UNIVERSIDAD DE MURCIA

DEPARTAMENTO DE MEDICINA INTERNA

Nuevos biomarcadores y tomografia de coherencia optica en el diagnostico precoz del rechazo agudo y la enfermedad vascular del injerto en el trasplante cardiaco

Iris P. Garrido Bravo

2013

Parte de los trabajos de investigación recogidos en la siguiente tesis doctoral han sido financiados por el siguiente proyecto

- Beca concedida por la Fundación Caja Murcia y gestionada por la Fundación para la formación e investigación sanitarias de la región de Murcia en el año 2007 para el perfeccionamiento y actualización de la formación del personal del sistema regional de salud en investigación biosanitaria, en etapas tempranas de la carrera investigadora y en áreas que sean interés estratégico para el sistema para el proyecto nº CJ/07/08, denominado: "Estudio de la enfermedad vascular del injerto en pacientes trasplantados cardiacos: epidemiología, diagnostico no invasivo y marcadores pronósticos".

Agradecimientos

En primer lugar me gustaría agradecer mis directores de tesis toda la ayuda la ayuda que me han prestado para llegar al final de este trabajo.

Quiero agradecer especialmente a Domingo su paciencia y su capacidad para transmitirme el impulso necesario para concluir este proyecto. Destacar su calidad científica y su espíritu crítico en la supervisión de los contenidos y por la orientación del enfoque de muchos aspectos de esta tesis. Y sobre todo agradecerle su apoyo y su amistad.

Agradecer al Prof. Dr. Mariano Valdés Chávarri todo el apoyo que me ha brindado desde que comencé mi etapa en Murcia. En todo momento, ha conseguido transmitirme su valor por el trabajo bien hecho y la necesidad de fusionar la actividad clínica e investigadora para obtener la excelencia.

Me gustaría resaltar la contribución en esta tesis de todos mis compañeros del Hospital Universitario Virgen de la Arrixaca. Especialmente agradecer al Dr. Francisco Pastor Pérez y Mº Rosario Gracia Rodenas su apoyo en la actividad asistencial y por hacer de este grupo de trabajo una gran familia.

A Juan, por estar siempre a mi lado, por apreciar mi esfuerzo y valorarlo. Por sus consejos y su ayuda en numerosas tareas permitiéndome mayor dedicación en este proyecto y sobre todo por conocerme, entenderme y quererme.

Mi más sincero agradecimiento a mis suegros, Juan y Marigel, sin su comprensión y apoyo logístico todo hubiese resultado mucho más difícil.

Finalmente quiero agradecer y dedicar esta tesis a mis padres, ejemplo de dedicación y constancia, que me han transmitido la perseverancia necesaria para desarrollar este proyecto.

Gracia a todos.

A mi familia.

El contenido de la presente tesis constituye un compendio de trabajos previamente publicados.

1. Usefulness of Serial Monitoring of B-Type Natriuretic Peptide for the Detection of Acute Rejection After Heart Transplantation. Iris P. Garrido, Domingo A. Pascual-Figal, Francisco Nicolás, Maria J. González-Carrillo, Sergio Manzano-Fernández, Jesús Sánchez-Mas, Mariano Valdés-Chavarri.

2. Usefulness of High Sensitivity Troponin T Assay in Detecting Acute Allograft Rejection After Heart Transplantation. Carmen Muñoz-Esparza, Iris P. Garrido, Rosa Blanco, Teresa Casas, Cristina González-Cánovas, Francisco Pastor-Pérez, Pablo Peñafiel, Alfredo Minguela, Mariano Valdés, Domingo A. Pascual-Figal.

3. Soluble ST2 Is a Marker for Acute Cardiac Allograft Rejection. Domingo A. Pascual-Figal, Iris P. Garrido, Rosa Blanco, Alfredo Minguela, Antonio Lax, Jordi Ordoñez-Llanos, Antoni Bayes-Genis, Mariano Valdés, Stephanie A. Moore, James L. Januzzi.

4. Optical Coherence Tomography and Highly Sensitive Troponin T for Evaluating Cardiac Allograft Vasculopathy. I.P. Garrido, J. García-Lara, E. Pinar, F. Pastor-Pérez, J. Sánchez-Mas, M. Valdés-Chavarri, D.A. Pascual-Figal.

General index / Índice de Contenidos

1. 1 Introduction

Among patients who have undergone orthotropic heart transplantation, despite the progress in immunosuppressive therapy, an important clinical issue remains being graft dysfunction due to either acute rejection or cardiac allograph vasculopathy.

