Diagnostic certainty of Multislice computerized tomography for the detection of Heart graft vasculopathy: comparison with invasive coronary angiography and intravascular ultrasound

Patricia Carrascosa (*), Carlos Capuñay (*), Jorge Carrascosa (*), Sergio Perrone (*), Gustavo Lev (†), Alejandro Deviggiano (*), Elba Martín López (*), Mario J. García (§)

Resumen

Objetivo: Evaluar la certeza diagnóstica de la tomografía computarizada multicorte (TCM) en pacientes trasplantados cardíacos para la detección de estenosis coronaria y vasculopatía del injerto cardíaco (VDI) en comparación con la angiografía coronaria (AC) y la ecografía intravascular (EIV), respectivamente.

Material y métodos: Diecinueve pacientes trasplantados cardíacos fueron estudiados con angiografía coronaria por TCM entre 7 a 14 días después del cateterismo (AD y EIV). Los estudios se llevaron a cabo con un tomógrafo multicorte de 16 filas. Dos observadores evaluaron en forma ciega los estudios de TCM para la detección de estenosis coronaria >50% y VDI.

Resultados: Para la detección de estenosis coronaria >50%, la sensibilidad fue: 80-88% y la especificidad: 98-99%; para la detección de VDI, 91-96% y 88-98%, respectivamente.

Conclusión: En esta serie preliminar, nuestros resultados mostraron que la TCM fue una técnica adecuada para evaluar pacientes trasplantados cardíacos y podría ser una alternativa a la AD y EIV para el seguimiento de estos pacientes.


Abstract

Accuracy of multidetector row computed tomography for the detection of transplant vasculopathy: comparison with invasive coronary angiography and intravascular ultrasound

Objective: To evaluate the diagnostic accuracy of multidetector computed tomography (MDCT) for detection of luminal stenosis and cardiac allograft vasculopathy in comparison with coronary angiography (CA) and intravascular ultrasound (IVUS) respectively.

Material and methods: Nineteen cardiac transplant patients scheduled for follow-up CA were included. MDCT coronary angiography was performed using a 16-row CT scanner within 7-14 days after CA and IVUS. Studies were analyzed by independent readers; two observers evaluated the CT datasets for the presence of coronary artery stenosis >50% and allograft vasculopathy.

Results: The sensitivity for detecting >50% luminal stenosis was 80-88% and specificity, 98-99% and for detection of cardiac allograft vasculopathy, the sensitivity was 91-96% and specificity, 88-91%.

Conclusion: In this preliminary series, our results indicate that MDCT coronary angiography was capable of detecting both significant coronary stenosis as well as diffuse intimal proliferation. This non-invasive procedure could be an alternative to CA and IVUS in the surveillance of heart transplant patients.

Key words: Allograft vasculopathy. Transplantation. Multidetector computed tomography. Intravascular ultrasound.

INTRODUCTION

Patients undergoing heart transplant require close follow up because graft vasculopathy (GV), a diffuse and unusually accelerated form of obliterating coronary atherosclerosis may develop. Its occurrence limits the long term survival of heart transplant recipients and is the main cause of death after the first year post-transplantation. The clinical diagnosis is difficult because the transplanted heart is denervated (1-4).

The incidence of angiographically visible GV is 50% five years post coronary transplant. The first changes show up after the first year as a result of endothelial dysfunction that cannot be detected by conventional angiography (CA) because it generally underestimates the extension of the disease (5, 6). Previous studies have shown the advantages of intravascular ultrasound (IVUS) in identifying this entity. Up to this date it remains as the most sensitive method to evaluate the severity and progression of

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the disease within the first stages (7-10). IVUS provides information of the vascular wall morphology and the degree of intimal thickening. However, it is an invasive technique involving significant risks and high cost for patients.

Coronary angiography through Multislice CT is a diagnostic imaging modality that is non-invasive and has shown high accuracy for the detection of obstructive coronary disease in non-transplanted patients (11, 12).

The aim of this study is to assess the diagnostic certainty of MSCT in the detection of heart graft vasculopathy and of coronary stenosis in transplanted patients in comparison with CA and IVUS, respectively.

