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Short communication

Usefulness of dual imaging stress echocardiography for the diagnosis of coronary allograft vasculopathy in heart transplant recipients☆

Irene Álvarez Pichel [a,*], Oliva C. Fernández Cimadevilla [b], Jesús María de la Hera Galarza [c], Emilio Pasanisi [d], José Manuel García Ruiz [c], Beatriz Díaz Molina [c], José Luis Lambert Rodriguez [c], Rosa Sicari [e], María Martín Fernández [c]

[a] Servicio de Cardiología, Hospital Vital Álvarez Buylla, Mieres, Asturias, Spain
[b] Servicio de Cardiología, Hospital San Agustin, Avilés, Asturias, Spain
[c] Area del Corazón, Hospital Central de Asturias, Oviedo, Asturias, Spain
[d] Fondazione "G. Monasterio", Pisa, Italy
[e] CNR Institute of Clinical Physiology, Pisa, Italy

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ABSTRACT

Background: Coronary allograft vasculopathy (CAV) is the main factor limiting long-term survival after cardiac transplantation. Dual imaging stress echocardiography with wall motion and Doppler-derived coronary flow reserve (CRF) of the left anterior descending artery (LAD) is a state-of-the-art methodology during dipyridamole stress echocardiography (DiSE). This study involving 74 heart transplanted patients has the purpose to assess the diagnostic value of dipyridamole stress echocardiography with evaluation of wall motion (WM) and Doppler-derived coronary flow reserve for the diagnosis of coronary allograft vasculopathy.

Methods and results: All patients underwent DiSE and coronary angiography. Moderate-severe CAV was defined according to International Society of Heart and Lung Transplant (ISHLT) recommended nomenclature for CAV, and CFR < 2 was considered to be impaired.

Moderate-severe CAV was present in 11 patients. WM analysis revealed four patients (5%) with rest WM abnormalities. CFR analysis revealed that 40 (54%) individuals had an abnormal result. The combined evaluation of WM analysis and CFR resulted in a sensitivity of 72.7% (95% CI: 39.3 to 92.6%), a specificity of 49.2% (95% CI: 36.5 to 61.9%), a positive predictive value of 20% (95% CI: 9.6 to 36.1%), and negative predictive value of 91.1% (95% CI: 75.1 to 97.6%) for the diagnosis of CAV.

Conclusions: Our results support the inclusion of DiSE performance in Heart transplant follow up protocol. The addition of CFR evaluation offers valuable information to the angiography findings in the detection of CAV and could be helpful in selected patients to adjust the time and indications of coronary angiography.

1. Introduction

Coronary allograft vasculopathy (CAV) is the main factor limiting long-term survival after cardiac transplantation [1]. Manifestations of CAV suppose the first cause of mortality between the first and fifth year after heart transplant [2]. Early detection of CAV is critical because it allows the identification of high-risk patients and the implementation of therapeutic strategies before end-stage heart failure [3,4].

Coronary angiography is routinely used to monitor the development and progression of CAV [5]. This procedure, however, has a number of major limitations: it is invasive and also carries an increased risk of morbidity in cyclosporine-treated transplant recipients, whose kidney function is frequently altered.

Several non-invasive imaging techniques, such as technetium-99m-MIBI perfusion tomography, exercise electrocardiography, exercise echocardiography and myocardial contrast echocardiography during dobutamine infusion, have been proposed to assess

Abbreviations: CFR, coronary flow reserve; DiSE, dipyridamole stress echocardiography; CAV, coronary allograft vasculopathy; LAD, left anterior descending artery; WMSI, wall motion score index; RWMA, rest wall motion abnormality.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

* Corresponding author at: Calle General Elorza número 7, 7°E, escalera izquierda, 33001 Oviedo, Asturias, Spain.
E-mail address: ireneapichel@gmail.com (I.Á. Pichel).

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CAV, but none of them has been accepted as an alternative to coronary angiography [6–8].

