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ORIGINAL ARTICLE

Diagnostic Accuracy of Dobutamine Stress Echocardiography for Detection of Cardiac Allograft Vasculopathy in Orthotopic Heart Transplant Patients

Mohammed Mahmoodurrahman [a,1], Josef Marek [b,1], Hamzah Ruxshan Juhardeen [a,1], Talal Al Otaibi [c], Vera Maria Cury Salemi [d], Najmeddine Echahidi [c], Jehad Al Buraiki [c], Bahaa M. Fadel [c], Dania Mohty [c,*]

[a] College of Medicine, Alfaisal University, Riyadh, Saudi Arabia
[b] 2nd Department of Medicine − Department of Cardiovascular Medicine, First Faculty of Medicine, Charles University and General University Hospital in Prague, Prague, Czech Republic
[c] King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia
[d] Heart Failure Clinics, Heart Institute (InCor) do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil

Abstract

Objective: **Cardiac allograft vasculopathy is one of the leading causes of late graft failure and subsequent death in orthotopic heart transplant. Although invasive coronary angiography is the gold standard modality for detection of cardiac allograft vasculopathy, dobutamine stress echocardiography has been recently frequently used as an alternative. Our aim was to evaluate the diagnostic performance of dobutamine stress echocardiography for detection of cardiac allograft vasculopathy in transplant patients.**

Methods: **A retrospective analysis was conducted using a total of 150 dobutamine stress echocardiographic exams that were performed on 99 patients in our institution, with paired coronary angiogram and no acute rejection, within a median of 538 [interquartile range 371−816] days. Sensitivity and specificity of dobutamine echocardiography to detect allograft vasculopathy was evaluated. Allograft vasculopathy was defined as Grade 1 or higher based on ISHLT criteria. A positive dobutamine stress echo result was defined by new or worsening wall motion abnormality.**

Results: **Median age of the population at transplant was 34 [interquartile range 22−46] years; 76 (77%) patients were male. Allograft vasculopathy was present in 31 (20.6%) out of 150 coronary angiograms. Only 7 (4.6%) of that number were positive on dobutamine stress echocardiography. Sensitivity and specificity for allograft vasculopathy detection was 3% and 94%, respectively. Out of 7 false positive dobutamine stress echocardiograms, two were in patients with myocardial bridging. Two patients with mild acute rejection had both negative dobutamine stress echo.**

Conclusions: **Overall, positivity of dobutamine stress echocardiography in patients after heart transplant is low. It has high specificity, but very low sensitivity for detection of cardiac allograft vasculopathy. Dobutamine stress echocardiography should only be cautiously used as an alternative to coronary angiography.**

Keywords: Dobutamine echocardiography, Stress echocardiography, Cardiac allograft vasculopathy, Heart transplantation, Myocardial ischemia, Diagnostic imaging tools

1. Introduction

Orthotopic heart transplant (OHT) is an established method for treating advanced heart failure that is unresponsive to conventional therapy. Since its establishment, the technique has continuously improved as is evident with the significant increase in post-OHT survival, where the

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* Corresponding author at: King Faisal Specialist Hospital & Research Center, Heart Center, PO Box: 3354, MBC # 16, Riyadh, 11211, Saudi Arabia.
Fax: +966 114427482.
E-mail address: dania.mohty@gmail.com (D. Mohty).
[1] 3 coauthors contributed equally to this manuscript.

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median survival after transplant is currently over 10 years [1].

However, cardiac allograft vasculopathy (CAV) remains one of the dominant causes of late graft failure and death [1]. CAV has an unpredictable course and can quickly transform into diffuse obstructive disease [2–6]. Various immunologic and non-immunologic factors play a role in the pathophysiology of CAV. Increased CRP (C-reactive protein) is a strong predictor of CAV development after heart transplantation, highlighting the role of inflammation [6]. Significant myocardial ischemia and infarctions may go unnoticed due to atypical presentations in denervated hearts. Early detection of coronary involvement with ischemia is therefore of paramount importance. Invasive coronary angiography is the gold standard method for the assessment of coronary artery disease [5], but in CAV its performance might be impaired by the diffuse nature of coronary involvement [7]. Furthermore, repeating coronary angiography for frequent assessment is not optimal due to its invasive nature, contrast use and radiation exposure. Intravascular ultrasound (IVUS) tends to be more sensitive [8], given the diffuse longitudinal concentric hypertrophy due to fibrous intimal hyperplasia that appears in the affected coronary arteries with CAV. However, it also needs invasive coronary access.