MATERIAL AND METHODS

Study population

Patients were prospectively included, the initial sample size was 24 recipients of a heart transplant scheduled to be followed up by CA. Nineteen were studied with IVUS and MSCT. The exclusion criteria were a history of contrast agent allergy, renal dysfunction (serum creatinine above 1.5 mg/dl) and diabetes. There were five patients that were not included because of renal dysfunction. Serum creatinine levels were tested at 24-48 hours before and 7 days after the test to monitor renal function. Table 1 lists the characteristics of the population under study.

The Institutional Review Board reviewed and approved the protocol and an informed consent was obtained from every patient.

MSCT Protocol

A coronary angiogram was obtained with the MSCT scanner 7 to 14 days after the CA. The images were obtained with a 16-slice CT scanner (Brillance-16, Philips Medical Systems, Cleveland, Ohio), with 0.8 mm thickness sections, 0.4 mm reconstruction interval, pitch 0.24, 120 Kv, 500 mAs and 420 ms of gantry rotation. No beta blockers were administered. The acquisition was performed with the intravenous administration of 100 ml of non-ionic contrast agent [350 mg/ml of iodine (Iobitridol); Xenetix® 350, Laboratory Temis-Lostaló, Buenos Aires, Argentina] in a dual phase-injection. The first 60 ml were applied at a rate of 4 ml/sec followed by 40 ml at a rate of 3.5 ml/s. A multicycle adaptive heart reconstruction technique (multi-segments) was used to combine the data of consecutive heart cycles significantly improving the temporal resolution between 53 and 210 ms (13, 14). The reconstructed phases were transferred to a workstation (Extended Brilliance Workspace (EBW), Philips Medical Systems, Highland Heights, OH) for post-processing. The MPR images were used to assess the presence of coronary stenosis and diffuse intimal proliferation. Measurements were made of the normal lumen diameters and the segments of the affected coronaries to calculate the percent stenosis. GV was defined as a segment of intimal proliferation > 0.5 mm in the axial and multi-planar reformatted images. Two independent observers blinded to the CA and IVUS results evaluated the MSCT data. The coronary artery analysis was performed in accordance with the 15-segment model of the American Heart Association (15).

CCA Protocol

The invasive CA was performed in the standard fashion using the Judkins technique. Every patient received 100 to 325 mg/day of aspirin during at least 72 hours before the acquisition, 70 UI/kg of unfractionated heparin and 0.2 mg of intra-arterial nitroglycerine immediately before the procedure. The segments analyzed had a diameter >1.5 mm using the quantitative measurement method (QCA). A stenosis >50% was considered as a truly positive result.

IVUS Protocol

After the CA diagnosis was made, an IVUS was obtained using a 30 MHz and 3.2-F ultrasound probe. All the coronary arteries were assessed by IVUS. We recorded cross section images of the selected arteries with 30 mm increments from the most distal location of the transducer (luminal diameter: 1.5 mm) up to the ostium through an automatic pullback system moving from distal to proximal with full video recording. The presence of graft vasculopathy was determined in every coronary segment.

Table 1: Characteristics of the population under study.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>n = 19</td>
</tr>
<tr>
<td>Age (years)</td>
<td>Mean (SD) 53 (12)</td>
</tr>
<tr>
<td>Gender</td>
<td>Males 17</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>Mean (SD) 27.04 (0.23)</td>
</tr>
<tr>
<td>Cardiovascular risk factors</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>11</td>
</tr>
<tr>
<td>Dislipidemia</td>
<td>12</td>
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<tr>
<td>Familial</td>
<td>3</td>
</tr>
<tr>
<td>Aetiology of heart disease before transplantation</td>
<td></td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>1</td>
</tr>
<tr>
<td>Ischemic dilated cardiopathy</td>
<td>9</td>
</tr>
<tr>
<td>Idiopathic dilated cardiomyopathy</td>
<td>5</td>
</tr>
<tr>
<td>Alcohol induced dilated cardiomyopathy</td>
<td>1</td>
</tr>
<tr>
<td>Cardiomyopathy secondary to valve disease</td>
<td>2</td>
</tr>
<tr>
<td>Dynamic obstructive hypertrophic cardiomyopathy</td>
<td>1</td>
</tr>
<tr>
<td>Time elapsed since transplant (months)</td>
<td>Mean(SD) 88.10 (35.48)</td>
</tr>
</tbody>
</table>

Table 1: Characteristics of the population under study.
Statistical Analysis

The CTA was the method of reference to determine luminal stenosis whilst IVUS was considered as the method of reference to determine diffuse intimal proliferation. The number of segments evaluated depended on the individual anatomy of each patient. The sensitivity, specificity and probability coefficients of every MSCT image were calculated using the binomial exact method. Inter-observer variability was evaluated using the Kappa coefficient.