According to registries, 20% to 30% of heart transplant patients experience at least one acute cellular rejection episode during the first year after transplantation, causing 8-12% of the deaths. Currently, endomyocardial biopsy is the standard procedure for diagnosis of acute rejection despite its invasive nature. The role of cardiac biomarkers on the detection of acute rejection is not well established. Given their non invasive nature and wide availability, cardiac biomarkers could be a useful tool in the diagnostic management of these patients.

Cardiac allograft vasculopathy causes the 14% of deaths after heart transplant, and is one of the most important causes of death in patients who survive the first year after transplantation. Currently, the diagnosis is based on angiography and intravascular ultrasound imaging. Non-invasive techniques in this setting are not recommended because the lack of standards and remain the subject of ongoing studies. In addition the role of Optical Coherence Tomography, a new imaging technique for studying coronary anatomy remains to be defined.

This doctoral thesis aimed to assess:

1- The role of different new biomarkers as B-Type Natriuretic Peptide, Highly Sensitivity Troponin T and ST2 in the monitoring and diagnosis of acute rejection in heart transplant patients

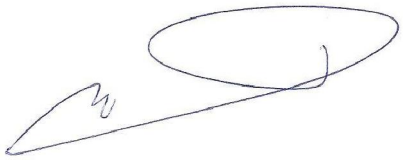
2- The role of Highly Sensitivity Troponin T and echocardiogram, as non invasive studies, and the Optical Coherence Tomography, as a new imaging techique, in the diagnosis of cardiac allograph vasculopathy in heart transplant.

As a result of these studies, four original articles have been published, that constitute the core of this doctoral thesis. In theses papers the questions originally proposed were answered and the conclusions were exposed. Therefore, our investigation have been approved by international scientific community and published in prestigious journals which recognize their quality.

Consequently, we favorable consider the presentation of this doctoral thesis by Iris Paula Garrido Bravo as the principal investigator and author of these works.

Mariano Valdés-Chávarri

Domingo A. Pascual Figal



Iris Paula Garrido Bravo

1.2 Introduccion

Entre los paciente sometidos a trasplante cardíaco, a pesar de los progresos en la terapia inmunosupresora, un problema clínico importante continúa siendo la disfunción del injerto debida a rechazo agudo o crónico (enfermedad vascular del injerto)

De acuerdo con los registros, entre un 20-30% de los pacientes trasplantados sufrirán al menos un episodio de rechazo en el primer años post trasplante, causando el 8-12% de las muertes. Actualmente, la biopsia endomiocárdica continúa siendo el estándar en el diagnostico del rechazo a pesar de su carácter invasivo. Hoy en día, el papel de los biomarcadores cardiacos en este contexto no está bien establecido. Dada su naturaleza no invasiva y su amplia disponibilidad los biomarcadores podrían ser una herramienta útil en el manejo diagnostico de estos pacientes.

La enfermedad vascular del injerto es una de las causas más importante de mortalidad tras el primer año post trasplante, suponiendo un 14% de la mortalidad global. Actualmente el diagnostico de esta patología se basa en la coronariografía y la ecografía intravascular. Las técnicas no invasivas en este contexto no están recomendadas debido a la falta de estándares y continúan siendo objeto de estudio. Además el papel de una nueva técnica de imagen intracoronaria, la tomografía de coherencia óptica, está por definir.

En el origen de esta tesis doctoral nos planteamos

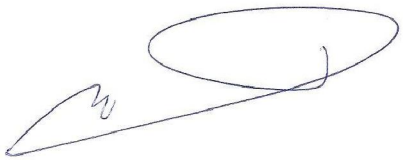
1. Evaluar el papel de distintos biomarcadores: péptido natriurético tipo B, troponina T ultrasensible y ST2 en la monitorización y diagnostico precoz del rechazo agudo en los pacientes trasplantados cardiacos
2. Evaluar el papel de la troponina ultrasensible y de una nueva técnica de imagen, la tomografía de coherencia óptica, en la detección precoz de la enfermedad vascular del injerto en pacientes trasplantados cardiacos.

Como resultado de ello, han sido publicados cuatro artículos que constituyen el cuerpo de esta tesis. En dichos artículos se dio respuesta a los objetivos del trabajo planteadas inicialmente y se presentaron las correspondientes conclusiones a los objetivos propuestos. Este trabajo ya ha sido reconocido favorablemente por la comunidad científica con su aceptación y publicación en revistas especializadas del máximo prestigio internacional avala la calidad del mismo.

