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RESEARCH ARTICLE

FUTURE PERSPECTIVES IN CARDIAC ALLOGRAFT VASCULOPATHY

[1]*Cottini, M., [3]Dominici, T., [1]Sbaraglia, F., [1]Pergolini, A., [1]Di Stefano, G., [1]Polizzi, V., [1]Feccia, M., [2]Buffa, V., [1]Lilla Della Monica, P. and [1]Musumeci, F.

[1]Department of Heart and Vessels, Cardiac Surgery Unit and Heart Transplantation Center, "S. Camillo-Forlanini" Hospital, 00149 Rome, Italy
[2]Division of Radiology, "S. Camillo-Forlanini" Hospital, 00149 Rome, Italy
[3]Department Heart and Vessels "A. Reale", Policlinico Umberto I, "Sapienza", 00161 Rome, Italy

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ABSTRACT

Background: Coronary allograft vasculopathy (CAV) limits long-term survival after heart transplantation, and screening for CAV is generally performed on an annual or biannual basis. It is usually detected by conventional coronary angiography (CCA). Coronary computed tomography angiography (CCTA) is currently not recommended for CAV screening due to the limited accuracy reported by early studies. Technological advances such as 64-slice dual-source CCTA might justify re-evaluation of this recommendation. We investigated: i) the new perspectives in CAV diagnostic imaging and ii) the prevalence of CCTA in the detection of CAV than the CCA.
Conclusion: According to our experience and scientific literature, the CCTA has been better and better quality of the images with high sensibility and specifity. The non invasive diagnostic technological imaging evolution could become the gold standard in the diagnosis of coronary allograft vasculopathy.

INTRODUCTION

The heart transplantation is the gold standard for the unsuccessful medical and surgical therapy in end-stage heart disease (Level of Evidence I C) (Clyde *et al*., 2013). The International Society for Heart and Lung Transplantation estimates that more than 5,000 heart transplants are performed each year worldwide (Lund *et al*., 2015). The long-time survival of heart transplanted patients is 87.8%, 78.5% and 71.7% at 1, 3 and 5 years after surgery respectively (Clyde *et al*., 2013; Lund *et al*., 2015). As the consequence of the improvement survival after heart transplantation, most of studies have evaluated the short and long-term outcome of this population demonstrating the most frequent short-term complications are allograft failure, right ventricle failure, infection and multiorgan failure. Considering the long-term outcome, the most frequent complications are coronary allograft vasculopathy (CAV) and neoplasm. CAV occurs in approximately 30% of patients by 5 years and 50% by 10 years, and is a major cause of graft loss and death (Mehra *et al*., 2010). CAV is an accelerated fibroproliferative process that affects the coronary arteries of cardiac allografts: CAV consists of concentric and diffuse proliferation of the arterial intima, resulting in thickening and pathological remodelling that lead to progressive narrowing of the lumen, preferentially of small and medium sized arteries with possible involvement of veins and intramyocardial vessels (Clyde *et al*., 2013; Mehra *et al*., 2010). The CAV is distincted with the general coronaropathy (GC, Table 1). The early detection of CAV is important because it may allow to prevent the end-stage evolution of the disease with prompt and effective medical therapy. Because of the inherent variability in clinical diagnosis and possible lack of symptoms, multiple methods of evaluating CAV have been employed (Zimmer and Lee, 2010). The gold standard for diagnosing and monitoring CAV is coronary angiography. Although angiography is particularly useful for discerning focal lesions, the diffuse concentric disease in CAV makes angiography a less sensitive modality for diagnosis in these cases. Intravascular ultrasound (IVUS) is an important and available diagnostic method to evaluate all layers of the vessel wall as well as the lumen, as suggested by the American College of Cardiology Clinical Expert Consensus Document on the standards for acquisition,

***Corresponding author: Cottini, M.,**
Department of Heart and Vessels, Cardiac Surgery Unit and Heart Transplantation Center, "S. Camillo-Forlanini" Hospital, 00149 Rome, Italy.

measurement, and reporting of IVUS studies. IVUS data have emerged indicating that inflammatory plaque (increased necrotic core and dense calcium) is associated with early recurrent rejection and higher progression of TCAD (Raichlin *et al*., 2009). Limitations of IVUS include higher cost compared with angiography, lack of general expertise in its use, requirement for concurrent invasive angiography, decreased ability to examine secondary and tertiary vessels because of the larger size of the catheter, and higher risk of complications compared with routine angiography (Kass *et al*., 2007). Cardiac computed tomography (CCT) could evaluate directly the wall and the lumen of coronary arteries giving important information in evaluation, grading, and monitoring of CAV.

