Coronary Stenosis Detection by 16-Slice Computed Tomography in Heart Transplant Patients
Comparison With Conventional Angiography and Impact on Clinical Management

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OBJECTIVES
We sought to find a non-invasive alternative to conventional coronary angiography (CCA) for serial detection and follow-up of coronary stenosis due to cardiac allograft vasculopathy in heart transplant patients.

BACKGROUND
Cardiac allograft vasculopathy is the main factor limiting long-term success of heart transplantation. It is usually detected by CCA. Multislice computed tomography (MSCT) coronary angiography has recently proven effective for the diagnosis of coronary stenosis in non-transplant patients.

METHODS
Fifty-three consecutive heart transplant patients underwent MSCT within 24 h before or after their annual routine CCA. Only angiographic segments >1.5 mm were considered for analysis; the coronary arterial tree was divided into nine segments. Three patients were excluded because of technical failure.

RESULTS
Of the 450 angiographic coronary segments, 432 (96%) were evaluable by MSCT. Of the nine coronary stents in seven patients, only three, including one intrastent restenosis, were correctly evaluated by MSCT, and two intrastent restenoses were missed. Complete analysis of the coronary tree was possible for 44 (88%) of the 50 patients. For detection of coronary stenosis >50%, sensitivity was 83%, specificity 95%, positive predictive value 71%, negative predictive value 95%, and accuracy 93%. In the 22 patients with strictly normal MSCT, no stenosis was found by CCA.

CONCLUSIONS
Our study suggests the following guidelines already applied in our institution: 16-slice MSCT can replace CCA in de novo heart transplant patients and patients with strictly normal MSCT at follow-up. Significant wall or lumen changes observed on annual MSCT or stents require further investigation by CCA. (J Am Coll Cardiol 2005;45:1826–31) © 2005 by the American College of Cardiology Foundation

Cardiac allograft vasculopathy (CAV) is the main factor limiting the long-term success of heart transplantation (1). The prevalence of CAV assessed by conventional coronary angiography (CCA) ranges from 7.9% one year after heart transplantation to 43% after seven years (2). It is a progressive and usually extensive disease involving both epicardial and small coronary vessels. Its origin is mostly immunologic (immune-mediated endothelial injury), but it may be influenced by non-immunologic factors, such as systemic hypertension, diabetes, and lipid disorders (1,3,4). It occurs most often without any ischemic symptoms, because the heart is partially denervated. Its progression in heart transplant patients can be very rapid, and the first manifestation of CAV can therefore be sudden death, congestive heart failure, or cardiac arrhythmia. Because of the silent nature of CAV, the rule is to perform annual screening for CAV in heart transplant patients. Currently available noninvasive functional tests (e.g., treadmill test, thallium scintigraphy, and dobutamine stress echocardiography) lack adequate sensitivity and specificity to predict either CAV or clinical outcome in heart transplant patients (5–8). For these reasons, routine CCA remains the gold standard for diagnosis and follow-up of CAV. Intravascular ultrasound (IVUS) has recently been recognized as the most sensitive diagnostic tool for early detection of CAV, but remains an invasive technique (1,9), thus preventing its widespread use.

New multislice computed tomography (MSCT) technology allows direct non-invasive visualization of the anatomy of coronary vessels, including the vessel wall and lumen (10–13).

The aim of this study was to assess the efficacy of MSCT for the detection of significant focal stenosis in heart transplant patients, using CCA as the reference method.

METHODS
Patients. Between April 2003 and July 2004, 53 consecutive heart transplant patients underwent 16-slice CT within the 24 h before or after their annual routine CCA. Exclusion criteria were severe renal insufficiency (blood creatinine >250 μmol/l), severe cardiac insufficiency, or an unstable clinical condition. Patients with a previous allergic reaction to iodinated contrast media received anti-allergic therapy for the three days preceding the examination. All patients gave written, informed consent, and the protocol had institutional review board approval. All patients were studied once.
The clinical characteristics of the patients are summarized in Table 1. The mean post-transplant time was 7.6 ± 3.8 years (range 1 to 14.5 years). The mean age was 48 ± 19 years (range 7.6 to 75 years). There were 40 men and 13 women. All patients received the same immunosuppressive regimen of cyclosporine, mycophenolate mofetil, and corticoids.