Por todo ello, consideramos adecuada la presentación por parte de Iris Paula Garrido Bravo de su Tesis Doctoral a modo de compendio de publicaciones, basada en los artículos previamente citados y en los que el mismo constituye el autor principal de la investigación llevada a cabo.

Mariano Valdés-Chávarri

Domingo A. Pascual Figal



Iris Paula Garrido Bravo

1.3 Bibliography/Bibliografia

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nomenclature for cardiac allograft vasculopathy-2010. J Heart Lung Transplant. 2010 Jul;29(7):717-27.

1. Usefulness of serial monitoring of B-type natriuretic peptide for the detection of acute rejection after heart transplantation.

Abstract

Serum B-type natriuretic peptide (BNP) is increased after heart transplantation (HT), but it has not been well established whether BNP could be used to detect acute rejection in asymptomatic patients after HT. A total of 259 routine endomyocardial biopsy specimens from 50 consecutive patients after HT (83% men; age 50 ± 15 years) were studied. Serial BNP measurements were performed at the time of each biopsy. BNP was evaluated as an absolute level (picograms per milliliter) and percentage of change from the previous biopsy (BNP – BNP at previous biopsy) / BNP at previous biopsy] x 100). Rejection was defined as grade ≥ 2R International Society of Heart and Lung Transplantation grading system.

BNP correlated independently with time after HT (p <0.001), pulmonary artery systolic pressure (p <0.001), creatinine (p = 0.001), and age (p = 0.0012). Asymptomatic rejection was found in 15 biopsy specimens (6%), for which absolute BNP (106 pg/ml; interquartile range [IQR] 67 to 495) did not differ from nonrejection biopsy specimens (92 pg/ml; IQR 49 to 230; p = 0.286). BNP percentage of change showed a median of +60% (IQR -29 to +154%) in rejection versus -17% (IQR -47 to +19%) in nonrejection biopsy specimens (p = 0.009). After multivariable adjustment, BNP percentage of change was a consistent predictor of rejection (+10%; odds ratio 1.05, 95% confidence interval 1.01 to 1.09, p = 0.021). Receiver-operator characteristic analysis showed an area under the curve of 0.71 (95% confidence interval 0.643 to 0.768) and identified percentage of change <+38% as an optimal cut-off point, with a negative predictive value of 97%. In conclusion, serial monitoring of BNP, evaluated as a percentage of change, may be a useful noninvasive tool in the clinical management of rejection.

http://dx.doi.org/10.1016/j.amjcard.2009.01.008,

2. Usefulness of high sensitivity troponin T assay in detecting acute allograft rejection after heart transplantation

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.

http://apps.elsevier.es/watermark/ctl_servlet?_f=10&pident_articulo=90040439&pident_usuario=0&pcontactid=&pident_revista=255&ty=47&accion=L&origen=cardio&web=http://www.revespcardiol.org&lan=en&fichero=255v64n12a90040439pdf001.pdf

3. Soluble ST2 is a marker for acute cardiac allograft rejection

Abstract

Background. Soluble ST2 (sST2), an interleukin (IL)-1 receptor family member, has a role in immunologic tolerance and has also emerged as a biomarker of cardiac stretch and remodeling. The sST2 role in heart transplantation is still unknown.

Methods. From the heart transplantation population at our institution (n = 74), we selected a subset of 26 patients who had an acute rejection episode in the first year after transplantation (35%; 52 ± 14 years; 76% men). Endomyocardial biopsy (EMB) results obtained at the time of the first rejection episode represented the rejection cohort (n =_ 26). Each patient served as a control to himself or herself, with EMB without rejection obtained before and after the rejection episode (n = 52). All laboratory measurements and blood samples were obtained at the time of EMB.

Results. sST2 concentrations rose significantly in the context of acute rejection (130 [60 to 238] versus 51 ng/mL [28 to 80]; p = 0.002). Tertile analyses of sST2 concentrations revealed a graded association with rejection (p = 0.002) and repeated measurement analyses showed that sST2 concentrations were significantly modulated by the presence of rejection (p = 0.001). In receiver operator characteristic (ROC) analysis, sST2 had an area under the curve (AUC) of 0.72; the optimal cutoff point was 68 ng/mL (positive predictive value of 53%, negative predictive value of 83%), which predicted acute cellular rejection (odds ratio [OR] 4.9; 95% confidence interval [CI], 1.7 to 14.5; p = 0.004). The addition of sST2 values to those for the N-terminal pro B-type natriuretic peptide (NTproBNP) resulted in a significant improvement on the integrated discrimination index (IDI) for rejection (relative improvement of 24%; p = 0.021).

