Total Creatin Kinase (CK) was measured by means of the Synchron LX-20® analyzer (Beckman Coulter Inc.), with a enzyme kinetic method. The upper reference limit was 200 IU/L with a declared detection limit of 10 IU/L.

Creatinine was measured by means of the Synchron LX-20® analyzer (Beckman Coulter Inc.) using a kinetic spectrocolorimetric method (modified Jaffé's method). The references values used are between 0.5-1.3 mg/dL, with a declared detection limit of 0.1 mg/dL. Glomerular filtration rate (GFR) has been estimated through the Levey's abbreviated MDRD formula.[8]

Statistical analysis

Non-parametric tests for median comparisons were used (Kruskal-Wallis and Mann-Whitney) and ROC curve analyses with the SPSS® v-10.0 software (SPSS Inc., USA). A p value < 0.05 was considered as being statistically significant.

RESULTS

During the study period, more than 6000 TnIc determinations were done in our laboratory, of which 13% corresponded to CRF patients, but only 8% (467 patients) were included in the study for being the first TnIc determination. Patients were assessed at the following medical departments: 64% (300) at the emergency room, 10% (47) at the ICU-Reanimation, 9% (43) by Internal Medicine, 6% (27) by Nephrology, 3% (13) by Cardiology, and 8% (37) by other departments.

Population characteristics

Sixty-seven percent (313) were men and 33% (154) were women; median age of the patients (central interval of 95% of the patients) was 80 (49-94) years, although the group with the higher amount of TnIc measurements was between 70-90 years, corresponding to 341 (73%) patients. Table I shows the characteristics of the sub-population with TnIc > 0.05 mg/dL. In patients of the AMI group, 49% had chest pain, 43% diabetes mellitus, and mortality was 45%, whereas in the angina group the values were 41%, 32%, and 7%, respectively. In all groups, it was considered that smoking is not adequately assessed in the clinical history since we found suspiciously low percentages. EKG data of the patients were as follows: 34.2% had sinusal rhythm, 15.3% had atrial fibrillation, 10.2% had left bundle branch block (BBB), 6.3% had right BBB, 9% had acute coronary syndrome (ACS) with no elevation of the ST segment, 7.2% had ACS with elevation of the ST segment, and 17.6% had other EKG changes.

Table II shows glomerular filtration rate (GFR) in the three groups of patients. Fifty-percent of the patients (232) had GFR between 15-29 mL/min/1.73m^2, which represents stage 4 renal disease.

TnIc results

Table III shows patients distribution by group and TnIc decision values (these results may be seen in graph 1). Two hundred and thirty-four patients were

Table I. Variables of the sub-population of de patients with TnIc > 0.05 ng/mL (expressed in percentages)

%	Chest pain	Dyspnea	Diabetes mellitus	Smoking	AHT	Exitus
AMI	49	40	43	4	60	45
ANGINA	41	51	32	7	66	7
OTHERS	3	16	9	2	19	12

Table II. Estimated GFR (mL/min/1.73 m^2) by the abbreviated MDRD formula

	GFR	AMI	Angina	Others	Total
30-59	12	15	131	158	(34%)
15-29	31	20	181	232	(50%)
< 15	4	6	67	77	(16%)
TOTAL	47	41	379	467	(100%)

found to have normal TnIc values, and they belonged to the other-diagnoses group. Fourteen patients with AMI, 29 with angina, and 125 with other diagnoses were in the gray zone of TnIc, whereas a TnIc value > 0.5 ng/mL was found in 33 patients with AMI, 12 with angina and 20 with other diagnoses. For a cut-off point of TnIc > 0.5 ng/mL the sensibility (95% CI) was 70% (57-83%) and specificity 92% (92-95%) for AMI diagnosis (table IV), with a positive predictive value (PPV) of 51% (39-63%) and negative predictive value (NPV) of 97% (95-98%). The percentage of false positive AMI diagnoses was 31% (20 patients). TnIc level does not correlate with creatinine level or GFR for no patient group, or as a whole.

There are few cases where cardiac markers TnIc, CK-MB, and CK-MB/CK have been determined at the same time. With the available data, we confirm that

Table III. Distribution of patients by groups of TnIc results (ng/mL). Apparent prevalence of AMI: 10%

	TnIc < 0.05	0.05 < TnIc ≤ 0.5	TnIc > 0.5
AMI (n = 48)	0	14	33
ANGINA (n = 41)	0	29	12
OTHERS (n = 378)	233	125	20

Table IV. Sensibility and specificity for deferent TnIc CUP

CUP (ng/mL)	Sensibility	Specificity
0.1	94%	74%
0.3	77%	90%
0.5 (*)	71%	93%
0.7	65%	95%
0.9	65%	96%

CUP: cut-off point.