Dobutamine stress echocardiography (DSE), which has acceptable sensitivity and specificity, was established in the 1990s as a feasible alternative to invasive coronary angiography [9]. The International Society of Heart and Lung Transplantation (ISHLT) guidelines classified DSE as Class IIa for CAV screening in patients that cannot undergo invasive evaluation or possibly in children [5]. DSE is the best validated noninvasive method, with the sensitivity of 85% as compared to angiography and IVUS and an outstanding negative predictive value [9,10]. Recently, however, the performance of DSE in this setting has been questioned [3,4]. A systematic review and meta-analysis study found that DSE had a limited sensitivity to detect early CAV, but its specificity was much higher [11]. A few studies have suggested using speckle tracking echocardiography or contrast echocardiography to improve the diagnostic accuracy of DSE in detecting CAV [12,13].

We were unable to find published literature on this concept in the Middle Eastern population. The purpose of this study is to evaluate the performance of DSE as a non-invasive screening modality in determining the presence of coronary vasculopathy in our population of patients with OHT at our tertiary care center, the only institution that performs OHT in the entire Middle East: King Faisal Specialist Hospital & Research Centre (KFSH&RC).

Abbreviations

CAV	Cardiac Allograft Vasculopathy
CHD	Coronary Heart Disease
DCM	Dilated Cardiomyopathy
DSE	Dobutamine Stress Echocardiography
FCMP	Familial Cardiomyopathy
HCM	Hypertrophic Cardiomyopathy
ICA	Invasive Coronary Angiography
ICM	Ischemic Cardiomyopathy
ISHT	International Society of Heart and Lung Transplantation
IQR	Interquartile range
IVUS	Intravascular ultrasound
LAD	Left Anterior Descending artery
LM	Left Main artery
OHT	Orthotopic Heart Transplant
RHD	Rheumatic Heart Disease
RCM	Restrictive Cardiomyopathy

2. Materials and methods

2.1. Population

A retrospective analysis on a consecutive set of 99 patients was performed. The main design of the study is shown in the Figure. These patients were evaluated in our clinic after orthotopic heart transplant. They underwent both coronary angiography (with or without endomyocardial biopsy) and DSE.

All included heart transplants were performed at the King Faisal Specialist Hospital, Riyadh, KSA.

Post-transplant, endomyocardial biopsy, echocardiography, chest X-ray, and laboratory evaluation are performed on week number 3–4 depending on whether the patient is being discharged. From the week of discharge, the biopsies were done every month until 6 months and then every two months until 12 months. Echocardiogram is performed more frequently if the patient presents pericardial effusion, or whenever it was clinically indicated. A total of approximately 10 biopsies and 5–6 echocardiograms were performed during the first year. Annual HT admission at 12 months with tests is performed (including cardiac catheterization with biopsy and echocardiography when clinically indicated).

After 1 year, a transthoracic echocardiography is usually performed every 6 months. Biopsy is done annually for 5 years and then every 2–3 years as required.

This medical chart retrospective study was approved by the institutional ethics committee (IRB number 2001055).

2.2. Echocardiography

Both resting echocardiography and DSE were performed using E7 or E9 (General Electric, Milwaukee, Wisconsin, USA) or iE33 or EPIQ 7 machines (Philips, Amsterdam, The Netherlands).

Routine resting echocardiography was performed in all patients according to current recommendations [14,15].

For the DSE, routine protocol was used as previously described [16]. Briefly, standard dosing of dobutamine was used, from 10 to 40 ug/kg/min with 10 ug/kg/min steps every 3 minutes to achieve $\geq$ 85% of the maximal target heart rate. Up to 1 mg of atropine was added if heart rate could not be achieved using dobutamine alone. Wall motion abnormalities, ECG changes, heart rate and blood pressure and occurrence of symptoms were evaluated at every stage.