Conclusions. sST2 concentrations are modulated by the presence of acute rejection and provide complementary predictive ability to NT-proBNP for the biochemical identification of rejection.

http://dx.doi.org/10.1016/j.athoracsur.2011.07.048

4. Optical coherence tomography and highly sensitivity troponin T for evaluating cardiac allograft vasculopathy.

Abstract

Cardiac allograft vasculopathy (CAV) is a major impediment to long-term graft survival after heart transplantation. Intravascular ultrasound (IVUS) is more sensitive than coronary angiography for diagnosis, but the identification of specific plaque components or plaque composition is limited. In addition, there is an evident need for other non-invasive tools for diagnosing CAV. We sought to assess the utility of two new techniques for evaluating CAV: Optical coherence tomography (OCT), and new highly sensitive troponin assays (hsTnT). In 21 heart transplant patients a coronary arteriography with IVUS and OCT was performed. Maximal intimal thickness (MIT) and luminal area at the most severe site were measured using both techniques. Immediately before the cardiac catheterization, blood samples were obtained and hsTnT levels were measured. The evaluation of CAV by OCT showed a good correlation with IVUS measurements, with a mean difference in MIT of 0.0033 (95%CI -0.049 – 0.043) taking advantage of lower interobserver variability (r=0.94 for OCT vs. r=0.78 for IVUS) and better plaque characterization. When independent predictors of MIT were assessed in a multiple linear regression model, time after transplantation (β=0.488, p=0.004) and hsTnT (β =0.392, p=0.011) were the only independent predictors of MIT (R2= 0.591). In conclusion, this study is the first to evaluate 2 new techniques, OCT and hsTnT, in the challenging setting of CAV. Our finding suggests that OCT provides lower interobserver variability and a better plaque characterization than IVUS. Also hsTnT could become a useful tool for ruling out CAV.

http://dx.doi.org/10.1016/j.amjcard.2012.04.047

8.1 Conclusions.

Concerning the utility of biomarkers in the noninvasive diagnosis of acute rejection the main findings of this study were:

1. BNP absolute levels decreased over time after transplant and correlated with renal function and right auricular pressure, but no by acute rejection.

2. BNP relative changes were influenced by the presence of acute rejection. An increment of less than 38% in BNP showed a negative predictive value of 97% for the diagnosis of rejection.

3. Due to this high negative predictive value, monitoring serial BNP could be useful in the noninvasive diagnosis of acute rejection and could reduce the number of programmed endomyocardial biopsies and related costs.

4. Whereas with conventional troponin T, 54% of patients present persistently undetectable concentrations, with highly sensitive troponin T was measureble in all samples of patients regardless the presence of rejection.

5. Highly sensitive troponin T levels decreased over time after transplant and correlated with right atrial pressure and N-terminal pro-brain natriuretic peptide concentration.

6. The highly sensitive troponin concentrations were significantly higher in the presence of rejection.

7. Although highly sensitive troponin T monitoring would not avert the need for EMB, this study indicates that maintained elevated troponin values in the early period were associated with a high positive predictive value.

8. sST2 levels correlated with C-reactive protein, N-terminal pro-brain natriuretic peptide concentration and lymphocyte count.

9. sST2 concentrations were significantly higher in the presence of acute cellular rejection. sST2 concentrations showed a dynamic behavior in response to

rejection (increase) and antirejection therapy (decrease), which suggests that sST2 concentrations are modulated by the appearance of acute rejection

10. sST2 concentrations provide complementary predictive ability to N-terminal pro-brain natriuretic peptide for the biochemical identification of rejection.

Regarding the early detection of cardiac allograph vasculopathy after heart transplantation the main findings of our investigations were:

1. Highly sensitive troponin T was a marker of cardiac allograph vasculopathy.

2. Concentrations of highly sensitive troponin T correlated with the grade of intimal thickness evaluated by intravascular ultrasound or optical coherence tomography

3. Conventional troponin T did not correlated with the grade of intimal thickness, therefore the highly sensitive troponin T is powerful in detection of cardiac allograph vasculopathy.

4. A value less than 21 pg/mL was associated with 100% sensitivity and negative predictive value for the detection of severe cardiac allograph vasculopathy.

5. Optical coherence tomography showed a good correlation with intravascular ultrasound measurements, with lower interobserver variability in the evaluation of cardiac allograph vasculopathy.

