ONLINE FIRST

CARDIOLOGY JOURNAL

ISSN: 1897-5593

e-ISSN: 1898-018X

The role of endomyocardial biopsy for surveillance of cardiac allograft rejection: time to move on?

Authors: Roberto Gómez-Sánchez, Carlos Ortiz-Bautista, Javier Castrodeza, Zorba Blázquez-Bermejo, Eduardo Zataraín-Nicolás, Adolfo Villa, Ricardo Sanz-Ruiz, Jaime Elízaga, Javier Bermejo

DOI: 10.5603/cj.99019

Article type: Research Letter

Submitted: 2024-01-18

Accepted: 2024-12-19

Published online: 2025-03-10

RESEARCH LETTER

DOI: 10.5603/cj.99019

Submitted: 18.01.2024

Accepted: 19.12.2024

The role of endomyocardial biopsy for surveillance of cardiac allograft rejection: time to move on?

Roberto Gómez-Sánchez, Carlos Ortiz-Bautista, Javier Castrodeza, Zorba Blázquez-Bermejo, Eduardo Zatarain-Nicolás, Adolfo Villa, Ricardo Sanz-Ruiz, Jaime Elízaga, Javier Bermejo

Cardiology Department, Hospital General Universitario Gregorio Marañon, Faculty of Medicine, Universidad Complutense de Madrid and CIBERCV, Madrid, Spain

Address for correspondence: Carlos Ortiz-Bautista, Cardiology Department, Hospital General Universitario Gregorio Marañón, Calle del Doctor Esquerdo 46, 28007, Madrid, Spain, e-mail: carlos.ortiz@salud.madrid.org

Endomyocardial biopsy (EMB) is the gold standard for diagnosing cardiac graft rejection [1]. However, its interpretation is associated with low sensitivity for early diagnosis, high interobserver variability, and it carries an invasive nature that is not free of complications [2].

The objective herein, was to review the utility of EMB in a contemporary cohort of heart transplant recipients. A retrospective study was conducted on heart transplants performed between 2017 and 2021 at the documented center, analyzing the follow-up through EMB in the first year, the diagnosis of rejection, and associated complications.

Between 2017 and 2021, 106 heart transplants were performed (mean age of 52 ± 13 years, 71.7% male). Ischemic heart disease was the most common etiology leading to transplantation (N = 35, 33%). Induction therapy was used in all cases, with basiliximab in 97 patients (91.5%) and anti-lymphocyte/anti-thymocyte immunoglobulins in 9 (8.5%). One-year transplant survival was 84% (Tab. 1). Among one-year survivors, 53

(59.6%) followed an immunosuppression regimen based on tacrolimus-mycophenolate mofetil (MMF)-prednisone, prednisone was withdrawn in 20 (22.5%), and in 16 (17.9%) another regimen was used (tacrolimus-everolimus-prednisone in 14, cyclosporine-MMF-prednisone in 2). The mean tacrolimus levels (ng/mL) were: 9.0 ± 2.0 in the first quarter, 10.1 ± 2.3 in the second, 9.8 ± 2.3 in the third, and 9.1 ± 2.5 in the fourth.

A total of 870 elective EMBs were performed during the first year, following the usual protocol of this center, which includes an EMB at two weeks, first month, second month, third month, fourth month, sixth month and first year. Complications were rare (0.7%): four vascular (hematoma, arteriovenous fistula, or vascular dissection), one cardiac perforation, and one tricuspid insufficiency; none of them were fatal. According to the International Society for Heart & Lung Transplantation (ISHLT) classification [1], a significant rejection requiring a change of treatment was only diagnosed in 2 patients (0.2%): one case with cellular rejection (2R) and another with mixed cellular and humoral rejection (3R + AMR). In the latter, there was clinical suspicion of acute rejection based on non-invasive tests. In the remaining cases, the results were: 0R in 569 samples (65.4%), 1R-1A in 296 samples (35%), 1R-1B in 1 sample (0.1%), and 1R-2 in 2 samples (0.2%).

The present results agree with previous studies in that, given the low incidence of rejection in the current era, the clinical utility of routine EMB is very limited. In a German retrospective cohort of 151 patients who underwent 1896 EMBs between 2000 and 2011, significant rejection requiring treatment was diagnosed in < 10% of cases with a complication rate of 1%; although this cohort also included cases with graft dysfunction or clinical suspicion of rejection [3]. In another American retrospective cohort, which included 326 heart transplants, 2769 EMBs were performed between 2019 and 2022; acute rejection was diagnosed in 4.8% overall (3.6% received specific treatment), and in 1.2% in the case of routine follow-up EMBs, with procedure-associated complications in 1.6% [4].

These results have led to the search for new non-invasive techniques for diagnosing acute graft rejection based on omics sciences [5]. The most clinically developed are the Gene Expression Profile (GEP) and Donor-Derived Cell-Free DNA (ddcfDNA), reflecting immunological activity and graft damage, respectively. Both techniques have shown a high negative predictive value to rule out clinically significant cellular rejection (ISHLT ≥ 2R); ddcfDNA has proven useful for early diagnosis, as well as for the

diagnosis of humoral rejection. Furthermore, both techniques have demonstrated to provide information of long-term prognosis [5]. It has recently been suggested that the combined use of GEP and ddcfDNA may improve diagnostic performance [6]. New studies will provide additional evidence, such as the DETECT trial (NCT05081739), which will randomize a follow-up with EMB vs ddcfDNA with a combined primary endpoint of rejection requiring treatment, retransplantation, or death.