Positive DSE was based on the appearance of or worsening of wall motion abnormality in at least two myocardial segments based on the 16 segments ASE model [15].

2.3. Invasive coronary angiography

Invasive coronary angiography and endomyocardial biopsy were performed in a routine manner at our institution whenever indicated as necessary by clinical findings and routine surveillance. Coronary angiography was evaluated for CAV based on the recommendations of the ISHLT [17]. Briefly, CAV Grade 0 was defined as no detectable angiographic lesions; Grade 1 (mild) was defined by angiographic left main (LM) < 50% stenosis or primary/branch vessel with a maximum lesion of <70% stenosis, including diffuse narrowing; Grade 2 (moderate) was angiographic LM < 50% stenosis, a single primary vessel $\geq$70% stenosis or isolated branch stenosis $\geq$70% in branches of two systems; Grade 3 (severe) was angiographic LM $\geq$ 50% stenosis, two or more primary vessels $\geq$70% stenosis, isolated branch stenosis $\geq$70% in all systems or graft dysfunction/evidence of restrictive physiology. Acute rejection was graded based on the revised ISHLT criteria [18]. Follow up/death of patients was obtained using patients' charts and/or hospital information.

2.4. Statistical analysis

Due to common non-normal distribution, continuous values are presented as median [25th-75th percentile] or median with interquartile range (IQR) and binary data as proportions. Due to non-normal distributions, differences in parameters of DSE were evaluated using Mann–Whitney U or chi-square tests, as appropriate. Results were evaluated using contingency tables and reported as sensitivity and specificity ± standard error (SE). Because of

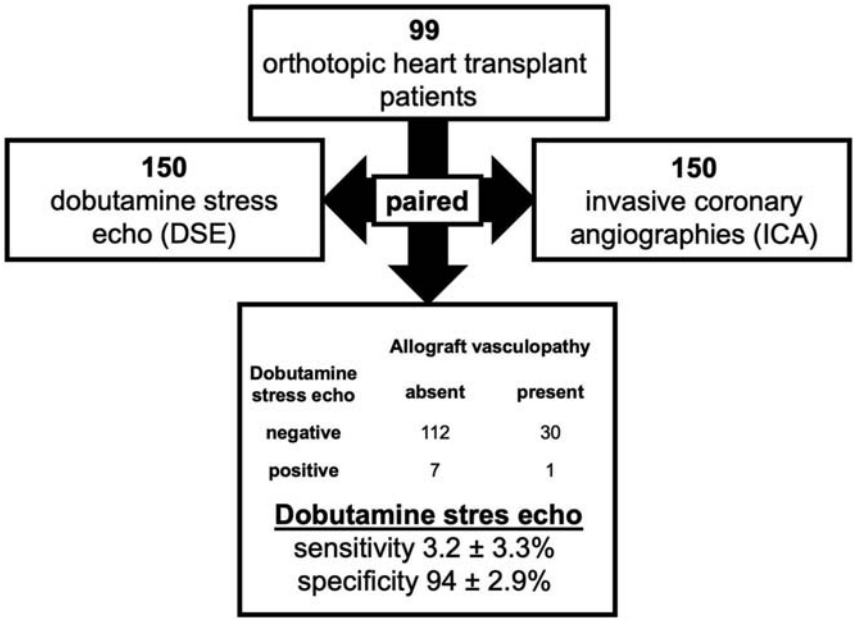

Figure. Showing main design of the study.

clustered nature of data, a correction for clustered observations using ratio estimator method was performed [19]. A p value < 0.05 was considered significant. Analysis was done using R software version 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results (figure)

3.1. Baseline characteristics

For evaluation of CAV, catheterizations with acute rejection on endomyocardial biopsy were excluded. In total, there were 150 DSE performed on 99 patients that had paired DSE and coronary angiography with no acute rejection. Baseline characteristics of our cohort are shown in Table 1. During follow-up period, 21 patients died.

Table 1. Baseline characteristics of the study population.