6. Optical coherence tomography showed advantage over intravascular ultrasound because a better plaque characterization that could determine the treatment management.

7. The main limitation of the optical coherence tomography was the attenuation in large vessels because the lack of light penetration into the artery wall.

8. Conclusiones

En relación con la utilidad de los biomarcadores en el diagnostico no invasivo del rechazo agudo los principales hallazgos de nuestro estudio fueron:

1 Los niveles absolutos de BNP disminuyeron a lo largo del tiempo post trasplante y correlacionaban con la función renal y la presión de aurícula derecha, pero no con la presencia de rechazo agudo.

2 Los cambios relativos de BNP si estaban influenciados por la presencia de rechazo. Un incremento de menos de 38% en los niveles de BNP mostro un valor predictivo del 97% para el diagnostico de rechazo.

3 Debido a su alto valor predictivo negativo, monitorización de BNP seriados podría ser útil en el diagnostico no invasivo del rechazo agudo y podría reducir el número de biopsias programadas y sus costes relacionados.

4 Mientras que con la troponina T convencional, un 54% de los pacientes presentaban concentraciones persistentemente indetectables, con la troponina T de alta sensibilidad se detectaron concentraciones medibles en todas las muestras de los pacientes independientemente de la presencia de rechazo.

5 Las concentraciones de troponina T de alta sensibilidad disminuyeron a lo largo del tiempo post trasplante y correlacionaban con la presión de aurícula derecha y la porción N terminal del péptido natriurético tipo B.

6 Las concentraciones de troponina T de alta sensibilidad son significativamente más elevadas en los casos de rechazo agudo.

7 Aunque su monitorización no evite la necesidad de biopsias, este estudio sugiere que concentraciones elevadas de forma mantenida de troponina T de alta sensibilidad en el periodo precoz post trasplante se asocian a una mayor probabilidad de rechazo.

8 Los niveles de sST2 correlacionaron con los niveles de proteína C reactiva, la porción N terminal del péptido natriurético tipo B y el recuento linfocitario.

9 Las concentraciones de sST2 eran significativamente más elevadas en la presencia de rechazo agudo. En nuestra población las concentraciones de sST2 en el momento de rechazo agudo eran más altas y presentaba un comportamiento dinámico en relación con el rechazo (aumento) y la respuesta al tratamiento anti rechazo (descenso), lo que sugiere que las concentraciones de sST2 son moduladas por la presencia de rechazo.

10 Las concentraciones de sST2 aportaban un valor añadido a la capacidad predictiva de rechazo de la porción N terminal del péptido natriurético B.

Sobre la detección precoz de la enfermedad vascular del injerto tras el trasplante cardiaco las principales conclusiones de nuestras investigaciones fueron:

1 La troponina T de alta sensibilidad fue un marcador de la enfermedad vascular del injerto.

2 Las concentraciones de la troponina T de alta sensibilidad se correlacionan con el grado de grosor intimal medido mediante ecografía intravascular o tomografía de coherencia óptica

3 La troponina T convencional no muestra esta correlación con el grado de grosor intimal.

4 Un valor inferior a 21 pg/mL se asocia con un 100% de sensibilidad y de valor predictivo negativo para la detección de enfermedad vascular del injerto severa.

5 La tomografía de coherencia óptica muestra una buena correlación con las medidas obtenidas mediante ecografía intravascular, con una menor variabilidad interobservador.

6 La tomografía de coherencia óptica tiene la ventaja de una mejor caracterización de la placa que puede determinar el manejo terapéutico.

7 La principal limitación de la tomografía de coherencia óptica es la atenuación en los grandes vasos debido a falta de penetración en la pared vascular.

9. Apendix / Apéndice

9.1 Acceptance submission letters / Cartas de aceptación de las publicaciones

9.1.1 Article 1 / Articulo 1

Date: Jan 05, 2009
To: "Iris P. Garrido" irisgarrido@secardiologia.es
From: "AJC Editorial Office" ajc@baylorhealth.edu
Subject: Your Submission

Ms. Ref. No.: AJC-D-08-02367R2
Title: Usefulness of Serial Monitoring of B-type Natriuretic Peptide for the Detection of Acute Rejection after Heart Transplantation
American Journal of Cardiology

Dear Dr. Iris P. Garrido,

Your manuscript is accepted and scheduled for publication in April 2009. Thanks for the changes.