Table 1. Histological features of the coronary allograft vasculopathy versus the general coronaropathy (1, 4). CAV: coronary allograft vasculopathy, GC: general coronaropathy

Differences in histological feature between CAV and GC		
	Cardiac allograft vasculopathy	General coronaropathy
Site	Arterial and venous	Prior arterial
Distribution	Widespread	Focal localization
Plaque type	Concentric	Eccentric
Characteristics	i) diffuse myointimal hyperplasia ii) internal elastic lamina intact iii)peri-avventitial inflammatory infiltration.	i)Subendothelial lipid component ii)peri-lesional inflammatory infiltration with disruption of the internal elastic lamina iii) thinning of the tunica media
Calcium deposits	No	Yes

Studies directly comparing CCT angiography (CCTA) with conventional coronary angiography (CCA) have demonstrated sensitivities of 70% to 86%, specificities of 92% to 99%, positive predictive values of 81% to 89%, and negative predictive values of 77% to 99%, with good to excellent image quality and moderate to excellent test characteristics for detecting CAV (Bogot *et al*., 2007; Gregory *et al*., 2006; Sigurdsson *et al*., 2006; Schepis *et al*., 2009; Iyengar *et al*., 2006; Tarun *et al*., 2013). In a study that analyzed the ability of dual source CT to detect CAV compared with IVUS as a standard, the sensitivity, specificity, and positive and negative predictive values for the detection of CAV by dual source CT were 85%, 84%, 76%, and 91%, respectively (10). CCTA requires the use of contrast and thus has limited utility in patients with renal insufficiency, but the Care Dose and ECG pulsing MinDose to reduce radiation-dose also retrospective cardiac synchronization contribute to a safe, non invasive, well-tolerated and rapid procedure gathering high-quality images with high spatial and contrast resolution and low use of contrast. The optical coherence tomography (OCT) has emerged as a novel intracoronary imaging technique using an optical analogue of ultrasound with a spatial resolution of 10-20 μm, which is 10 times greater than IVUS.

MATERIALS AND METHODS

Population

Between January 2001 and December 2014, 78 patients undergoing heart transplantation at Heart Transplantation Center, Department of Heart and Vessels (San Camillo Forlanini Hospital, Rome) and followed by Heart Transplantation Ambulatory (San Camillo Forlanini Hospital, Rome) were screened for this retrospective observational study. Patients undergoing heart transplant in other Institution and subjects with renal failure were excluded from the analysis. All data were prospectively collected and recorded onto computerized database registries that remained consistent over the study period. Information about demographics, comorbidities, medical and surgical history, operative details and postoperative events during the hospital stay were all registered. The study was approved by the Ethics Committee of our Institution (C. E. Lazio 1, Rome, Italy) and the patient consent was waived.

Clinical and demographical data

Data collection included patient demographics (age, sex, height, and weight), donor age, CAD risk factors (hypertension, diabetes mellitus, dyslipidemia, and current smoking history), dates of CCTA, CCA or IVUS procedures, and current medications. Blood glucose, glomerular filtration rate according to MDRD (Modification of Diet in Renal Disease), and creatinine levels were also recorded.

Conventional coronary arteriography

Based on the ISHLT guidelines, CAV was classified by CCA as follows: CAV0 (not significant) indicates no detectable angiographic lesion; CAV1 (mild) indicates angiographic left main <50%, primary vessel with a maximum lesion of <70%, or any branch stenosis <70% (including diffuse narrowing) without allograft dysfunction; CAV2 (moderate) indicates angiographic left main <50%, a single primary vessel >70%, or isolated branch stenosis >70% in branches of 2 systems without allograft dysfunction; and CAV3 (severe) indicates angiographic left main >50%, ≥2 primary vessels with >70% stenosis, isolated branch stenosis >70% in all 3 systems, or CAV1 or CAV2 with allograft dysfunction (defined as left ventricular ejection fraction <45%, usually in the presence of regional wall motion abnormalities) (3).