**MSCT technique.** All examinations were performed with a Siemens Sensation 16-slice CT (Siemens AG, Erlangen, Germany). Oral beta-blockers (metoprolol 100 mg) were administered to all patients 1 h before MSCT to obtain a resting heart rate <70 beats/min. No sedation was required. The standard acquisition protocol included a 420-ms rotation time, a 0.75-mm slice thickness, and a 70 to 90 ml injection of iodine contrast medium (concentration 370 mg/ml) (iopamidol, Schering S.A., Berlin, Germany). The flow rate was 3.5 ml/s. The images were acquired using 120 kV and 500 mAs in normal weight patients. Parameters were adapted for light or overweight patients.

A first set of images was reconstructed systematically at −400 ms before the QRS complex, using a 1-mm slice thickness and a 0.8-mm increment per slice, with a smooth kernel and mediastinum windows. Additional reconstructions were performed in the presence of coronary stents, substantial calcifications, or heart motion artifacts, or if images were excessively noisy. In cases of heart motion artifacts, additional sets of images were created for various points of the cardiac cycle, and the data set with the least motion artifact was selected for further analysis.

Even if a cross-sectional image of the coronary artery could be easily obtained, spatial resolution with 16-slice CT is insufficient for reliable quantitative measurements in diseased areas. Therefore, as in other studies (10,13), coronary wall thickening and stenosis were assessed visually by an experienced observer blind to the CCA findings. The visual assessments of coronary anatomy were graded on a three-step severity scale: N = normal; WT = wall thickening without significant stenosis (calcified or non-calcified plaque restricting the lumen of <50% in diameter); S = stenosis (>50%) or occlusion. Calcifications were rare in this population, often small and localized, and did not impair visual assessment of coronary lesions. Only vessels >1.5 mm in diameter were considered for MSCT evaluation. Each coronary tree was divided into nine main coronary segments for analysis: left main artery, left anterior descending (LAD) artery (proximal, middle, and distal), left circumflex artery (proximal and distal), right coronary artery (first, second, and third segments). The first and second diagonal branches were considered to be parts of the middle and distal LAD, respectively. The first and second marginal branches were considered to be parts of the distal circumflex artery.

**CCA.** Coronary angiography was performed according to standard technique, using 4- or 5-F catheters. Coronary wall thickening was defined as an arterial wall irregularity or loss of concentric profile of the vessel without significant stenosis (<50% in diameter). The degree of stenosis was evaluated visually by two experienced operators and scored using the scale described earlier.

The status of each of the nine coronary segments for each patient, as assessed by MSCT, was compared with the findings by CCA used as the reference standard. Sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) were calculated for detection of significant stenosis by MSCT.

## RESULTS

The MSCT imaging was performed without complications in all patients. The duration of MSCT did not exceed 20 s. The mean heart rate before the administration of metoprolol was 83 ± 13 beats/min and fell to 69.5 ± 11 beats/min (range 43 to 95 beats/min) at the time of MSCT. The entire nine-segment coronary tree was successfully visualized by MSCT in 50 of 53 of the heart transplant patients (a total of 450 coronary arterial segments). In three patients, the coronary arteries could not be correctly evaluated because of technical failure, due to the patient being unable to hold their breath (n = 2) or irregular heart rhythm (n = 1). These three patients were excluded from further evaluation. Eighteen segments <1.5 mm in six patients could not be correctly analyzed, including six of nine stents. Visualization was thus satisfactory in 432 (96%) of 450 segments, and complete analysis of the coronary arterial tree was possible for 44 (88%) of 50 patients. Calcifications were detected by MSCT in 15 (30%) of the 50 patients. They were limited to small, calcified, parietal nodules in 13 patients and did not impair visual assessment of coronary lesions. Only two patients had heavy calcifications impairing coronary analysis.

### Analysis by coronary segments

The results of the analysis by coronary segments are detailed in Table 2.