Sincerely,

William C. Roberts, MD
Editor-in-Chief

9.1.2 Article 2 / Articulo 2

De: ees.rec.0.11f86a.a5aece89@eesmail.elsevier.com [mailto:ees.rec.0.11f86a.a5aece89@eesmail.elsevier.com] En nombre de Rev Esp Cardiol
Enviado el: martes, 21 de junio de 2011 11:12
Para: dapascual@servicam.com
Asunto: Decisión artículo / Article decission

Ms. Ref. No.: REC-D-11-00237R1
TITULO: Utilidad de la troponina T de alta sensibilidad en la detección de rechazo agudo en trasplante cardiaco - Usefulness of High Sensitivity Troponin T Assay in Detecting Acute Allograft Rejection After Heart Transplantation

Estimado Dr. Pascual-Figal,

Tengo el placer de comunicarle que su artículo de ref. REC-D-11-00237R1 ha sido aceptado para publicación en nuestra Revista.

En un futuro nuestra editorial le enviará pruebas de autor que usted deberá corregir y le informará sobre la fecha estimada de publicación. Tras este paso, tenga en cuenta que su artículo no se corregirá exhaustivamente, aunque sí pasará un proceso de corrección estilística.

Muchas gracias por enviar su trabajo a Revista Española de Cardiología.

Reciba un cordial saludo,
Magda Heras

Editora Jefe

9.1.3 Article 3 / Articulo 3

De: ats@uphs.upenn.edu [mailto:ats@uphs.upenn.edu]
Enviado el: lunes, 18 de julio de 2011 15:22
Para: Domingo A. Pascual-Figal
Asunto: ATS/2011/302315 - Manuscript Accepted

RE: MS ID# ATS/2011/302315
TITLE: Soluble ST2 is a marker for acute cardiac allograft rejection.

Dear Dr. Pascual-Figal:

Your revised paper has been received and is accepted for publication in The Annals of Thoracic Surgery. Thank you for being responsive.

The Editorial Office will check your submission for style points prior to transmitting it to our publisher. You will be contacted via email if more information is required, or if a correction needs to be made.

Congratulations and thank you for permitting us to publish this excellent contribution in The Annals.

Sincerely,

L. Henry Edmunds, Jr, M.D.
Editor

9.1.4 Article 4 / Articulo 4

Date: Apr 26, 2012
To: "Iris P. Garrido" irisgarrido@secardiologia.es
From: "AJC Editorial Office" ajc@baylorhealth.edu
Subject: Your Submission

Ms. Ref. No.: AJC-D-12-00415R1
Title: Optical Coherence Tomography and Highly Sensitivity Troponin T for Evaluating Cardiac Allograft Vasculopathy
American Journal of Cardiology

Dear Dr. Iris P. Garrido,

Your manuscript is accepted and scheduled for publication in September 2012. Thanks for the changes.