Total number	99
Age at transplant (years)	34 [22, 47]
Male gender	76 (77%)
Diabetes mellitus	31 (31%)
Atrial fibrillation	10 (10%)
Creatinine (μmol/l)	84 [66, 107]
Arterial Hypertension	29 (29%)
Heart failure etiology	
DCM	59 (60%)
ICM	25 (26%)
RHD	2 (2%)
HCM	2 (2%)
CHD	2 (2%)
Peripartum	2 (2%)
FCMP	1 (1%)
Chemotherapy induced	1 (1%)
RCM	2 (2%)
Other/unknown	3 (3%)

DCM - Dilated Cardiomyopathy, ICM - Ischemic Cardiomyopathy, RHD - Rheumatic Heart Disease, HCM - Hypertrophic Cardiomyopathy, CHD - Coronary Heart Disease, FCMP - Familial Cardiomyopathy, RCM - Restrictive Cardiomyopathy.

3.2. Prevalence of CAV

There were 150 coronary angiographies done on the 99 patients, out of which 31 (20.6%) were positive for CAV. Out of the 31, 24 had Grade 1 CAV, 4 had Grade 2, and 3 had Grade 3.

3.3. Characteristics of DSE

Baseline characteristics by DSE are shown in Table 2. No significant differences were seen when comparing positive and negative DSE, but there was a trend towards lower baseline LVEF in the positive patients (p = 0.086).

3.4. Dobutamine stress echocardiography for detection of CAV

Overall, DSE and ICA were done 538 (IQR 371–816) days apart. Cross tabulation is shown in Table 3 and reveals sensitivity of 3.2 ± 3.3% and specificity of 94 ± 2.9% for CAV on invasive angiography.

We have analyzed the 23 false negative dobutamine echocardiograms and 3 of them had Grade 2

Table 3. Dobutamine stress echocardiography for detection of CAV.

Dobutamine Echocardiography	Cardiac allograft vasculopathy (Invasive Coronary angiography)		
	Negative	Positive	Total
Negative	112	30	142
Positive	7	1	8
Total	119	31	150

CAV – cardiac allograft vasculopathy.

Table 2. Characteristics of dobutamine stress echocardiography.

	Total (n = 150)	Positive for RWMA (n = 8)	Negative for RWMA (n = 142)	p-value
Years from heart transplant	4.26 [2.87, 6.68]	6.00 [4.10, 6.72]	4.19 [2.87,6.67]	0.57
LV EF (%)	63 [59, 70]	61 [57, 63]	63 [60,71]	0.086
Mitral regurgitation Grade ≥ 2	3 (2%)	0 (0%)	3 (2.1%)	1
Maximal dobutamine dose (μg/kg/min)	40 [30,40]	40 [38, 40]	40 [30, 40]	0.39
Atropine used	14 (9.3%)	1 (12%)	13 (9.2%)	1
At Baseline				
Heartrate (s^{-1})	87 [80, 96]	89 [88, 92]	85 [79, 96]	0.24
SBP (mmHg)	124 [116, 135]	122 [114,132]	124 [116, 135]	0.81
DBP (mmHg)	78 [70, 86]	82 [78, 85]	78 [69, 86]	0.32
At max dobutamine				
Heartrate (s^{-1})	145 [135, 154]	148 [143, 158]	145 [134, 154]	0.32
SBP (mmHg)	154 [138, 170]	142 [114, 163]	154 [140, 170]	0.8
DBP (mmHg)	75 [62, 82]	64 [57, 90]	75 [63, 82]	0.39

DBP – diastolic blood pressure, LV EF – left ventricular ejection fraction, RWMA – regional wall motion abnormality, SBP – systolic blood pressure.

CAV while the remaining had Grade 1. There were 7 false positive DSE, two of them were from one patient who did have a myocardial bridge in the mid left anterior descending artery (LAD).

3.5. Dobutamine stress echocardiography in patients with acute cellular rejection

There were 2 patients with DSE that were excluded from the main analysis of our cohort of 99 patients because they had shown acute cellular rejection, both of them Grade 1R. There were 3 DSEs performed on these patients, 1883 days before, 617 days before and 798 days after their ICA. All of the DSE were negative.

