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BRIEF COMMUNICATION

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Acute cellular rejection and HLA mismatch in heart transplantation: insights from a developing country

Lígia Beatriz Chaves Espinoso Schtruk[1] | Tereza Cristina Fellipe Guimarães[1] | Luis Cristóvão Pôrto[2] | Maria Cristina Caetano Kuschnir[2] | Alexandre Siciliano Colafranceschi[1] | Paulo Moreira da Silva Filho[1] | Andrea De Lorenzo[1]

[1]Instituto Nacional de Cardiologia, Rio de Janeiro, RJ, Brazil

[2]Universidade Estadual do Rio de Janeiro, Rio de Janeiro, RJ, Brazil

Correspondence
Lígia Beatriz Chaves Espinoso Schtruk, Instituto Nacional de Cardiologia, Rio de Janeiro, RJ, Brazil.
Email: lschtruk@ig.com.br

Abstract

The notable evolution of heart transplant (HTX) has paralleled the capacity of diagnosing rejection and, consequently, initiating timely treatment. Acute cellular rejection, diagnosed by endomyocardial biopsy, is the most frequent in the first 6 months after HTX. HLA matching is not routinely performed in HTX due to the absence of consensus regarding its usefulness. However, the use of HLA typing might be underscored if it could predict an increased risk of rejection. Therefore, the aim of this study was to evaluate, at a public cardiology center in Brazil, the association between HLA mismatches and the incidence of acute cellular rejection in the first 6 months after HTX. Data were obtained from hospital records and from the National Transplant System. Overall, there was no association between the number of HLA mismatches and the frequency of acute cellular rejection, but there was a tendency toward a higher incidence of rejection with HLA-DR incompatibility.

KEYWORDS
cardiac transplantation, HLA, HLA incompatibility, rejection

1 | INTRODUCTION

Refractory heart failure patients, who still increase despite the gains in survival and quality of live obtained with the clinical treatment of heart failure,[1,2] have their final resource in heart transplant (HTX), which strongly relies on the timely diagnosis of rejection followed by appropriate treatment. Acute cellular rejection is frequent, especially 3–6 months after HTX, and up to 40% of HTX receptors have at least one episode in the first postoperative year.[3] The diagnosis of acute cellular rejection is made by endomyocardial biopsy with histological identification of interstitial leukocyte infiltration with various degrees of myocyte damage, which are sensitive and specific criteria that correlate with allograft dysfunction.[4]

The role of HLA matching has long been established in kidney transplantation, as the association with graft outcome has been demonstrated.[5] However, in HTX there is not a consensus regarding the usefulness of HLA matching.[6–10] Further data on the association between HLA matching and rejection would help substantiate its use, especially at developing countries, where the costs determined by complications are especially striking. In Brazil, between 2004 and 2014 there were 2504 HTX, with a 4-year survival of 68%.[11] The aim of this study was to evaluate, in a Brazilian cohort, the association between HLA mismatches and the incidence of acute cellular rejection after HTX.

2 | METHODS

Patients >18 years who underwent HTX at the National Cardiology Institute between 2008 and 2013 were considered candidates for the study. HLA typing was performed by polymerase chain reaction-reverse sequence-specific oligonucleotide (PCR-RSSO),[12,13] with commercial kits (HLA-A: RSSO1A-013-05, HLA-B: 1B-016-07, and DRB1: 2B-017-06; One Lambda, Canoga Park CA, USA).

The diagnosis of cellular rejection was defined by endomyocardial biopsies, performed according to standardized protocols.[14,15] The biopsies were classified according to the 1990 criteria of the International Society of Heart and Lung Transplantation (ISHLT), revised in 2005.[4] These grading criteria have four levels of rejection according to histopathologic findings: 0R, none; 1R, mild (interstitial and/or perivascular infiltrate with up to one focus of myocyte damage); 2R, moderate (two or more foci of infiltrate with associated myocardial damage); and 3R, severe (diffuse infiltrate with multifocal myocyte damage±edema±hemorrhage±vasculitis). In this study, only biopsies classified as 2R or 3R were considered clinically significant, as therapeutic intervention is indicated only in these cases. According to the institution's protocol, biopsies were performed twice in the first month post-HTX, and once on months 2, 6, and 12 post-HTX. If rejection was detected, the biopsy was repeated after 2 weeks of treatment.