Sincerely,

William C. Roberts, MD
Editor-in-Chief

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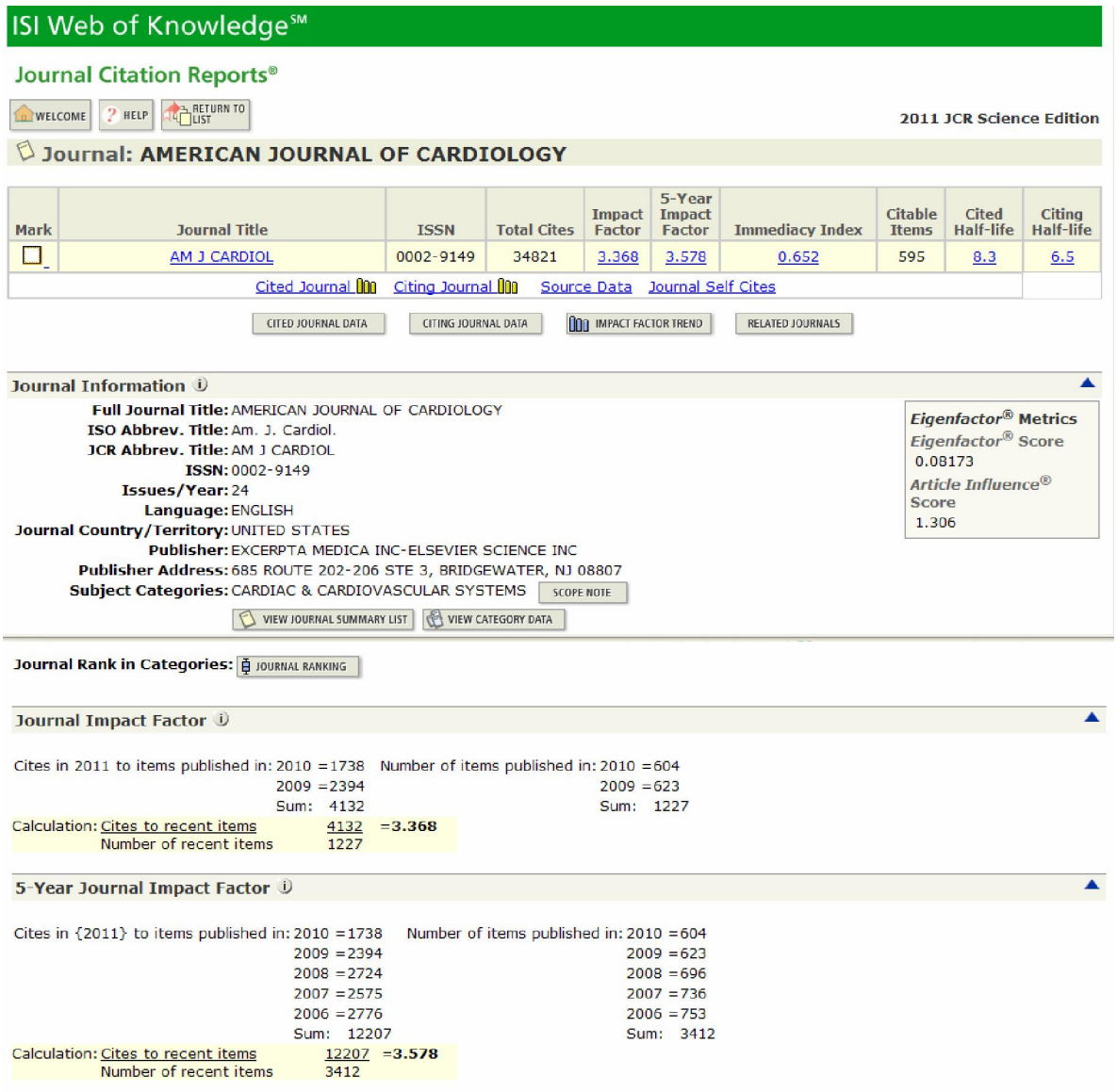
9.6 Impact factor of journals / Índice de impacto de las revistas



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2011 JCR Science Edition

Journal: AMERICAN JOURNAL OF CARDIOLOGY

Mark	Journal Title	ISSN	Total Cites	Impact Factor	5-Year Impact Factor	Immediacy Index	Citable Items	Cited Half-life	Citing Half-life
☐	AM J CARDIOL	0002-9149	34821	3.368	3.578	0.652	595	8.3	6.5

Cited Journal | Citing Journal | Source Data | Journal Self Cites

CITED JOURNAL DATA | CITING JOURNAL DATA | IMPACT FACTOR TREND | RELATED JOURNALS

Journal Information

Full Journal Title: AMERICAN JOURNAL OF CARDIOLOGY
ISO Abbrev. Title: Am. J. Cardiol.
JCR Abbrev. Title: AM J CARDIOL
ISSN: 0002-9149
Issues/Year: 24
Language: ENGLISH
Journal Country/Territory: UNITED STATES
Publisher: EXCERPTA MEDICA INC-ELSEVIER SCIENCE INC
Publisher Address: 685 ROUTE 202-206 STE 3, BRIDGEWATER, NJ 08807
Subject Categories: CARDIAC & CARDIOVASCULAR SYSTEMS SCOPE NOTE

VIEW JOURNAL SUMMARY LIST | VIEW CATEGORY DATA

Eigenfactor® Metrics
Eigenfactor® Score 0.08173
Article Influence® Score 1.306

Journal Rank in Categories: JOURNAL RANKING

Journal Impact Factor

Cites in 2011 to items published in: 2010 =1738, 2009 =2394, Sum: 4132
Number of items published in: 2010 =604, 2009 =623, Sum: 1227

Calculation: Cites to recent items 4132 / Number of recent items 1227 = **3.368**

5-Year Journal Impact Factor

Cites in {2011} to items published in: 2010 =1738, 2009 =2394, 2008 =2724, 2007 =2575, 2006 =2776, Sum: 12207
Number of items published in: 2010 =604, 2009 =623, 2008 =696, 2007 =736, 2006 =753, Sum: 3412

Calculation: Cites to recent items 12207 / Number of recent items 3412 = **3.578**

