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Screening of cardiac allograft vasculopathy in heart transplant patients with coronary computed tomography angiography

Ana Filipa Amador,[1] Sandra Amorim,[1] Tânia Proença,[1] Mariana Vasconcelos,[1] Marta Tavares Da Silva,[1] João Rebelo,[2] André Carvalho,[2] José Pinheiro-Torres,[3] Paulo Pinho,[3] Rui Rodrigues[1]

[1]Department of Cardiology, São João Hospital and University Center, Porto; [2]Department of Radiology, São João Hospital and University Center, Porto; [3]Department of Cardiothoracic Surgery, São João Hospital and University Center, Porto, Portugal

Correspondence: Ana Filipa Polido Amador, Department of Cardiology, São João Hospital and University Center, Alameda Hernani Monteiro, Porto, 4200-319, Portugal.
Tel.: +351933176428.
E-mail: a.filipa.amador@gmail.com

Key words: screening, heart transplant, coronary allograft vasculopathy, coronary computed tomography angiography.

Contributions: AFA, SA, were responsible for the design of the work, acquisition, analysis, and interpretation of the data, as well as drafting the paper; TP, designed the CT protocol and contributed to the paper draft; MV, was responsible for the design of the work; MV, MTDS, JR, AC, performed the CT and revised of the paper; JPT, PP, RAR, reviewed the paper critically for important intellectual content. All authors finally approved the submitted version and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of interest: the authors declare no potential conflict of interest.

Ethics approval and consent to participate: the study was performed according to the recommendations of the Helsinki Declaration and patients' consent was acquired. Observational studies are not mandatory to be proposed to the local ethical committee.

Informed consent: acquired.

Patient consent for publication: acquired.

Availability of data and materials: raw data were generated at Hospital Universitário de São João, Porto. Derived data supporting the findings of this study are available from the corresponding author on request. Data was collected anonymously.

Funding: none.

Received: 26 December 2023.
Accepted: 29 January 2024.
Early view: 12 February 2024.

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Licensee PAGEPress, Italy
Monaldi Archives for Chest Disease 2025; 95:2890
doi: 10.4081/monaldi.2024.2890

Abstract

Although coronary angiography (CA) is the gold standard for coronary allograft vasculopathy (CAV) screening, non-invasive modalities have arisen as potential alternatives, such as coronary computed tomography angiography (CCTA). CCTA also quantifies plaque burden, which may influence medical treatment. From January 2021 to April 2022, we prospectively included heart transplant recipients who performed CCTA as a first-line method for CAV detection in a single center. Clinical, CCTA, and CA data were collected. 38 patients were included, 60.5% men, aged 58±14 years. The most frequent cause of transplantation was dilated cardiomyopathy (42.1%), and the median graft duration was 10 years [interquartile range (IQR) 9]. The median left ventricle ejection fraction was 61.5% (IQR 6). The median calcium score was 17 (IQR 231) and 32 patients (84.2%) proceeded to CCTA: 7, 24, and 1 patients had a graded CAV of 0, 1, and 2, respectively. Most patients (37.5%) had both calcified and non-calcified plaques, and the median number of affected segments was 2 (IQR 3). The remaining 6 patients had extensive coronary calcification, so CA was performed: 4 had CAV1, 1 had CAV2, and 1 had CAV3. During follow-up (12.2±4.2 months), there were neither deaths nor acute coronary syndromes. After CCTA, therapeutic changes occurred in about 10 (26.3%) of patients, mainly related to antilipid intensification; such changes were more frequent in patients with diabetes after heart transplant. In this cohort, CCTA led to therapeutic changes in about one-quarter of patients; more studies are needed to assess how CCT may guide therapy according to plaque burden.

Introduction

Cardiac allograft vasculopathy (CAV) is the leading cause of long-term graft dysfunction of the heart transplant (HT) patients [1]. It is an accelerated fibro-proliferative coronary disease whose pathological hallmark is intimal thickening, with progressive luminal narrowing, potentially leading to ischemia, heart failure, arrhythmias, and death [2]. According to the 2019 International Heart Lung Transplant Society (ISHLT) report, CAV incidence increases over time, developing in about 30% of HT patients at 5 years and almost 50% at 10 years [3]. The ISHLT grading system for angiographic CAV includes the categories of CAV0 (non-significant), CAV1 (mild), CAV2 (moderate), and CAV3 (severe) disease, which are designated based on the severity of angiographic stenosis as well as on the presence of allograft dysfunction [1]. HT patients need to be regularly monitored for CAV as it is usually symptomatically silent or atypical due to heart denervation. At the time of this study, according to the latest 2010 ISHLT guidelines,