RESULTS

No complication developed in the patients studied. Mean heart rate during the study was $90 \pm 13.5$ beats per minute with a variability of $2.5 \pm 3$ b/m. The mean SD of the previous serum creatinine levels and those obtained 7 days after the MSCT were $1.1 (0.2)$ mg/dl and $1.1 (0.1)$ mg/dl respectively. All the patients were under immunosuppressive therapy (prednisone, n=14; cyclosporine n=13; micofenolate mofetil n=15; tacrolimus, n=9) and 14 were treated with statins.

Heart Graft Vasculopathy

A total of 227 segments evaluated with MSCT correlated with the IVUS findings. GV was detected in 24.6% of the coronary segments (56/227) and in 73.7% of the patients (14 out of 19) (Fig. 1). The MSCTA sensitivity reached 91.07% for Observer 1 and 96.43% according to Observer 2. The MSCTA and IVUS match was 89% (202/227) according to Observer 1 and 93% (211/227) according to Observer 2. The MSCTA inter-
observer variability was $k = 0.848998$ ($0.731895 - 0.966101$), $p < 0.0001$. Table 2 shows the complete results of the statistical analysis.

**Luminal Stenosis**

A total of 280/285 vascular segments were compared with both methods (MSCT and CA). Only five segments were not feasible of being evaluated due to movement artefacts. CA detected 26 stenotic coronary segments in 13 patients (Fig. 2). The MSCTA sensitivity was as high as 88.46% according to Observer 1 and 80.77% according to Observer 2. The MSCTA concordance with CA was 98.2% (275/280) for Observer 1 and 96.0% (270/280) for Observer 2. The MSCTA inter-observer variability was $k = 0.917917$ ($0.789227 - 1.046608$), $p < 0.0001$. Table 2 shows the complete results of the statistical analysis.

**DISCUSSION**

In this preliminary series MSCTA proved as an adequate technique to evaluate heart transplant patients. In spite of the particular characteristics of the population under study (patients subjected to surgery, high heart rates (mean HR: 90 b/m), there was a low number of coronary segments that were not feasible of being evaluated. As a result of the autonomic denervation of the grafted heart the action of beta blockers on heart rate is poor and the positive inotropic effect that is usually associated in normal conditions to the contrast injection is practically inexistent. For this reason, and although these patients’ heart rate is high their minimal variability during the acquisition ($2.5 \pm 3$ bpm) added to the utilization of multi-segment reconstruction algorithms facilitated the acquisition of images free of heart movement artifacts.

Classically speaking, graft vasculopathy at an early stage is clinically silent and therefore CTA is essential to be able to watch its occurrence \(^1\). However, CA is poorly sensitive in the early detection of the disease and tends to underestimate its extension. In a recent study Kobashigawa \(^10\) reported that 28% of heart transplant recipients did not present angiographic evidence of coronary disease. IVUS, on the other hand is a very sensitive method to evaluate GV providing quantitative information on wall morphology, the degree of intimal proliferation, luminal diameter, plaque characteristics and total vessel area \(^7,8,9\). Its wide utilization is however limited by its cost and invasive nature. Over the last few years several non-invasive imaging methods were proposed for the routine detection of GV. However, neither stress echocardiography with dobutamine, nuclear studies or electron beam tomography have shown to be sufficiently sensitive or specific to be considered as reliable tests \(^10,16-19\).

MSCT is a non-invasive imaging modality that has shown to be highly accurate in the detection of...
obstructive coronary disease in non-transplanted patients (11, 12). Significant improvements have been achieved in terms of spatial and temporal resolution, both factors of substantial importance for the study of cardiac images. Romeo et al. (20), using a 16-slice MSCT scanner showed in heart transplant patients a sensitivity of 83%, a specificity of 95% and a diagnostic accuracy of 93% for the detection of coronary stenosis > 50%. In another article Sigurdsson et al. (21) showed in 54 heart transplant recipients a good correlation between 16-slice MSCT and quantitative coronary angiography (r = 0.75, p < 0.01). They showed on the basis of 754 segments feasible of being analyzed in MSCT, a sensitivity of 86% and a negative predictive value of 99% in the detection of segments with stenosis > 50% and proposed that the CA follow up requirement of patients could be mitigated by using MSCT.