Cardiac computed tomography angiography

A CCTA with a 64-section scanner was used. The CCTA images were systematically analyzed for image quality. Degree of CAV was assessed by using a 15-coronary segments model. The area under the receiver operating characteristic curve, sensitivity, specificity, and negative and positive predictive values of cardiac CT angiography for detection of CAV with any degree of stenosis and greater than or equal to 50%. The CCTA was performed with CareDose and ECG pulsing MinDose to reduce radiation-dose and on retrospective cardiac synchronization.

Statistical analysis

Clinical data were prospectively recorded and tabulated with Microsoft Excel (Microsoft Corp, Redmond, Washington). Continuous variables were tested for normal distribution by the Kolmogorov-Smirnov test and compared between groups with unpaired Student *t* test for normally distributed values; otherwise, the Mann-Whitney U test was used. In case of dichotomous variables, group differences were examined by Pearson chi-square or Fisher exact tests as appropriate. All variables subjected to univariate analysis and statistical value of $p < 0.10$ were further subjected to multivariate analysis (logistic regression). For evaluation of diagnostic CCTA versus CCA, we calculated sensitivity, specificity, positive predictive value, negative predictive respectively. All analyzes were performed with Excel and Statplus 5.9 (AnalystSoft Inc., Walnut, CA). The sensitivity, specificity, positive predictive value and negative predictive value of CCTA for the detection of significant CAV versus CCA was assessed using 2 x 2 cross tabulation model.

DISCUSSION

Cardiac allograft vasculopathy is a specific form of coronary artery disease in the transplanted heart and the major long-term complication in the survival after heart transplantation. In our study, we highlighted the relevance rule of CCTA in the early detection of CAV by comparing the CCTA with CCA in heart transplanted patient follow up. Although early survival after heart transplantation is limited by acute rejection, annual reports of the Registry of the International Society for Heart and Lung Transplantation (ISHLT) have suggested that CAV combined with late graft failure (likely because of allograft vasculopathy) accounted for 33% of deaths for those recipients who survived 5 years after transplant, followed in frequency by malignancies and non–cytomegalovirus transplantation, approximately 50% of recipients had angiographic evidence of CAV (10). Our study attempts to provide a strategy by which to potentially reduce the incidence of CAV by easily and early detection. There are many observations to explain our findings:

i) The most likely explanation is that an early diagnosis of CAV could contribute a prompt medical therapy hence increasing survival in heart transplanted patients. According to the literature we have reviewed the data about sensibility (Se), specificity (Sp), positive predictive value (PPV) and negative predictive value (NPV) of the image procedure in the detection of CAV comparing to CCA. In our experience the incidence of CAV was 14.1 % (n=11) and the CCTA showed interesting results comparing with CCA (Table 2).

ii) An easily available and reproducible diagnostic procedure could help to detection of CAV with low costs and more Institution. The way to increase survival of the patient (Figure 1) is the follow: checking periodically patient and diagnosing possible disease and/or complication after heart transplantation. Considering the patient needs and the institutional limits, the follow up could be more specific and rapid for the patient but less expensive for the Institution. The CCTA satisfies these requests.

iii) A non invasive and rapid exam could be more tolerate than others. The CCTA is non invasive exam: a contrast material is injected by an automatic injection pump connected to the IV at a controlled rate. The CCTA was performed with Care Dose and ECG pulsing MinDose to reduce radiation-dose and on retrospective cardiac synchronization. These features allow high quality images with best spatial and contrast resolutions.

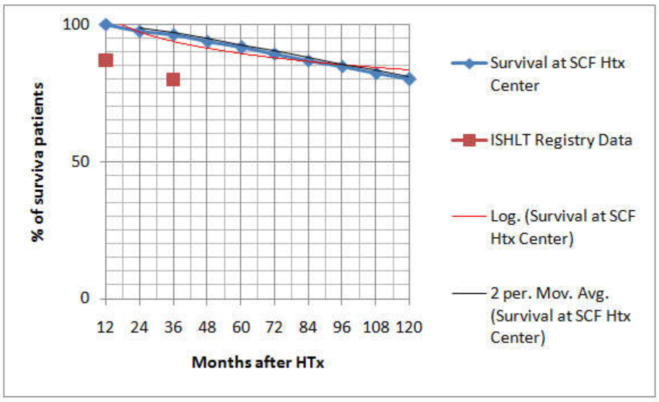

Figure 1. Percentage of survival in the patients after heart transplantation following at the Heart Transplantion Ambulatory, San Camillo Forlanini (SCF) Hospital, Rome, Italy. ISHLT: International Society of Heart and Lung Transplantation, HTx: heart transplantation

Comparing with CCA, there isn't arterial puncture, the Care Dose and ECG pulsing Mindose system reduces the contrast material dose and radiation-dose. Although the progress in technologies, CCTA is limited for patient with moderate to severe renal failure.