The combined evaluation of wall motion and coronary flow reserve (CFR) of the left anterior descending artery (LAD) during dipyridamole vasodilatory stress echocardiography (DiSE) has been proposed by the European Association of Echocardiography [9] as a feasible and accurate method for the diagnosis of coronary artery disease due to its increased test sensitivity and modest loss in specificity [10–12]. Previous reports have shown that DiSE is feasible and safe in transplanted patients and that the best marker of acute cardiac rejection was dipyridamole stress-induced ST segment depression without a detectable impairment in regional systolic function [13].

The aim of this prospective and observational study is to evaluate the diagnostic value of combined wall motion and CFR (dual imaging) on LAD for predicting CAV in heart transplant recipients. The hypothesis of the study is that in heart transplant patients, a reduction in CFR as assessed by DiSE can effectively identify patients with CAV.

2. Materials and methods

The initial population included 82 heart transplant patients who required routine coronary angiography within the monitoring transplant protocol of our hospital (at 12 months, 3°, 5° and 10° year from transplant) between November 2011 and November 2013.

Exclusion criteria were: relevant non-cardiac diseases (e.g., cancer, end-stage renal disease, or severe obstructive pulmonary disease), an inadequate acoustic window precluding satisfactory imaging of the left ventricle or LAD flow Doppler, or contraindications to dipyridamole infusion. 8 patients were excluded according to these criteria. Thus, 74 patients formed the final study cohort.

Coronary angiography was performed in multiple views according to the standard Judkins technique. CAV was defined following the International Society for Heart and Lung Transplantation (ISHLT) Recommended Nomenclature for CAV [5].

All patients provided written informed consent prior to undergoing stress echocardiography. Stress echocardiography was performed within a maximum of 12 weeks of coronary angiography. Two-dimensional echocardiography and 12-lead electrocardiographic monitoring were performed in combination with high-dose dipyridamole (up to 0.84 mg over 6 min) [10]. Echocardiographic images were semiquantitatively assessed using a 17-segment, 4-point scale model of the left ventricle [10]. CFR was assessed during the standard stress echo examination by intermittently imaging of both wall motion and LAD flow [12]. Coronary flow in the mid-distal portion of the LAD was identified in the low parasternal long-axis section under the guidance of colour Doppler flow mapping. Flow velocities were measured >2 times for each study at baseline and at peak stress prior to aminophylline injection Coronary flow parameters were analysed off-line using the built-in calculation package of the ultrasound unit. CFR was defined as the ratio between the hyperemic peak and basal peak diastolic coronary flow velocities. A CFR value <2.0 was considered abnormal.

Stress echo data were analysed by two specialists not involved in patient care and without information of the coronary angiography result.

The statistical analysis included descriptive statistics (frequency and percentage of categorical variables, and mean and standard deviation of continuous variables). Calculation of sensitivity, specificity and predictive values was performed according to standard definitions, and a 95% CI was estimated using the Wilson method. Interobserver variability was assessed using the intraclass correlation coefficient (i.e., Kappa index). All analyses were performed using SPSS statistical software (SPSS 15.0 Inc., Chicago, Illinois).

3. Results

74 patients (men 72%; age 60.3 ± 10.3 years) formed the final study sample. Time since heart transplant: 64.4 months at the time of DiSE (media 64.4 ± 43.1 SD). Age of the heart donors: 39.6 years (media 39.6 ± 13.3 SD). The mean duration of DiSE was 44 ± 6 min, and no major advents occurred during the procedure. The main clinical findings for the study population are reported in Table 1a.

Table 1a
Aetiology of heart transplant and medical treatment.