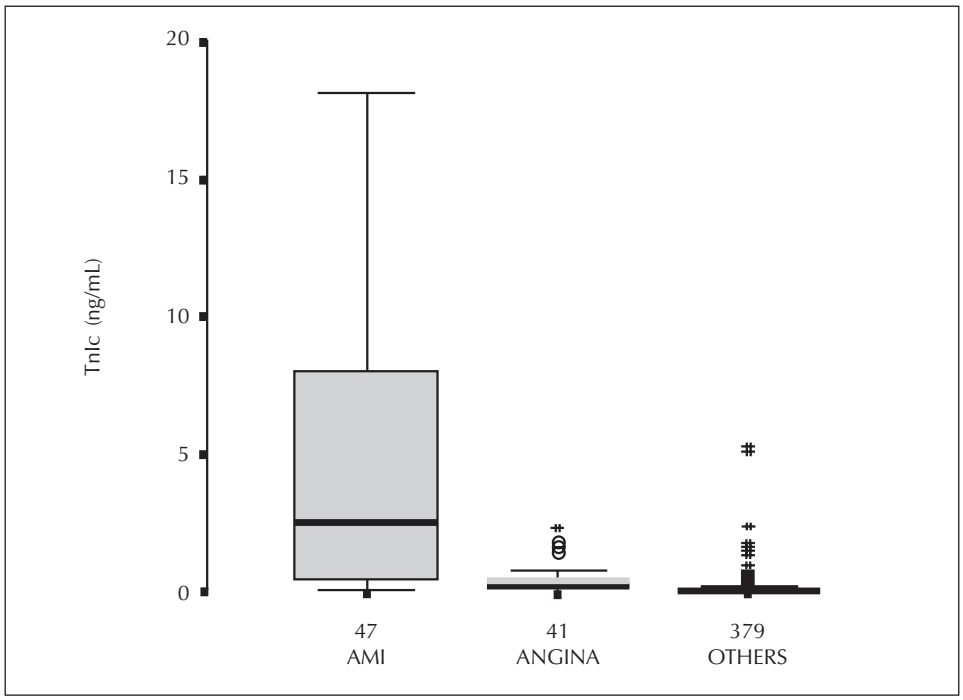

Fig. 1.—Distribution of patients by groups by TnIc results.

TnIc presents the best diagnostic performance in this study, which may be seen in graph 2. The area under the ROC curve (95% CI) for TnIc was 0.935 (0.876-0.994) versus 0.824 (0.708-0.940) and 0.747 (0.569-0.925) for CK-MB and CK-MB/CK(%), respectively; therefore, TnIc is the first choice marker in our study for diagnosing AMI.

Table V shows the distributions of TnIc results by groups and median comparison. In the AMI group, the media value for the TnIc level was 2.58 ng/mL, as compared to 0.21 ng/mL in the angina group and 0.04 ng/mL in other-diagnoses group.

Table V. Comparison of TnIc results (ng/mL)

	p_{50}	$(p_{2.5}-p_{97.5})$	Significance
AMI (n = 48)	**2.58**	(0.06-93.2)	AMI –ANGINA
			P < 0.0001
ANGINA (n = 41)	**0.21**	(0.06-97.2)	ANGINA-OTHERS
OTHERS (n = 378)	**0.04**	(0.01-1.60)	P < 0.001

DISCUSSION

Myocardial damage diagnosis in CRF patients is difficult because sometimes the clinical picture is atypical, cardiac markers may be elevated with no real impairment, and the electrocardiogram may show unspecific data; therefore, rapid confirmation of TnIc level is important because, in this way, clinicians are helped establishing the diagnosis of AMI. Our study, which included 467 CRF patients, assessed at the hospital because of concern of myocardial damage for a 7-month period, and in which TnIc determination was requested (and in some, CK and CK-MB also), showed a 10% prevalence for AMI, 9% for angina, and the remaining (81%) had other diagnoses. Raised TnIc levels and absence of heart pathology were found in 31% (20 patients), which indicates the number of false positive results. Our results with the Access AccuTnI® (Beckman Coulter Inc) assay represents twice the value obtained by Choy et al.[3]; in their prospective study with 113 patients on hemodialysis, they used a similar TnIc assay (Dade Behring Inc.), finding an elevation of cardiac markers without coronary syndrome in 42% with TnTc, 15% with TnIc, and 4% with CK-MB. Roogsritong et al.[5] propose some causes for false positive results with TnIc, among which they include acute pericarditis, acute pulmonary embolism, cardiac failure, myocarditis, severe sepsis, and renal failure. With regards TnIc concentration in CRF patients, the results are inconsistent since Musso et al.[9], using a TnIc immunoassay (Stratus II, Dade International, and the previous one), find raised TnIc in two patients. The 20 patients identified as false positive for TnIc will be further evaluated in another review.