coronary angiography (CA) and/or intravascular ultrasound was the gold standard for screening of CAV and should be performed annually or biannually [class I, levels of evidence (LOE) C] [4]. However, its invasive nature and inability to thoroughly examine the distal coronary vessels present is a current limitation. According to these guidelines, coronary computed tomography angiography (CCTA) shows promise in the evaluation of CAV in HT recipients, although higher resting heart rates in these patients limit the technical quality of this study (class IIb, LOE C) [4]. However, CCTA has had new technological advancements, providing high-resolution anatomical images of the lumen, but also on the wall of the coronary arteries. Therefore, CCTA has the potential to be a non-invasive alternative to invasive CA for the diagnosis of CAV. Besides its role in evaluating CAV, CCTA also quantifies plaque burden, which may influence medical treatment.

In the present article, we describe our experience during the first months of implementation in clinical practice of CCTA as the first-line test for CAV detection and seek to find how CCT findings impact subsequent medical approaches.

Materials and Methods

This prospective observational study included HT recipients who performed a CCTA for routine monitoring of CAV in a tertiary care center over a 16-month period from January 2021 to April 2022. If the calcium score was <400, a CCTA was completed; if it was ≥400, a CA was performed as an alternative.

Patients with previous diagnoses of CAV2 and CAV3 were excluded (maintained monitorization with CA). Clinical characteristics, including the patient's medical history, CAV classification, and medication use, were obtained from the medical records of the most recent outpatient visit. HT recipient patients with resting high heart rate (>100/min), typical of cardiac denervation, were medicated with 5 mg twice a day ivabradine within the 3 days before the exam and/or had an additional dose of verapamil or metoprolol to achieve a compatible heart rate for obtaining gating images.

Regarding the CCTA protocol, a dual-source system was used (SOMATON Definition Flash CT scanner, by Siemens (Munich, Germany), of 2×128 slices. Either prospective electrocardiogram (ECG)-gated high-pitch acquisition (if the heart rate was <70 bpm) or retrospective ECG-gated acquisition (if the heart rate was ≥70 bpm) was used. For contrast injection, we used contrast agents with high iodine concentrations of 370 mg/mL; time monitoring was made at the ascending aorta and with bolus tracking. A biphasic injection was performed with 50-80 mL (1 mL/kg/weight) contrast media of 5 mL/s and a 40-50 mL saline chaser of 5 mL/s. A representative image of CCTA is depicted in Figure 1.

Results

A total of 38 patients were included, with 23 (60.5%) men and a mean age of 58±14 years old. Table 1 lists some clinical characteristics. The main cause of transplantation was familial dilated cardiomyopathy (42.1%), and the median graft duration was 10

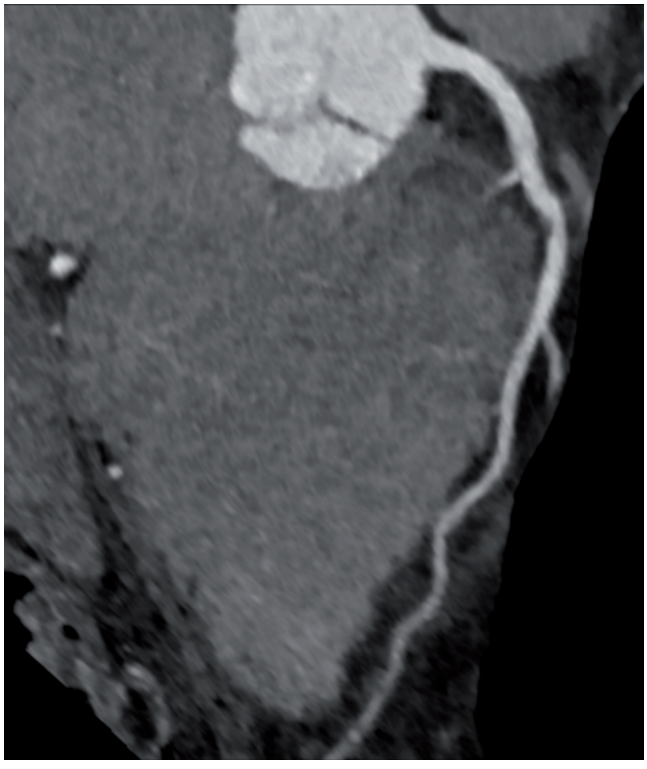

Figure 1. Representative coronary computed tomography angiography image of a 56 year-old male heart transplant patient. Anterior descending artery of good calibre, with a non calcified plaque at its medium segment, conditioning a luminal stenosis of up to 25%.

Table 1. Heart transplant patients' characteristics.