Aetiology of heart transplant	
– Idiopathic dilated myocardiopathy	21(28%)
– Ischemic myocardiopathy	35(46.7%)
– Alcoholic myocardiopathy	1(1.3%)
– Acute or sub-acute myocarditis	2(2.7%)
– Valvulopathy	4(5.3%)
– Other	12(16%)
Medical treatment	
– Diuretics	25(33.8%)
– Calcium antagonist	24(32%)
– Antiagregants	65(86.7%)
– Angiotensin-converting enzyme inhibitors/angiotensin II receptor antagonists	38(51.4%)
– Anticoagulants	1(1.3%)
– Statins	55(74.3%)
– Corticoids	6(8%)
– Cyclosporine	10(13.5%)
– Tacrolimus	64(85.3%)
– Everolimus	25(33.8%)
– Mofetil mycofenolate	48(64%)

3.1. Angiographic findings

Coronary angiography revealed significant CAV (ISHLT CAV_2 or CAV_3) in 11 (14.8%) patients, 9 of whom had LAD stenosis; mild stenosis (ISHLT CAV_1) in 13 (17.5%) patients; and normal coronary arteries (ISHLT CAV_0) in 50 (67.5%) patients.

3.2. Echocardiographic findings

Four patients (5%) had rest wall motion abnormality (RWMA). An evaluation with RWMA resulted in a sensitivity of 15.3% (95% CI: 2.7 to 46.3%), a specificity of 96.7% (95% CI: 87.6 to 99.4%), a positive predictive value (PPV) of 50% (95% CI: 9.1 to 90.8%), and a negative predictive value (NPV) of 84.2% (95%CI: 73.1 to 91.5%) for detecting significant CAV. During DiSE performance, no test was positive for myocardial ischemia. Basal and Stress echocardiographic findings are included in Table 2a.

Mean CFR value was 2.07 ± 0.59. 34 patients exhibited normal (CFR ≥ 2.0) and 40 abnormal CFR on LAD (CFR < 2). CFR values were abnormal in the four patients who also presented RWMA. Thus, the combined evaluation of wall motion analysis and CFR evaluation resulted in a sensitivity of 72.7% (95% CI: 39.3 to 92.6%), a specificity of 49.2% (95% CI: 36.5 to 61.9%), a PPV of 20% (95% CI: 9.6 to 36.1%), and an NPV of 91.1% (95% CI: 75.1 to 97.6%) for detecting significant CAV. Clinical findings in function or normal or abnormal CFR are included in Table 1b.

3.3. Correlation between DiSE and angiographic findings (Table 2b)

Note that only 3 of the 34 patients with a dual DiSE result normal exhibited significant CAV.

3.4. Interobserver variability

Intraclass correlation coefficient absolute agreement: 0.876 (CI 95%: 0.754–0.940). Kappa index: 0.930.

4. Discussion

Coronary allograft vasculopathy affects over 50% of recipients within 10 years of transplant and represents an important cause of mortality [2–14]. In this study, no test was positive for myocardial ischemia by wall motion criteria during DiSE. However, analysis of CFR values was abnormal in 40 patients. CFR values were also abnormal in the four patients who presented rest wall motion abnormalities. Abnormal result of CFR does not correlate with the presence of significant CAV according to ISHLT definition, and this result is according with the known fact that there is a small but

Table 1b
Clinical findings in function of abnormal and normal CFR.

	CFR < 2	CFR ≥ 2	*p*-Value
Male	28 (70%)	24 (71%)	0.956
Recipient age (years)	58.53 ± 13.17	59.99 ± 8.27	0.564
Donor age (years)	39.60 ± 14.47	39.68 ± 12.17	0.981
Time since heart transplant (months)	67.08 ± 42	57.96 ± 44.76	0.368
Hypertension	9 (22.5%)	16 (47%)	0.026
Diabetes mellitus	11(27.5%)	10 (29.41%)	1
Dyslipidaemia	14(35%)	12 (35.29%)	0.79
Ex-smoker	22 (55%)	18 (53%)	0.589
Carotid disease (pre-HT)	1 (2.5%)	0	1
Renal insufficiency	25 (62.5%)	23 (67.5%)	0.644
Body mass index (kg/m^2)	28.03 ± 5.21	26.36 ± 4.49	0.147
LDL-cholesterol (mg/dl)	101.31 ± 35.87	102.18 ± 41.91	0.924
HDL-cholesterol (mg/dl)	47.79 ± 14.83	49.71 ± 14.36	0.579
Triglycerides (mg/dl)	151.05 ± 89.13	129.94 ± 58.48	0.231

significant group of heart transplanted patients who manifest primarily small vessel CAV with normal angiography which is likely the cause for the false negative cases using angiography as the gold standard in the detection of CAV.