Additionally, imaging techniques such as the cardiac magnetic resonance are emerging as non-invasive alternatives in diagnosis or rejection. The elevation of native T1 values or the identification of diffuse fibrosis and/or late graft dysfunction by measuring extracellular volume allows the characterization of rejection. A multiparametric approach with magnetic resonance has been shown to improve the diagnostic accuracy and reduce the need for EMB [1].

In conclusion, given the current low incidence of rejection, the limitations of EMB, and the growing development of non-invasive diagnosis techniques ("liquid biopsy"), it may be considered that perhaps it is time to abandon the indiscriminate and undirected use of EMB as a cornerstone of the strategy for monitoring acute rejection in heart transplantation.

Data availability statement: The datasets used and analyzed in the current study are made available from the corresponding author on reasonable request.

Ethics statement: All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki.

Funding: This research received no external funding.

Authors contribution: Conceptualization — C.O.-B.; Investigation — R.G.-S., C. O.-B., J.C., Z.B.-B., E.Z.-N.; Original manuscript writing — R.G.-S., C.O.-B.; Review and editing — J.C., Z.B.-B., E.Z.-N., R.S.-R., A.V., J.E., J.B.

Conflict of interest: None declared.

References

1. Velleca A, Shullo MA, Dhital K, et al. The International Society for Heart and Lung Transplantation (ISHLT) guidelines for the care of heart transplant

recipients. J Heart Lung Transplant. 2023; 42(5): e1–e141, doi: 10.1016/j.healun.2022.10.015, indexed in Pubmed: 37080658.

2. Holzhauser L, DeFilippis EM, Nikolova A, et al. The End of Endomyocardial Biopsy?: A Practical Guide for Noninvasive Heart Transplant Rejection Surveillance. JACC Heart Fail. 2023; 11(3): 263–276, doi: 10.1016/j.jchf.2022.11.002, indexed in Pubmed: 36682960.
3. Strecker TRJ, Weyand M, Agaimy A, et al. Endomyocardial biopsy for monitoring heart transplant patients: 11-years-experience at a german heart center. Int J Clin Exp Pathol. 2013; 6(1): 55–65, indexed in Pubmed: 23236543.
4. Cusi V, Vaida F, Wettersten N, et al. Benefit versus Risk of Endomyocardial Biopsy for Heart Transplant Patients in the Contemporary Era. medRxiv. 2023, doi: 10.1101/2023.05.19.23290196, indexed in Pubmed: 37293037.
5. Ortiz-Bautista C, Fernández-Avilés F, Delgado Jiménez JF. Serum biomarkers of acute rejection: Towards precision medicine in heart transplant. J Heart Lung Transplant. 2021; 40(10): 1090–1097, doi: 10.1016/j.healun.2021.07.002, indexed in Pubmed: 34330605.
6. Henricksen EJ, Moayedi Y, Purewal S, et al. Combining donor derived cell free DNA and gene expression profiling for non-invasive surveillance after heart transplantation. Clin Transplant. 2023; 37(3): e14699, doi: 10.1111/ctr.14699, indexed in Pubmed: 35559582.

Table 1. Clinical characteristics of the heart transplant cohort between years 2017 and 2021

	Heart transplants (N = 106)
Age (years), mean ± SD	52 ± 13
Male sex, N (%)	76 (71.7)
Body mass index (kg/m^2), mean ± SD	25.2 ± 3.9
Previous heart disease	
Ischemic heart disease, N (%)	35 (33)
Nonischemic dilated cardiomyopathy, N (%)	23 (21.7)
Hypertrophic cardiomyopathy, N (%)	15 (14.2)
Complex congenital heart disease, N (%)	15 (14.2)
Valvular heart disease, N (%)	7 (6.6)

Restrictive cardiomyopathy, N (%)	4 (3.8)
Myocarditis, N (%)	3 (2.8)
Retransplant, N (%)	4 (3.8)
Cardiovascular risk factors	
Hypertension, N (%)	31 (29.2)
Diabetes mellitus, N (%)	24 (22.6)
Dyslipidemia, N (%)	43 (40.6)
Smoking (last year), N (%)	7 (6.6)
Kidney disease, N (%)	31 (29.2)
Transplant code (elective), N (%)	59 (55.7)
Inotropic support, N (%)	46 (43.4)
Mechanical support bridge to transplant, N (%)	37 (40.6)
Intra-aortic balloon pump, N (%)	4 (3.8)
Extracorporeal membrane oxygenation, N (%)	8 (7.5)
Continuous/pulsatile flow ventricular assist device, N (%)	28 (26.4) / 3 (2.8)
Surgery	
Surgical technique (standard), N (%)	79 (74.5)
Combined transplant, N (%)	2 (1.9)
Ischemic / cardiopulmonary bypass time (min), mean ± SD	214 ± 67 / 189 ± 81
Mechanical ventilation time (days), mean ± SD	5 ± 8
Intensive care unit stay (days), mean ± SD	15 ± 14
Primary graft failure, N (%)	27 (25.5)
First year infection, N (%)	67 (63.2)
Cardiac allograft vasculopathy, N (%)	10 (9.4)
First year survival, N (%)	89 (84)