### NORMAL SEGMENTS

There were 314 of 432 segments scored as normal by MSCT analysis. All segments identified as normal by MSCT were also found to be normal with CCA, except for seven segments scored as thickened by CCA.

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**Table 1. Clinical Characteristics of the Patients**

<table>
<thead>
<tr>
<th>Years After HT</th>
<th>No. of Patients</th>
<th>Age at HT (yrs)</th>
<th>No. of Stents</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–5</td>
<td>12</td>
<td>44.5 ± 17.5</td>
<td>0</td>
</tr>
<tr>
<td>5–10</td>
<td>20</td>
<td>36 ± 21</td>
<td>3</td>
</tr>
<tr>
<td>10–15</td>
<td>18</td>
<td>41.5 ± 18</td>
<td>6</td>
</tr>
</tbody>
</table>

HT = heart transplantation.
WALL THICKENING ASSESSMENT. A total of 108 coronary segments were scored as thickened by MSCT, whereas only 60 were by CCA (p = 0.000 by the Fischer exact test): 55 of the 108 segments considered as thickened by MSCT were considered normal by CCA. These 55 discordant findings were only in five patients. Two segments considered as thickened by MSCT were found to have significant stenosis with CCA (one proximal LAD and one first marginal branch).

STENOSIS DETECTION. Significant stenosis was diagnosed by MSCT in 10 segments, but only eight of them were considered as stenotic by CCA. Two segments in the middle and distal LAD, considered as having significant stenosis by MSCT, were only scored as thickened on CCA. These two segments were not assessed by physiologic testing. Ten significant stenoses (≥50% in diameter) were diagnosed by CCA in six patients. Three were located in the LAD and seven in the circumflex artery. Two occurred within a previously implanted intracoronary stent. Two patients had multivessel disease, and in all the other patients, one single vessel was affected.

STENT EVALUATION. Nine stents were analyzed in seven patients (two in the LAD, three in the diagonal branches, two in the circumflex artery, and two in the right coronary artery). Only three stents could be correctly evaluated by MSCT, including one intrastent restenosis (ISR) correctly detected. In the other six cases, MSCT failed to analyze intrastent anatomy, and significant ISR was missed by MSCT in two stented segments, probably because of the small size of the stent and heart rate >70 beats/min.

NON-INTERPRETABLE SEGMENTS. Eighteen segments could not be correctly evaluated by MSCT, and they included six stents (with two cases of ISR missed). In the remaining 12 segments, three stenoses and two wall thickenings located in coronary segments <1.5 mm were identified by CCA but not by MSCT.

Analysis by Patients. Results of analyses by patients are detailed in Table 3.

PATIENTS WITH NORMAL CORONARY ARTERIES (FIG. 1). In the 22 patients with completely normal MSCT, no stenosis was found by CCA, and 20 (91%) of 22 also had strictly normal CCA. Two patients had normal MSCT, but wall thickening without significant stenosis was detected by CCA.

DISCUSSION

Although considerable progress has been made in the avoidance of early acute rejection, due to the recent emergence of new immunosuppressive agents, including mycophenolate mofetil, no real preventive treatment against CAV has been available until recently. Still, CAV remains the inevitable stumbling block of heart transplantation, and the only effective treatment is retransplantation. However, efforts are continuing to improve early detection of the disease, with the hope that palliative treatments such as coronary angioplasty with or without the use of stents could increase the survival of the graft. This assumption is increasingly disputed (14), and the clinical utility of routine coronary angiography, still used in most centers including ours, has been questioned (15,16).

However, the recent clinical evaluations of molecular target of rapamycin inhibitors (sirolimus and everolimus) provide a new hope. These drugs could, for the first time since heart transplantation has been used, prevent CAV, slow its progression, and even (one case reported with sirolimus) allow regression of coronary lesions (17). Everolimus, administered in association with cyclosporine, seems to be the only effective treatment is retransplantation. However, efforts are continuing to improve early detection of the disease, with the hope that palliative treatments such as coronary angioplasty with or without the use of stents could increase the survival of the graft. This assumption is increasingly disputed (14), and the clinical utility of routine coronary angiography, still used in most centers including ours, has been questioned (15,16).