Cause of transplantation, n (%)	
Dilated cardiomyopathy	16/38 (42.1)
Ischemic cardiopathy	12/38 (31.6)
Others*	10/18 (26.3)
Median graft duration, in years	10 (IQR 9)
Median left ventricle ejection fraction, %	62 (IQR 6)
Dyslipidemia, n (%)	28/38 (73.7)
Hypertension, n (%)	24/38 (63.2)
Diabetes mellitus, n (%)	14/38 (36.8)
Smoking history, n (%)	10/38 (26.3)
Obesity, n (%)	6/38 (15.8)
Peripheral arterial disease, n (%)	4/38 (10.5)
Cerebrovascular disease, n (%)	4/38 (10.5)
Medicated with aspirin or clopidogrel, n (%)	33/38 (86.8)
Medicated with anti-coagulant, n (%)	4/38 (10.5)
Medicated with lipid-lowering agent, n (%)	38/38 (100)
Statin alone	27/38 (71.1)
Ezetimibe alone	1/38 (2.6)
Statin and ezetimibe	10/38 (26.3)
Median serum creatinine, mg/dL	1.5 (IQR 0.5)
Median glomerular filtration rate**, mL/min/1.73m^2	56 (IQR 39)
Glomerular filtration rate categories, mL/min/1.73m^2	
Grade 1 (≥90 mL/min/1.73m^2)	1/38 (2.6)
Grade 2 (60-89 mL/min/1.73m^2)	15/38 (39.5)
Grade 3a (45-59 mL/min/1.73m^2)	9/38 (23.7)
Grade 3b (30-44 mL/min/1.73m^2)	6/38 (15.8)
Grade 4 (15-29 mL/min/1.73m^2)	4/38 (10.5)
Grade 5 (<15 mL/min/1.73m^2)	3/38 (7.9)

IQR, interquartile range; *other causes, with one or two cases which: valvular disease, myocarditis, cardiotoxicity, Fontan Failure; **glomerular filtration rate, estimated by modified modification of diet in renal disease 4-variable equation, including sex, age, black race and serum creatinine (mg/dL).

years [interquartile range (IQR) 9]. Only one patient had impaired left ventricle ejection fraction (of 45%) and all had preserved right ventricle systolic function. Most patients had at least one cardiovascular risk factor (89.5%) and took anti-platelet or anti-thrombotic drugs (97.4%). A total of 25 (65.8%) patients had a history of a previous rejection: 7 (18.4%) patients had at least one episode of antibody-mediated rejection and 24 (63.2%) had at least one episode of cellular rejection; 4 patients had previous cytomegalovirus infection.

Regarding immunosuppression, 32 (84.2%) patients received prednisolone and 36 (94%) took calcineurin inhibitors; 18 (47.4%) patients were treated with mycophenolate mofetil/mycophenolic acid, and 3 (7.9%) patients with mTOR inhibitors.

At CCTA preparation, three patients with stage 4 chronic kidney disease were hospitalized for contrast nephropathy prophylaxis; due to resting high heart rate, 35 (81.6%) received verapamil 72 hours before the exam. Additionally, immediately before the exam, 24 (63.2%) patients required verapamil [17 intravenous (iv) and 7 oral] and one patient (2.6%) needed metoprolol iv.

After performing a CT calcium score, 32 (84.2%) patients proceed to CCTA (see Table 2 for findings of CCTA). The remaining 6 patients had extensive coronary calcification (≥400), and a CA was performed in replacement: 4 had CAV1, 1 had CAV2, and 1 had CAV3.

After CCTA, 4 (10.5%) patients needed additional ischemia testing: one that had CAV3, both the patients with CAV2, and one patient with CAV1 but suboptimal quality of CCTA images. All four patients underwent myocardial perfusion scintigraphy (MPS); no significant ischemia was detected for any patient.

During the follow-up of 12.2±4.2 months, there were no deaths, no percutaneous revascularization, no acute coronary syndrome, no ventricular arrhythmias, or stroke. Three patients had de novo rejection (1 humoral, 1 cellular, and 1 both); the patient with both subtypes of rejection evolved from CAV1 to CAV3, was submitted to coronary artery bypass graft surgery, and underwent re-transplantation later.

Table 2. Coronary computed tomography angiography characterization – some technical aspects and findings.