Recently, Gregory et al. (22) reported that 64-slice MSCT provides good to excellent image quality in heart transplant recipients with a sensitivity of 70% and a specificity of 92% in comparison with IVUS for the detection of GV.

In our series, 16-slice MSCT showed a sensitivity of 91-96% and a specificity of 88-92% in GV detection compared to IVUS with a very good inter-observer variability.

Our results show that GV diagnosis is feasible with MSCT.

However, the method showed a lower sensitivity (81-88%) for the detection of coronary stenosis a fact attributable to the small number of patients included in the sample and the low prevalence of obstructive disease.

Limitations

Although MSCT is a non-invasive method it does require an injection of intravenous contrast. This is an important factor to bear in mind since a considerable number of these patients present renal function impairment or are at a high risk of developing contrast-associated nephropathy. In spite of this fact MSCT may be a viable method in patients with mild renal failure because good quality images have been obtained with lower contrast agent doses (23). No adverse reactions were found in our series related to the contrast agent administered but one should not overlook the fact that all the patients included in this study had normal renal function (5 patients excluded due to renal failure).

Radiation is the other point to be considered. The radiation dose with MSCT was somewhat higher than the one used in routine CA (10 to 13 mSv vs. 5 to 6 mSv). The use of tube current modulation and prospective acquisition techniques significantly reduces the total radiation dose but its application in patients with high heart rate is limited.

In terms of the technical factors, we should point out that the section thickness of the 16-slice scanner was 0.75 mm. Consideration must be given to the fact that IVUS images indicate GV through the presence of an intimal thickening of > 0.5 mm that may change the outcome of the disease significantly and that 16-slice MSCT limits the detection to moderate and severe vasculopathy. The new generation of 64-slice and 256-slice CT scanners provides not only an improved temporal resolution but also a spatial resolution under 0.5mm that potentially broadens the diagnostic range of this entity.

**CONCLUSIONS**

In our preliminary series MSCT showed adequate diagnostic quality in patients receiving a heart transplant in spite of the high heart rate that prevails in the population under study and may thus be considered as an alternative to CTA and IVUS to detect the exis-

<table>
<thead>
<tr>
<th>Detection of stenosis &gt; 50 % *</th>
<th>Detection of intimal proliferation §</th>
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<tbody>
<tr>
<td><strong>Observer 1</strong></td>
<td><strong>Observer 2</strong></td>
</tr>
<tr>
<td>TP (n)</td>
<td>23</td>
</tr>
<tr>
<td>TN (n)</td>
<td>252</td>
</tr>
<tr>
<td>FP (n)</td>
<td>2</td>
</tr>
<tr>
<td>FN (n)</td>
<td>3</td>
</tr>
<tr>
<td>S (%(CI 95%))</td>
<td>88.46 (66.85-97.55)</td>
</tr>
<tr>
<td>Sp (%(CI 95%))</td>
<td>99.21 (97.18-99.9)</td>
</tr>
<tr>
<td>PC positive</td>
<td>112.34 (31.07-411.38)</td>
</tr>
<tr>
<td>PC negative</td>
<td>0.11 (0.04-0.29)</td>
</tr>
<tr>
<td>Abbreviations: TP: truly positive; TN: truly negative; FP: false positive; FN: false negative; S: sensitivity; Sp: specificity PC: probability coefficients; CI: confidence intervals. * Compared with coronary angiography. § Compared with intravascular ultrasound.</td>
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</table>
Fig. 3. Patient with signs of mild, diffuse intimal proliferation in the right coronary artery. This finding is visible in the curved multiplanar reconstructions in the CT orthogonal to the Wessel axis and in the intravascular ultrasound (arrows). A & B. curved multiplanar reconstruction. C. Axial MSCT image at the level of intimal thickening (arrow). D. Intravascular ultrasound image of the intimal thickening (arrow). E. Volume rendering reconstruction of the right coronary artery. Intimal thickening is hard to identify in this kind of reconstruction. F. The conventional coronary angiogram does not show signs of the disease.
tence of coronary stenosis as well as of diffuse myointimal proliferation in the non-invasive follow up and control of heart transplant recipients.

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Bibliography