4. Discussion

DSE remains used and recommended for noninvasive detection of CAV [5]; however, recent studies have questioned its validity and predictive value [3,4]. Our data seem to support this conclusion. We have found low sensitivity of DSE to detect CAV. This can be explained by a relatively low prevalence of significant CAV in our population and/or a mild degree of CAV. Indeed, our data are in agreement with recent publications where sensitivity was as low as 7% when patients with Grade 1 CAV were included and has risen to 28% after only patients with Grade 2 or higher were considered [3]. In another study, a sensitivity as low as 0% has been reported [4]. We have shown a relatively high specificity that is comparable to previous reports [2]. The specificity can be probably even higher, since one of our patients without significant CAV had myocardial bridge in mid LAD which might have reasonably caused the positivity of DSE [20].

Recently, it has also been shown that DSE might not be predictive of outcome in patients after OHT [3], while other studies have shown prognostic significance [9,21]. Unfortunately, our data is too small to draw any definitive conclusions.

Other improvements for echocardiographic detection of allograft vasculopathy have been proposed. Coronary blood flow assessment can be used alone or in conjunction with dobutamine stress echocardiography to improve detection [13,22]. Other studies have evaluated myocardial deformation imaging during stress echocardiography have found significant association with CAV [12]. However, these methods are not yet reflected in current guidelines and it remains to be seen whether they will be able to improve echocardiographic detection of CAV in clinical practice.

The incidence of CAV based on invasive coronary angiography was comparable to some previous studies [22] while others have reported somewhat higher prevalence [23]. However, local differences in our population might be accountable for that.

Interestingly, all our patients with acute cellular rejection had negative DSE. This can be probably explained by large time differences between DSE and ICA as well as the mild degree of cellular rejection (Grade 1R) in both patients.

4.1. Limitations

The main limitation remains the retrospective nature of our study where indication for DSE and coronary angiography was driven by clinical need, making a systematic assessment difficult. Furthermore, low prevalence of significant CAV in our young patient population, and large interval time between DSE and ICA reduces the statistical power of the study. We have not used intravascular ultrasound as that was not the routine practice at our institution, therefore the true prevalence of CAV on ICA might be underestimated [8,9].

5. Conclusion and clinical perspectives

This study indicates that DSE has a very low sensitivity and excellent specificity for the detection of CAV in the OHT patient population. Based on our findings, which are in agreement with previous series, the routine clinical use of DSE as a diagnostic tool for the assessment of CAV could not be the most suitable technique. Therefore, other imaging modalities should be considered for the evaluation of CAV post OHT.

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Author contribution

Conception and design of Study: Mohammed Mahmoodurrahman, Hamzah Ruxshan Juhardeen, Talal Al Otaibi, Bahaa M Fadel, Dania Mohty. Literature review: Mohammed Mahmoodurrahman, Josef Marek, Hamzah Ruxshan Juhardeen, Vera

Maria Cury Salemi, Dania Mohty. Acquisition of data: Mohammed Mahmoodurrahman, Hamzah Ruxshan Juhardeen, Talal Al Otaibi, Vera Maria Cury Salemi, Najmeddine Echahidi, Jehad Al Buraiki, Bahaa M Fadel, Dania Mohty. Analysis and interpretation of data: Mohammed Mahmoodurrahman, Josef Marek, Hamzah Ruxshan Juhardeen, Dania Mohty. Research investigation and analysis: Mohammed Mahmoodurrahman, Hamzah Ruxshan Juhardeen, Talal Al Otaibi, Najmeddine Echahidi, Jehad Al Buraiki, Bahaa M Fadel, Dania Mohty. Data collection: Mohammed Mahmoodurrahman, Josef Marek, Hamzah Ruxshan Juhardeen, Dania Mohty. Drafting of manuscript: Mohammed Mahmoodurrahman, Josef Marek, Hamzah Ruxshan Juhardeen, Bahaa M Fadel, Dania Mohty. Revising and editing the manuscript critically for important intellectual contents: Mohammed Mahmoodurrahman, Josef Marek, Hamzah Ruxshan Juhardeen, Talal Al Otaibi, Vera Maria Cury Salemi, Najmeddine Echahidi, Jehad Al Buraiki, Bahaa M Fadel, Dania Mohty. Data preparation and presentation: Mohammed Mahmoodurrahman, Josef Marek, Hamzah Ruxshan Juhardeen, Dania Mohty. Supervision of the research: Talal Al Otaibi, Vera Maria Cury Salemi, Najmeddine Echahidi, Jehad Al Buraiki, Bahaa M Fadel, Dania Mohty. Research coordination and management: Talal Al Otaibi, Vera Maria Cury Salemi, Najmeddine Echahidi, Jehad Al Buraiki, Bahaa M Fadel, Dania Mohty.