Median dose-length product, in mGy*cm	233 (IQR 297)
Median calcium score	17 (IQR 231)
Quality of images, n (%)	
Excellent	3/32 (9.4)
Good	21/32 (65.6)
Moderate	8/32 (25.0)
ISHLT – CAV classification, n (%)	
CAV 0	7/32 (21.9)
CAV 1	24/32 (75.0)
CAV 2	1/32 (3.1)
CAV 3	0/32 (0)
Coronary plaques, n (%)	
None	7/32 (21.9)
Exclusively calcified	5/32 (15.6)
Exclusively non calcified	8/32 (25.0)
Both calcified and non-calcified	12/32 (37.5)
Median of affected coronary segments, n (%)	2 (IQR 3)
Extra-coronary findings, n (%)	6/32 (18.8)
Cardiac thrombus	4/32 (12.5)
Pulmonary nodules	2/32 (6.3)

IQR, interquartile range; IHLTS, International Heart Lung Transplant Society; CAV, cardiac allograft vasculopathy.

Overall, there was an association between previous antibody-mediated rejection and CAV1/2/3 (p=0.005). No association was found between previous cellular rejection and CAV1/2/3 (p=0.216) or between previous overall rejection and CAV1/2/3 (p=0.166).

Findings in CCTA led to therapeutic changes in 10 (26.3%) of patients – all ten patients had lipid drug intensification, with increased statin dose in one patient, a switch from low to high-intensity statin in 5 patients, and the addition of ezetimibe in 4 patients. Moreover, antithrombotic therapy was changed from platelet anti-aggregation to warfarin due to intra-cardiac thrombus in 3 patients; one patient with CAV1, non-calcified plaques, and 21 years of graft duration had immunosuppressant switched to everolimus.

Medical therapy changes after CCTA were more frequent in patients with diabetes (p=0.043), but no other association was found with other cardiovascular risk factors, sex, age, previous plasma assisted chemical vapor deposition, ischemic etiology, graft duration, plaque characteristics, calcium score, CAV classification, or previous rejection (p>0.05).

Discussion

This real-life single-center experience of CCTA in CAV monitoring in HT patients reinforces the safety of this non-invasive technique, with limited need for additional ischemic or invasive testing.

The potential problem of the negative effect of high resting heart rates on image quality was surpassed by using negative chronotropic drugs pre-examination. As CA, CCTA also uses iodine contrast in an already vulnerable population for acute kidney injury, and it is fundamental to anticipate who will require contrast nephropathy prophylaxis. The potential lower use of radiation with CCTA is an advantage in this population needing long-term life monitoring of CAV.

A meta-analysis of 13 prospective CCTA studies in 615 HT patients showed a mean weighted 94% sensitivity, 92% specificity, 99% negative predictive value, and 67% positive predictive value for detecting stenosis ≥50% on invasive angiography, and the addition of quantitative plaque analysis may also improve sensitivity for CAV detection [5,6].

After the end of our study, new ISHLT guidelines were pre-published in December 2022, giving CCTA an updated recommendation as it may be used as a non-invasive alternative to CA for the detection of CAV in ≥2 mm epicardial vessels (class IIa, LOE B). In parallel, positron emission tomography (PET) was also a recommended class IIa for screening of CAV. On the other side, stress echocardiogram, MPS, and cardiovascular magnetic resonance imaging myocardial perfusion reserve have low sensitivity for CAV detection; nevertheless, they may be useful for prognostication in HT recipients unable to undergo invasive evaluation, CCTA, or PET (class IIb, LOE B/C) [7].

Similarly to previous studies, our study also supports antibody-mediated rejection as a risk factor for the development of CAV – the produced antibodies damage endothelial cells of the coronary arteries of the allograft, triggering an inflammatory response and atherosclerotic plaque formation [8,9].

CCTA adds important information on plaque burden, which may guide therapeutic changes. In fact, after CCTA, therapeutic changes occurred in about one-quarter of patients, mainly related to anti-lipidemic optimization, but also regarding anti-thrombotic drugs and changes in immunosuppressants. These changes were more frequent in patients with diabetes, reinforcing the need to

intensify anti-lipidemic therapy in this population at high risk of coronary events, despite the possibility of interactions between high-intensity statins and immunosuppressive medication and their side effects. More studies are needed to assess how CCT may guide therapy according to plaque burden.

Limitations

One limitation of this study is the small sample size, which may affect the generalizability and statistical power of our findings. CCTA has limited spatial resolution, not allowing assessment of arteries <2 mm in diameter. We did not perform a direct and simultaneous comparison of CA and CCTA for assessing the sensitivity and specificity of CCTA, given that it could not be advantageous for the patient and would increase the risks of exposure to radiation and contrast nephropathy.

Conclusions

In this cohort, CCTA allowed detailed and accurate assessment of CAV with limited need for additional invasive testing. CCTA leads to therapeutic changes in about one-quarter of patients, and this was more frequent in diabetic patients. More studies are needed to assess how CCT may guide therapy according to plaque burden.

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