Coronary microvascular dysfunction defined by means of a reduced CFR, is emerging as a strong predictor of outcome in heart transplantation. CFR assessed during adenosine stress echocardiography has resulted in good diagnostic accuracy for the recognition of a maximal intimal thickness of 0.5 mm on IVUS [15]. Ciliberto et al. [16] have shown that normal resting wall motion observed by echocardiography coupled to normal stress myocardial perfusion rules out the presence of significant CAV in many heart transplant recipients. Otherwise, Sade et al. proposed that in heart transplant patients, the assessment of CFR together with dobutamine stress echocardiography improved the sensibility and diagnostic accuracy of the latter method [17]. Finally, in the study published by Tona et al. the non-invasive assessment of microvascular coronary dysfunction, defined as a reduced CFR with a CFR < 2.5 was independently associated with a higher probability of new onset CAV and a higher probability of death [18].

Table 2a
Basal and stress echocardiographic findings.

LV ejection fraction (%)	63 ± 0.07
IV septum (mm)	11.2 ± 2.3
Diastolic function	
– Normal (Type I)	55(75.3%)
– Impaired relaxation (Type II)	10(13.7%)
– Pseudonormal (Type III)	1(2.7%)
– Restrictive (Type IV)	7(9.6%)
E/E′	8.6 ± 3.5
TAPSE (mm)	16.1 ± 3.6
Mitral regurgitation	
– No/mild	71(96%)
– Moderate	2(2.7%)
– Severe	1(1.4%)
Basal-wall motion score index	
1 (normal)	69(93.2%)
>1 (pathologic)	5(6.8%)
Peak stress-wall motion score index	
1 (normal)	69(93.2%)
>1 (pathologic)	5 (6.8%)
Coronary flow reserve (m/s)	2.07 ± 0.59
Basal systolic blood pressure (mmHg)	124.47 ± 21.72
Peak stress systolic blood pressure (mmHg)	113.34 ± 16.26
Clinical adverse events	
– None	57 (77%)
– Symptom-associated blood pressure decrease	1(1.4%)
– Headache	6 (8.1%)
– Nausea	6 (8.1%)
– Stifling sensation	4 (5.4%)

Table 2b
Correlation between DiSE and angiographic findings.

Angiographic findings	CFR < 2	CFR ≥ 2
CAV 0	26	24
CAV 1	6	7
CAV 2/3	8	3

In the other hand, when we evaluate the coronary anatomy in the group of 34 patients who presented a normal value of CFR, the results of coronary angiography was not significant in 24 patients, mild CAV in 7 patients and moderate or severe CAV in 3 patients. This finding supports the main result of the present study: A negative DiSE for wall motion and a normal CFR are predictive of the absence of significant CAV.

Our results do not support the systematic substitution of coronary angiography by dual DiSE for the screening of CAV, but it could be useful in addition to transthoracic echocardiography in Heart transplant follow up protocol. The addition of CFR evaluation could be helpful in selected patients to adjust the time and indications of coronary angiography.

Longer series are needed to validate this proposal.

5. Study limitations

Several limitations of the present study must be acknowledged:

- The size of the sample is limited due to the single-centre nature of the study, and the low prevalence of CAV can lead to the overestimation of negative predictive value in our series.
- The time since transplant to testing was highly variable (media 64.4 ± 43.1 SD) and may have resulted in the inclusion of patients with different microvascular and macrovascular impairments. In fact, we suspect that this reveals the wider spectrum of CAV and improves the external validity of the study.
- IVUS was not use as the gold standard.

6. Conclusions

The main and relevant data provided by the present study is the high value of exclusion of disease (represented by the high NPV (91%) demonstrated by the evaluation of coronary reserve flow by means of stress ultrasound with dipyridamole to rule out CAV according to the current definition criteria of the ISHLT, which provides new evidence and not previously evaluated in the literature in this pathology.

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