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Original article

Usefulness of High Sensitivity Troponin T Assay in Detecting Acute Allograft Rejection After Heart Transplantation

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ABSTRACT

Introduction and objectives: Detection of acute allograft rejection in heart transplant recipients by noninvasive methods is a challenge in the management of these patients. In this study, the usefulness of a new highly sensitive method for the measurement of troponin T is evaluated.
Methods: We designed a case-crossover study, in which each patient served as his or her own control, by selecting samples from treated acute rejection episodes (29 cases) and samples obtained immediately before and/or after rejection (38 controls). The highly sensitive troponin T was measured by a new pre-commercial test (Elecsys Troponin T HS).
Results: In all samples, highly sensitive troponin was detectable, with a median of 0.068 ng/mL (IQR, 0.030-0.300 ng/mL). The levels correlated with right atrial pressure (r = 0.37; $P = .002$), N-terminal pro-brain natriuretic peptide concentration (r = 0.67; $P < .001$), and time since transplantation (r = –0.81; $P < .001$). The highly sensitive troponin concentrations were higher in patients with rejection (0.155 ng/mL vs 0.047 ng/mL; $P = .006$). In the receiver operating characteristic analysis, the area under the curve was 0.67 (95% confidence interval, 0.53-0.77) and the best cutoff was 0.035 ng/mL, which was associated with rejection (odds ratio = 3.7; 95% confidence interval, 1.2-11.9; $P = .02$). By restricting the analysis to the first 2 months, the area under the curve increased to 0.86 (95% confidence interval 0.66-0.97), with an optimal cutoff of 1.10 ng/mL (S = 58% [28%-85%]; E = 100% [74%-100%]).
Conclusions: Troponin T was detectable in all samples when a new highly sensitive assay was used, and at higher concentrations in the presence of acute rejection; however, the usefulness of this test in patient management is limited to support for clinical or histological suspicion of rejection, especially in the early post-transplant period.

Utilidad de la prueba de troponina T de alta sensibilidad en la detección de rechazo agudo en trasplante cardiaco

Palabras clave:
Trasplante
Rechazo
Troponina

RESUMEN

Introducción y objetivos: La detección del rechazo agudo en pacientes trasplantados cardiacos mediante métodos no invasivos representa un reto. La disponibilidad de un nuevo método de alta sensibilidad para la determinación de troponina T podría ayudar a su detección.
Métodos: Estudio *case-crossover*, en el que cada paciente sirvió como control de sí mismo, mediante la selección de muestras obtenidas en episodios de rechazo agudo tratados (29 casos) y muestras sin rechazo obtenidas inmediatamente antes y/o después (38 controles). La determinación de alta sensibilidad de troponina T se realizó mediante un nuevo test precomercial (Elecsys Troponina T HS).
Resultados: La troponina T fue detectable en todas las muestras: mediana, 0,068 ng/ml [intervalo intercuartílico, 0,030-0,300 ng/ml]. Sus concentraciones se correlacionaron con la presión auricular derecha (r = 0,37; p = 0,002), la fracción aminoterminal del propéptido natriurético cerebral (r = 0,67; p < 0,001) y el tiempo transcurrido desde el trasplante (r = –0,81; p < 0,001). Las concentraciones de troponina T fueron mayores en presencia de rechazo (0,155 frente a 0,047 ng/ml; p = 0,006). En el análisis operador-receptor, el área bajo la curva fue 0,67 (intervalo de confianza del 95%, 0,53-0,77) y el mejor punto de corte, 0,035 ng/ml, que se asoció con mayor riesgo de rechazo (*odds ratio* = 3,7; intervalo de confianza del 95%, 1,2-11,9; p = 0,02). Durante los primeros 2 meses, el área bajo la curva aumentó hasta 0,86 (intervalo de confianza del 95%, 0,66-0,97), con un punto de corte óptimo de 1,10 ng/ml (sensibilidad, 58% [28-85%]; especificidad, 100% [74-100%]).

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Conclusiones: El análisis de alta sensibilidad detectó troponina T en todas las muestras tras el trasplante, en mayor concentración en caso de rechazo agudo, si bien su utilidad en la monitorización se limitaría a servir como apoyo ante la sospecha clínica o histológica, especialmente en los primeros meses.

Abbreviations

EMB: endomyocardial biopsy
hsTnT: highly sensitive troponin T
NT-proBNP: N-terminal pro-brain natriuretic peptide

INTRODUCTION

Despite the current advances in immunosuppressive therapy, 20% to 30% of patients undergoing heart transplantation require an increased immunosuppression level for acute cellular or humoral rejection.[1,2] The associated mortality is 6% in the first month and reaches 12% at the end of the first year.[3] Currently, endomyocardial biopsy (EMB) is the standard tool for the diagnosis of acute rejection, despite its invasive nature and low sensitivity due to considerable variability in sampling and in intraobserver and interobserver interpretation.