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STENOSIS DETECTION (FIG. 3). Among the seven patients having at least one >50% stenosis detected by MSCT (both in cross section and multiple views of the vessel), CCA diagnosed only wall thickening and no stenosis in two (two false-positives, located in the middle and distal LAD). Physiologic testing was not performed in these two cases. One significant stenosis detected by CCA in the distal left posterior descending artery was wrongly considered as wall thickening by MSCT (one false-negative). This last stenosis was not amenable to intervention.

For the 44 patients in whom coronary arteries could be evaluated by MSCT, the overall sensitivity of MSCT for detection of stenosis was 83%, specificity 95%, PPV 71%, NPV 95%, and accuracy 93%.

Table 2. Analysis by Coronary Segments

<table>
<thead>
<tr>
<th>MSCT/CCA</th>
<th>N</th>
<th>WT</th>
<th>S</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>307</td>
<td>7</td>
<td>0</td>
<td>314</td>
</tr>
<tr>
<td>WT</td>
<td>55</td>
<td>51</td>
<td>2</td>
<td>108</td>
</tr>
<tr>
<td>S</td>
<td>0</td>
<td>2</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>362</td>
<td>60</td>
<td>10</td>
<td>432</td>
</tr>
</tbody>
</table>

CCA = conventional coronary angiography; MSCT = multislice computed tomography; N = normal; S = stenosis; WT = wall thickening.

Table 3. Analysis by Patients

<table>
<thead>
<tr>
<th>MSCT/CCA</th>
<th>N</th>
<th>WT</th>
<th>S</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>20</td>
<td>2</td>
<td>0</td>
<td>22</td>
</tr>
<tr>
<td>WT</td>
<td>5</td>
<td>9</td>
<td>1</td>
<td>15</td>
</tr>
<tr>
<td>S</td>
<td>0</td>
<td>2</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>25</td>
<td>13</td>
<td>6</td>
<td>44</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 2.
particularly promising (18). If these preliminary results are confirmed, the widespread use of these new immunosuppressors will renew the importance of early detection of CAV to allow appropriate medical treatment. In this context, a reliable and noninvasive method of detection is required. Conventional coronary angiography has been proven to underestimate the severity of CAV, because these lesions particular to heart transplant patients develop in a concentric fashion, mimicking normal coronary arteries during the early phase. It is an invasive technique and inevitably involves some degree of risk. In addition, routine annual CCA is perceived as uncomfortable and psychologically painful to heart transplant patients. It is now recognized that the long-term success of heart transplantation largely depends on the patient’s compliance with a treatment and follow-up regimen (19). Any opportunity to alleviate the burden on these patients must be seized.

Here, we demonstrate that MSCT can provide an accurate, non-invasive evaluation of CAV by showing coronary wall thickening and by detecting significant coronary stenosis in heart transplant patients.

Because CCA shows only luminal changes, without
direct visualization of the arterial wall, early assessment of mural changes induced by this vasculopathy is limited. In addition, CAV is typically a diffuse phenomenon, which may be difficult to detect during the early phase. Several studies report that CCA is less sensitive than IVUS studies to detect wall thickening (20).

Multislice CT could be more appropriate than CCA for this kind of evaluation, by showing both mural and luminal coronary changes associated with this vasculopathy. Our study suggests that MSCT may be more sensitive than CCA for detection of thickened segments (108 vs. 60) (Table 2).

However, for ethical and also practical reasons, we did not compare MSCT findings to IVUS. The aim of this study was not to evaluate wall thickening but to investigate how to detect and above all not miss coronary stenosis in this particular population. However, only 51 (85%) of 60 segments considered as thickened by CCA were also found thickened by MSCT. Wall changes were assessed visually by one experienced radiologist, using cross-sectional views of the artery to ensure a concentric gray area surrounding the wall lumen, opacified with contrast medium. Most of these findings were unambiguous (Fig. 1), but minor wall changes may be missed. Recent reports showed that MSCT is valuable for detecting atherosclerotic plaques and that the findings correlate well with those by IVUS (11,12). Multislice CT is thus a promising technique for coronary wall evaluation.