Conflict of interest

None.

References

[1] Lund LH, Khush KK, Cherikh WS, Goldfarb S, Kucheryavaya AY, Levvey BJ, et al. The registry of the international society for heart and Lung transplantation: thirty-fourth adult heart transplantation report-2017; focus theme: allograft ischemic time. J Heart Lung Transplant 2017;36:1037–46. https://doi.org/10.1016/j.healun.2017.07.019.

[2] Badano LP, Miglioranza MH, Edvardsen T, Colafranceschi AS, Muraru D, Bacal F, et al. European Association of Cardiovascular Imaging/Cardiovascular Imaging Department of the Brazilian Society of Cardiology recommendations for the use of cardiac imaging to assess and follow patients after heart transplantation. Eur Heart J Cardiovasc Imag 2015;16:919–48. https://doi.org/10.1093/ehjci/jev139.

[3] Chirakarnjanakorn S, Starling RC, Popovic ZB, Griffin BP, Desai MY. Dobutamine stress echocardiography during follow-up surveillance in heart transplant patients: diagnostic accuracy and predictors of outcomes. J Heart Lung Transplant 2015;34:710–7. https://doi.org/10.1016/j.healun.2014.11.019.

[4] Clerkin KJ, Farr MA, Restaino SW, Ali ZA, Mancini DM. Dobutamine stress echocardiography is inadequate to detect early cardiac allograft vasculopathy. J Heart Lung Transplant 2016;35:1040–1. https://doi.org/10.1016/j.healun.2016.05.012.

[5] Costanzo MR, Dipchand A, Starling R, Anderson A, Chan M, Desai S, et al. The international society of heart and Lung transplantation guidelines for the care of heart transplant recipients. J Heart Lung Transplant 2010;29:914–56. https://doi.org/10.1016/j.healun.2010.05.034.

[6] Rahmani M, Cruz RP, Granville DJ, McManus BM. Allograft vasculopathy versus atherosclerosis. Circ Res 2006;99:801–15. https://doi.org/10.1161/01.RES.0000246086.93555.f3.

[7] Billingham ME. Histopathology of graft coronary disease. J Heart Lung Transplant 1992;11:S38–44.

[8] Tuzcu EM, Kapadia SR, Sachar R, Ziada KM, Crowe TD, Feng J, et al. Intravascular ultrasound evidence of angiographically silent progression in coronary atherosclerosis predicts long-term morbidity and mortality after cardiac transplantation. J Am Coll Cardiol 2005;45:1538–42. https://doi.org/10.1016/j.jacc.2004.12.076.

[9] Spes CH, Klauss V, Mudra H, Schnaack SD, Tammen AR, Rieber J, et al. Diagnostic and prognostic value of serial dobutamine stress echocardiography for noninvasive assessment of cardiac allograft vasculopathy: a comparison with coronary angiography and intravascular ultrasound. Circulation 1999;100:509–15.

[10] Derumeaux G, Redonnet M, Soyer R, Cribier A, Letac B. Assessment of the progression of cardiac allograft vasculopathy by dobutamine stress echocardiography. J Heart Lung Transplant 1998;17:259–67.

[11] Elkaryoni A, Abu-Sheasha G, Altibi AM, Hassan A, Ellakany K, Nanda NC. Diagnostic accuracy of dobutamine stress echocardiography in the detection of cardiac allograft vasculopathy in heart transplant recipients: a systematic review and meta-analysis study. Echocardiography 2019;36:528–36. https://doi.org/10.1111/echo.14268.