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2011 JCR Science Edition

Journal: REVISTA ESPANOLA DE CARDIOLOGIA

Mark	Journal Title	ISSN	Total Cites	Impact Factor	5-Year Impact Factor	Immediacy Index	Citable Items	Cited Half-life	Citing Half-life
☐	REV ESP CARDIOL	0300-8932	1932	2.530	2.131	1.089	124	4.2	5.0

Cited Journal | Citing Journal | Source Data | Journal Self Cites

CITED JOURNAL DATA | CITING JOURNAL DATA | IMPACT FACTOR TREND | RELATED JOURNALS

Journal Information

Full Journal Title: REVISTA ESPANOLA DE CARDIOLOGIA
ISO Abbrev. Title: Rev. Esp. Cardiol.
JCR Abbrev. Title: REV ESP CARDIOL
ISSN: 0300-8932
Issues/Year: 12
Language: SPANISH
Journal Country/Territory: SPAIN
Publisher: EDICIONES DOYMA S A
Publisher Address: TRAV DE GRACIA 17-21, 08021 BARCELONA, SPAIN
Subject Categories: CARDIAC & CARDIOVASCULAR SYSTEMS | SCOPE NOTE

VIEW JOURNAL SUMMARY LIST | VIEW CATEGORY DATA

***Eigenfactor*® Metrics**
***Eigenfactor*® Score**
0.00446
***Article Influence*® Score**
0.447

Journal Rank in Categories: JOURNAL RANKING

Journal Impact Factor

Cites in 2011 to items published in: 2010 = 280, 2009 = 312, Sum: 592
Number of items published in: 2010 = 111, 2009 = 123, Sum: 234

Calculation: Cites to recent items 592 / Number of recent items 234 = **2.530**

5-Year Journal Impact Factor

Cites in {2011} to items published in: 2010 = 280, 2009 = 312, 2008 = 208, 2007 = 167, 2006 = 190, Sum: 1157
Number of items published in: 2010 = 111, 2009 = 123, 2008 = 100, 2007 = 105, 2006 = 104, Sum: 543

Calculation: Cites to recent items 1157 / Number of recent items 543 = **2.131**

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Journal Citation Reports®

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2011 JCR Science Edition

Journal: ANNALS OF THORACIC SURGERY

Mark	Journal Title	ISSN	Total Cites	Impact Factor	5-Year Impact Factor	Immediacy Index	Citable Items	Cited Half-life	Citing Half-life
☐	ANN THORAC SURG	0003-4975	28219	3.741	3.503	0.774	610	7.8	6.8

Cited Journal | Citing Journal | Source Data | Journal Self Cites

CITED JOURNAL DATA | CITING JOURNAL DATA | IMPACT FACTOR TREND | RELATED JOURNALS

Journal Information

Full Journal Title: ANNALS OF THORACIC SURGERY
ISO Abbrev. Title: Ann. Thorac. Surg.
JCR Abbrev. Title: ANN THORAC SURG
ISSN: 0003-4975
Issues/Year: 12
Language: ENGLISH
Journal Country/Territory: UNITED STATES
Publisher: ELSEVIER SCIENCE INC
Publisher Address: 360 PARK AVE SOUTH, NEW YORK, NY 10010-1710
Subject Categories: CARDIAC & CARDIOVASCULAR SYSTEMS SCOPE NOTE VIEW JOURNAL SUMMARY LIST VIEW CATEGORY DATA
RESPIRATORY SYSTEM SCOPE NOTE VIEW JOURNAL SUMMARY LIST VIEW CATEGORY DATA
SURGERY SCOPE NOTE VIEW JOURNAL SUMMARY LIST VIEW CATEGORY DATA

***Eigenfactor*® Metrics**
***Eigenfactor*® Score** 0.06791
***Article Influence*® Score** 1.262

Journal Rank in Categories: JOURNAL RANKING

Journal Impact Factor

Cites in 2011 to items published in:	2010 =	1440	Number of items published in:	2010 =	510
	2009 =	2260		2009 =	479
	Sum:	3700		Sum:	989

Calculation: Cites to recent items 3700 / Number of recent items 989 = **3.741**

5-Year Journal Impact Factor

Cites in {2011} to items published in:	2010 =	1440	Number of items published in:	2010 =	510
	2009 =	2260		2009 =	479
	2008 =	2248		2008 =	511
	2007 =	2300		2007 =	597
	2006 =	2032		2006 =	838
	Sum:	10280		Sum:	2935

Calculation: Cites to recent items 10280 / Number of recent items 2935 = **3.503**