Three hundred and seven (71%) of 432 segments, including two stented segments, were considered as normal by MSCT, none of them being stenotic by CCA, and none of the 22 patients with normal coronaries, as assessed by MSCT, had coronary stenosis, as assessed by CCA. This represents the main point of interest of our study for clinical management of heart transplant patients: the NPV was high (95%). This high NPV is comparable to that observed in coronary atherosclerosis (10,13). A normal MSCT in this clinical setting may make subsequent annual CCA unnecessary. This was the secondary aim of this study: to find a noninvasive technique to replace CCA.

In the subgroup of 15 patients with wall thickening but no significant stenosis detected by MSCT, two stenoses were missed in the same patient. Because the spatial resolution of MSCT is lower than that of CCA, detection of stenosis may be more difficult in thickened segments, because the artery lumen is already smaller in a diffuse fashion. Such findings in heart transplant patients should lead to careful analysis before excluding significant narrowing, and in some cases, CCA may be required for confirmation.

Eight stenoses were correctly diagnosed by MSCT in 10 evaluable segments, but three were missed in non-evaluable vessels <1.5 mm. In addition, two cases of ISR were missed. Intrastent analysis was not reliable with 16-slice CT, because only three (33%) of nine of the stents could be correctly visualized. Our study clearly indicates that the only reliable tool for detection of ISR at the present time remains CCA.

Study limitations. The main limitation of this study concerns the size of the vessels, which must be >1.5 mm in diameter to be correctly evaluated. Three stenoses were missed in vessels <1.5 mm. However, these stenoses would not have been accessible to percutaneous angioplasty because of the small size of the vessel.

Another limitation is that the heart rate must be <70 beats/min, which is rarely the case in this population.

Figure 3. (A) Multislice computed tomography: severe stenosis of the first segment of the circumflex artery (Cx) associated with distal stenosis in the circumflex artery (arrows). (B) Same patient, with conventional coronary angiography: severe stenosis of the first segment of the circumflex artery associated with distal stenosis in the circumflex artery (arrows). Ao = aorta; LAD = left anterior descending artery.
Cardiac re-innervation is highly variable in heart transplant patients, and the efficacy of beta-blockers is also, consequently, variable and often limited. However, the mean heart rate decreased from 83 to 69.5 beats/min after oral administration of metoprolol, permitting good-quality images in the majority of our patients.

The requirement for an experienced observer for MSCT analysis, because of the necessity of visual assessment of wall thickening and stenosis, is another limiting factor. Coronary calcifications often impair assessment of stenosis by MSCT in atherosclerotic patients (13), but the calcifications observed in our population of heart transplant patients were of a different nature and hindered the analysis in only two cases.

The radiation dose is a real problem in this population. These patients are exposed to repeated examinations. However, in our institution, we systematically use an electrocardiographic pulsing technique to reduce the radiation dose during systole, allowing a reduction of up to 40% of the radiation dose (21). We also apply individual adaptation according to the patient’s morphology. Due to these adaptations, the radiation doses used are 3 to 8 mSv, in the same range as CCA.

Patients with moderate renal insufficiency were hydrated after MSCT, and creatinine did not increase.

Conclusions. Our study provides information on the potential of MSCT for non-invasive follow-up of heart transplant patients. Our results suggest the following guidelines, which are already applied in our institution:

1. Multislice CT can replace CCA for annual screening of coronary stenosis in de novo heart transplant patients.
2. For other transplant patients, a strictly normal MSCT at follow-up indicates that subsequent CCA is not necessary.
3. Patients with coronary wall thickening on MSCT should be closely monitored, and CCA could be proposed on a case-by-case basis.
4. Patients with coronary stenosis detected by MSCT must undergo CCA to confirm the stenosis and, if necessary, undergo angioplasty.
5. Patients with stents are not eligible for MSCT and require CCA.

These preliminary results are sufficiently encouraging to have modified our protocol for annual screening of CAV in heart transplant patients. In the near future, the expected improvements in MSCT technology may allow a better analysis of coronary lesions and ISR. Further evaluation is warranted to confirm that the guidelines we propose herein are clinically appropriate.

References


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