[12] Clemmensen TS, Eiskjaer H, Logstrup BB, Tolbod LP, Harms HJ, Bouchelouche K, et al. Noninvasive detection of cardiac allograft vasculopathy by stress exercise echocardiographic assessment of myocardial deformation. J Am Soc Echocardiogr 2016;29:480–90. https://doi.org/10.1016/j.echo.2016.01.012.

[13] Tona F, Osto E, Tarantini G, Gambino A, Cavallin F, Feltrin G, et al. Coronary flow reserve by transthoracic echocardiography predicts epicardial intimal thickening in cardiac allograft vasculopathy. Am J Transplant 2010;10:1668–76. https://doi.org/10.1111/j.1600-6143.2010.03160.x.

[14] Lancellotti P, Tribouilloy C, Hagendorff A, Popescu BA, Edvardsen T, Pierard LA, et al. Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imag 2013;14:611–44. https://doi.org/10.1093/ehjci/jet105.

[15] Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification: a report from the American society of echocardiography's guidelines and standards committee and the chamber quantification writing group, developed in conjunction with the European association of echocardiography, a branch of the European society of cardiology. J Am Soc Echocardiogr 2005;18:1440–63. https://doi.org/10.1016/j.echo.2005.10.005.

[16] Pellikka PA, Nagueh SF, Elhendy AA, Kuehl CA, Sawada SG, American Society of E. American Society of Echocardiography recommendations for performance, interpretation, and application of stress echocardiography. J Am Soc Echocardiogr 2007;20:1021–41. https://doi.org/10.1016/j.echo.2007.07.003.

[17] Mehra MR, Crespo-Leiro MG, Dipchand A, Ensminger SM, Hiemann NE, Kobashigawa JA, et al. International Society for Heart and Lung Transplantation working formulation of a standardized nomenclature for cardiac allograft vasculopathy-2010. J Heart Lung Transplant 2010;29:717–27. https://doi.org/10.1016/j.healun.2010.05.017.

[18] Stewart S, Winters GL, Fishbein MC, Tazelaar HD, Kobashigawa J, Abrams J, et al. Revision of the 1990 working formulation for the standardization of nomenclature in the diagnosis of heart rejection. J Heart Lung Transplant 2005;24:1710–20. https://doi.org/10.1016/j.healun.2005.03.019.

[19] Genders TS, Spronk S, Stijnen T, Steyerberg EW, Lesaffre E, Hunink MG. Methods for calculating sensitivity and specificity of clustered data: a tutorial. Radiology 2012;265:910–6. https://doi.org/10.1148/radiol.12120509.

[20] Lin S, Tremmel JA, Yamada R, Rogers IS, Yong CM, Turcott R, et al. A novel stress echocardiography pattern for myocardial bridge with invasive structural and hemodynamic correlation. J Am Heart Assoc 2013;2:e000097. https://doi.org/10.1161/JAHA.113.000097.

[21] Bacal F, Moreira L, Souza G, Rodrigues AC, Fiorelli A, Stolf N, et al. Dobutamine stress echocardiography predicts cardiac events or death in asymptomatic patients long-term after heart transplantation: 4-year prospective evaluation. J Heart Lung Transplant 2004;23:1238–44. https://doi.org/10.1016/j.healun.2003.09.007.

[22] Sade LE, Eroglu S, Yuce D, Bircan A, Pirat B, Sezgin A, et al. Follow-up of heart transplant recipients with serial echocardiographic coronary flow reserve and dobutamine stress echocardiography to detect cardiac allograft vasculopathy. J Am Soc Echocardiogr 2014;27:531–9. https://doi.org/10.1016/j.echo.2014.01.020.

[23] Khush KK, Cherikh WS, Chambers DC, Goldfarb S, Hayes Jr D, Kucheryavaya AY, et al. The international thoracic organ transplant registry of the international society for heart and Lung transplantation: thirty-fifth adult heart transplantation report-2018; focus theme: multiorgan transplantation. J Heart Lung Transplant 2018;37:1155–68. https://doi.org/10.1016/j.healun.2018.07.022.