Determination of cardiac troponins in blood is a standard method for prompt detection of ischemic injury in acute coronary syndromes. Acute rejection is also associated with cardiomyocyte necrosis and, therefore, with release of cardiac troponins.[4,5] Nonetheless, the low sensitivity of conventional techniques for troponin determination limits the clinical applicability of this test for heart transplant recipients, in whom the initial troponin release is of very low magnitude.[6] In recent years, highly sensitive methods with significantly lower limits of detection have been developed for troponin determination.[7] Thus, these tests might be feasible for less invasive clinical monitoring of acute allograft rejection.

The aim of this study was to evaluate a new, highly sensitive method for troponin T (hsTnT) detection in the diagnosis of acute rejection in heart transplant recipients.

METHODS

Population and Study Design

A case-crossover study was designed in which each patient served as his or her own control, by selecting samples obtained during a rejection episode (cases) and samples taken immediately before or after the episode (controls). Between 2000 and 2008, 72 heart transplants were performed, in which EMB was carried out as part of the regular monitoring protocol or for clinically suspected rejection. Blood samples were drawn immediately before each EMB, as required in the Transplant Immunology protocol of the research group network (File G03/114; *Instituto de Salud Carlos III*), and serum was obtained, processed, and frozen at -80 °C. Within this total population, 29 (40%) patients (mean age, 53±13 years; 75% males) presented a first acute rejection episode during the first year, as defined by treatment with an intravenous bolus of methylprednisolone at a dose of ≥250 mg based on clinical or histological criteria of rejection. We selected samples obtained during the rejection episode (n = 29 cases, rejection group) and those obtained in the biopsy performed immediately before (n = 17) and/or after (n = 21) rejection (n = 38 controls, no rejection group). For each biopsy, the degree of histological rejection was classified in accordance with the criteria of the International Society of Heart and Lung Transplantation.[8] The clinical and laboratory characteristics at the time of biopsy were recorded prospectively on the patient's medical chart, in keeping with the regular clinical practice for this population, and the data were later collected for the study analysis.

Laboratory Measurements

Samples underwent a single thawing cycle before troponin T determination using a highly sensitive electrochemiluminescence immunoassay (Elecsys Troponin T hs) on an Elecsys 2010 analyzer (Roche Diagnostics GmbH, Mannheim, Germany). The test has an analytic range of 0.003 to 10 ng/mL, a lower detection limit of 0.003 ng/mL, and a value of 0.013 ng/mL for the 99th percentile of the normal population (coefficient of variation for this value, 9%). This commercial test was validated recently, and meets the consensus requirements and recommendations for use in the diagnosis of myocardial necrosis.[9] Concentrations of N-terminal pro-brain natriuretic peptide (NT-proBNP) were also measured using the above-mentioned Elecsys 2010 system; total imprecision of the technique was <3%.

Statistical Analysis

Differences between the rejection and nonrejection groups were analyzed with the Student *t* test for variables with a normal distribution or the nonparametric Mann-Whitney *U* test for those with nonnormal distribution. The chi-square test was used to compare qualitative variables. To study possible influences on the hsTnT values obtained, linear multiple regression analysis was carried out, including in the model variables that showed a significant correlation. The diagnostic utility of hsTnT for predicting acute cellular rejection was evaluated with a receiver operating characteristic (ROC) analysis, calculating the area under the curve and confidence interval (CI) using the DeLong method.[10] The best cut-off for the diagnosis was the one in which the highest product was obtained by multiplying the specificity by the sensitivity. The association of risk with rejection was determined with logistic regression analysis, adjusted by other significant variables. *P* values <.05 were considered statistically significant. Statistical calculations were performed with MedCalc 11.3.0 (MedCalc Software, Mariakerke, Belgium) for the ROC analysis, and with PASW 18.0 (SPSS Inc., Chicago, Illinois) for the other analyses.

RESULTS

The clinical and biochemical characteristics according to the presence or absence of rejection are shown in Table 1. In the overall population, troponin T was detectable in all samples (100%) at a median of 0.068 (0.030-0.300) ng/mL, and significantly higher concentrations were found in patients with rejection (Fig. 1). When the population was stratified into tertiles of troponin T concentration, there was also an association with a higher prevalence of rejection (*P* = .02): 23% (<0.035 ng/mL), 48% (0.035-0.176 ng/mL), and 59% (>0.176 ng/mL). Clinical variables correlating with