Table 2. Scientific literature review of the reported sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of CCTA versus CCA or IVUS in the detection of CAV. ND: non defined, MDCT: multi slice computed tomography. DSCT: dual slide computed tomography

The best diagnostic work up of CAV according to the scientific literature							
Author	Year	Comparison	N° of patient	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Romeo *et al*[15]	2005	MDCT-16 vs CCA	50	80	99	80	99
Gregory *et al*[17]	2006	MDCT-64 vs IVUS	20	70	92	89	77
Sigurdsson *et al*[13]	2006	MDCT-16 vs CCA	54	86	99	81	99
Sigurdsson *et al*[13]	2006	MDCT-16 vs IVUS	13	96	88	80	98
Pichler *et al*[14]	2008	MDCT-16 vs CCA	60	71	99	91	99
Schepis *et al*[10]	2009	DSCT vs CCA	30	93	80	48	98
Schepis *et al*[10]	2009	DSCT vs IVUS	30	85	84	76	91
Von Ziegler *et al*[16]	2009	MDCT-64 vs CCA	26	88	97	48	100
Nunoda *et al*[21]	2010	MDCT-64 vs CCA	22	90	97.5	81.8	98.7
Kepka *et al*[20]	2012	DSCT vs CCA	20	100	96.6	ND	ND
Barthélémy *et al*[20]	2012	MDCT-64/256 vs CCA	102	62.5	93.3	45.5	96.6
Mittal *et al*[18]	2013	MDCT-64 vs CCA	82	98	78	77	98
Wever-Pinzon *et al*[19]	2014	MDCT-64 vs CCA	615	97	81	78	97
Cottini *et al* (present case)	2016	MDCT-64 vs CCA	11	99.2	99.5	86.8	98.1

We always tested renal function before the exam. Possible study limitations are as follows: first, the number of sample sizes was relatively small; second, an intrinsic limitations is its retrospective and monocentric nature.

Conclusion

The conventional coronary angiography is actually the gold standard in the diagnosis and surveillance of cardiac allograft vasculopathy and the combination CCA with IVUS demonstrated the successful, excellent and specific detection the disease. As the CCA, the optimal coherence tomography (OCT) is considered a sensible and specific intravascular imaging exam to detect CAV by the current literature opinions. In our opinion, although the CCA/IVUS and OCT holding the roles of the best diagnostic exams for CAV, the continued technological advances associating with improvement of the non-invasive imaging could offer a new and powerful CCTA to assess the most of arterial wall and distal small vessel details but with requiring less contrast, radiation, cost and time.

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Human rights statements and informed consent: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later revisions. Informed consent was obtained from all patients for being included in the study.

REFERENCES

Bogot, N.R., Durst, R., Shaham, D. and Admon, D. 2007. Cardiac CT of the transplanted heart: indications, technique, appearance, and complications. Radiographics 27:1297–309.

Clyde W. Yancy, Mariell Jessup *et al*. 2013 ACCF/AHA Guideline for the Management of Heart Failure. J Am Coll Cardiol.2013;62(16):e147-239.

Gregory, S.A., Ferencik, M., Achenbach, S., *et al*. 2006. Comparison of sixtyfour- slice multidetector computed tomographic coronary angiography to coronary angiography with intravascular ultrasound for the detection of transplant vasculopathy. *Am. J. Cardiol.,* 98:877– 84.

Gregory, S.A., Ferencik, M., Achenbach, S., *et al*. 2006. Comparison of sixtyfour- slice multidetector computed tomographic coronary angiography to coronary angiography with intravascular ultrasound for the detection of transplant vasculopathy. *Am J Cardiol.,* 98:877– 84.

Iyengar, S., Feldman, D.S., Cooke, G.E., Leier, C.V. and Raman, S.V. 2006. Detection of coronary artery disease in orthotopic heart transplant recipients with 64-detector row computed tomography angiography. *J Heart Lung Transplant,* 25:1363– 6.