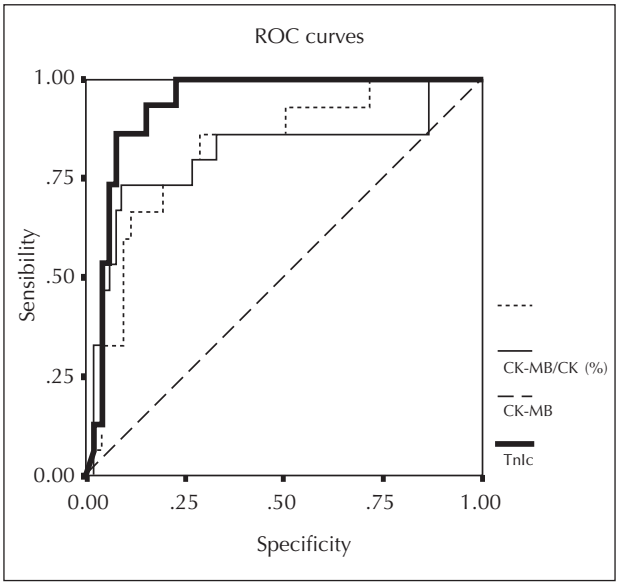

Fig. 2.—ROC curves for TnIc, CK-MB and CK-MB/CK (%). CK-MB: creatin kinase MB. CK-MB/CK (%): percentage of creatin kinase MB.

The prognostic value of TnIc levels in CRF patients is still controversial. Lang et al.[10] carried out a retrospective study on 100 hemodialysis patients; they evaluated two TnIc assays, one applicable at bedside, with which they found TnTc elevation in 41% and TnIc elevation in 27%, whereas the quantitative determination identified TnTc elevation in 22%, TnIc elevation in 7%, and CK-MB elevation in 2%, which confirms that cardiac troponins (TnTc and TnIc) have no prognostic value for acute and chronic cardiac events in asymptomatic patients with end-stage chronic renal failure. Khan et al.[11] conclude that TnIc has a limited role for predicting mortality and hospital admissions in asymptomatic patients with CRF, whereas Wayand et al.[12], in their prospective study o 59 patients with end-stage renal failure, found raised TnTc and TnIc in 16.6% and 12%, respectively, indicating that TnTc and TnIc elevations may predict cardiac complications.

Collinson et al.[13] affirm that troponin levels represent a better diagnostic performance than CK or CK-MB, which is in agreement with our results, thus we consider that TnIc has replaced CK and CK-MB with evident advantages.

Global mortality of CRF patients in our study was 15% (45% in the AMI group and 7% in angina group). Calculated mortality in the group of false positive results was 25%, therefore we consider it is important to detect these results and try to reduce them by following the recommendations of the National Academy of Clinical Biochemistry (NACB)[14] about requesting at least two TnIc determinations.

Patients included in the study presented renal disease at stages 3, 4, and 5[15] and showed no correlation between TnIc level and creatinine level or GFR. We could not find either a relationship between TnIc level and GFR in the subgroup of false positive patients.

The TnIc cut-off value for AMI diagnosis used at our laboratory under usual conditions is > 0.5 ng/mL, with sensibility and specificity (according to the manufacturer's declaration) of 96% and 94%, respectively, in the general population. For CRF patients in our study, sensibility was 70%, specificity 92%, PPV 51%, and NPV 97%; as shown in Table IV, when the cut-off value decreases sensibility increases up to 94% for a TnIc level of 0.1 ng/mL and specificity is reduced to 74%, whereas increasing the cut-off value sensibility decreases to 65% for a TnIc value of 0.9 ng/mL, and specificity increases up to 96%, which means that using a cut-off value in the 99% percentile of the healthy population (as recommended by the European Society of Cardiology and the American College of Cardiology)[6] the number of cases of AMI is increased.

Among the study limitations, there are those derived from the fact this is a retrospective review and we had to exclude a high number of patients due to lack of information on the discharge report, as well as the lack of serial determinations of TnIc ad CK-MB, unknowing the time interval between the second and third determinations after hospital admission. A prospective study is proposed, designed in such a way to avoid some of these limitations, which will allow establishing a cut-off value with higher diagnostic performance in these patients.

We may conclude that the application of a different cut-off value[16,17] may increase for AMI detection in these patients, reducing the number of false positives, thus taking benefit of early therapies.

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