Kass, M., Allan, R. and Haddad, H. 2007. Diagnosis of graft coronary artery disease. *Curr Opin Cardiol.,* 22:139–45.

Kepka, C., Sobieszczansk-Malez, M., Pregowski, J. *et al*. Usefulness of dual-source computed tomography for the evaluation of coronary arteries in heart transplant recipients. *Kardiol Pol.* 70(11):1111-9.

Lund, L.H., Edwards, L.B., Kucheryavaya, A.Y., *et al*. 2015. The Registry of the International Society for Heart and Lung Transplantation: Thirty-second Official Adult Heart Transplantation Report—2015; Focus Theme: Early Graft Failure *J Heart Lung Transplant.,* 2015 Oct; 34(10): 1244-1254.

Mehra, M.R., Crespo-Leiro, M.G., Dipchand, A., *et al*. 2010. International Society for Heart and Lung Transplantation working formulation of a standardized nomenclature for cardiac allograft vasculopathy-2010. *J Heart Lung Transplant.,* Jul;29(7):717-27.

Mittal, T.K., Panicker, M.G., Mitchell, A.G. and Banner, N.R. Cardiac allograft vasculopathy after heart transplantation: electrocardiographically gated cardiac CT angiography for assessment.

Nunoda, S., Machida, H., Sekikawa, A. *et al*. 2010. Evaluation of cardiac allograft vasculopathy by multidetector computed tomography and whole-heart magnetic resonance coronary angiography. *Circ J.* May;74(5):946-53. Epub 2010 Mar 10.

Pichler, P., Loewe, C., Roedler, S., *et al*. 2008. Detection of high-grade stenoses stenoses with multislice computed tomography in heart transplant patients. *J Heart Lung Transplant.,* 27:310 – 6.

Radiology, 2013 Aug;268(2):374-81. doi: 10.1148/radiol.13121440. Epub 2013 May 8.

Raichlin, E., Bae, J.H., Kushwaha, S.S., *et al*. 2009. Inflammatory burden of cardiac allograft coronary atherosclerotic plaque is associated with early recurrent cellular rejection and predicts a higher risk of vasculopathy progression. *J. Am. Coll. Cardiol.,* 53:1279–86.

Romeo, G., Houyel, L., Angel, C.Y., *et al*. 2005. Coronary stenosis detection by 16-slice computed tomography in heart transplant patients: comparison with conventional angiography and impact on clinical management. *J Am Coll Cardiol.,* 45:1826 –31.

Schepis, T., Achenbach, S., Weyand, M., *et al*. 2009. Comparison of dual source computed tomography versus intravascular ultrasound for evaluation of coronary arteries at least one year after cardiac transplantation. *Am. J Cardiol.,* 104:1351– 6.

Sigurdsson, G., Carrascosa, P., Yamani, M.H., *et al*. 2006. Detection of transplant coronary artery disease using multidetector computed tomography with adaptative multisegment reconstruction. *J. Am. Coll. Cardiol.,* 48:772– 8.

Sigurdsson, G., Carrascosa, P., Yamani, M.H., *et al*. 2006. Detection of transplant coronary artery disease using multidetector computed tomography with adaptative multisegment reconstruction. *J Am Coll Cardiol.,* 48: 772–8.

Tarun K. Mittal, Mathen G. Panicker, Andrew G. Mitchell, Nicholas R. Banner, 2013. Cardiac allograft vasculopathy after heart transplantation: Electrocardiographically Gated Cardiac Ct Angiography for Assessment Radiology, 2013 Volume 268: Number 2.

von Ziegler, F., Leber, A.W., Becker, A., *et al*. 2009. Detection of significant coronary artery stenosis with 64-slice computed tomography in heart transplant recipients: a comparative study with conventional coronary angiography. *Int J Cardiovasc Imaging,* 25:91–100.

Wever-Pinzon, O., Romero, J., Kelesidis, I., *et al*. 2014. Coronary computed tomography angiography for the detection of cardiac allograft vasculopathy: a meta-analysis of prospective tirals. Am Coll Cardiol. 2014 May 20; 63 (19): 1992-2004. doi: 10.1016/j.jacc.2014.01.071. Epub 2014 Mar 26.

Zimmer, R.J. and Lee, M. 2010.Transplant coronary artery disease. *JACC,* 3 (4): 367-77

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