Data were collected from hospital charts and from the National Transplant System. Categorical variables were described as number and percentage and compared with Fisher's exact test. Continuous variables were described as mean±standard deviation or median and compared with Student's *t*-test or Mann-Whitney *U*-test. A value of $P<.05$ was considered statistically significant.

This study was approved by the local ethics committee and is in accordance with the Declaration of Helsinki.

3 | RESULTS

From 39 HTX patients, 14 were excluded due to the absence of HLA typing, from either donor or receptor. Among the 25 remaining receptors, 84% were male, with a mean age of 46.9 years, 52% blood type O, 27% A, 13% B, and 8% AB. The etiology of heart failure was idiopathic dilated cardiomyopathy in 24%, ischemic cardiomyopathy in 28%, Chagas' disease in 20%, valve disease in 8%, or amyloidosis, alcoholic cardiomyopathy, myocarditis, peripartum cardiomyopathy, or post-chemotherapy (4% each). All patients took full immunosuppressive treatment. None had class I or class II anti-HLA antibodies pre-transplantation. Among the donors, 68% were male, with a mean age of 28.5 years, and 63% blood type O, 24% A, 13% B, and none AB. The cause of death was hemorrhagic stroke in 52% and head trauma in 48%.

Among 142 biopsies, 5% were 2R and there was no 3R. 0R and 1R results were analyzed together as absence of significant rejection. The number of HLA mismatches (MM) is shown in Table 1. Interestingly, there were no cases of zero, one, or two MM, while 80% had five or six MM. The association between clinical variables, HLA mismatch, and rejection was evaluated (Table 2), and only HLA-DR showed a tendency toward association with rejection.

4 | DISCUSSION

The usefulness of HLA matching for receptor selection in HTX is controversial,[6] even though there is evidence that HLA mismatch may

TABLE 1 HLA mismatches

Number of mismatches	Donor/receptor pairs n (%)
HLA-A	
0	0
1	9 (36)
2	16 (16)
HLA-B	
0	0
1	7 (28)
2	18 (72)
HLA-DR	
0	0
1	8 (32)
2	17 (68)
Total (HLA-A+HLA-B+HLA-DR)	
3	2 (8)
4	3 (12)
5	12 (48)
6	8 (32)

TABLE 2 Associations between clinical variables, HLA mismatch, and rejection

	With rejection (n=6)		Without rejection (n=19)	
Mean receptor age (years)	54		46	
Mean donor age (years)	24		28	
Receptor gender: male	5 (83%)		16 (84%)	
Donor gender: male	4 (67%)		13 (68%)	
Gender compatibility				
Female/female	0		1 (5%)	
Female/male	1 (17%)		2 (11%)	
Male/female	2 (33%)		5 (26%)	
Male/male	3 (50%)		11 (58%)	
Receptor blood type				
A	1 (17%)		6 (32%)	
B	1 (17%)		2 (10%)	
AB	1 (17%)		1 (5%)	
O	3 (50%)		10 (53%)	
Donor blood type				
A	0		6 (32%)	
B	1 (17%)		2 (10%)	
AB	0		0	
O	5 (83%)		11 (58%)	
Number of HLA mismatches	1 MM	2 MM	1 MM	2 MM
HLA-A	3 (50%)	3 (50%)	6 (32%)	13 (68%)
HLA-B	1 (17%)	5 (83%)	6 (32%)	13 (68%)
HLA-DR	0	6 (100%)*	8 (42%)	11 (58%)

MM, mismatch.
*$P=.05$.

reduce survival and increase rejection.[7–9] Further evaluation of the role of HLA typing in HTX is therefore necessary to help decisions regarding the incorporation of this test into practice, especially in a scenario with limited resources, such as in a developing country with a growing transplantation program, where HLA matching might offer benefit in improving receptor selection.

In this study, 24% of the patients had acute cellular rejection in the first 6 months after HTX. Other studies have described 20%–40% rates in the first year.[2] Antibody-mediated rejection and acute cellular rejection may coexist in up to one-quarter of the rejection episodes,[16] but unfortunately, at the time of data collection, the technical ability to detect and quantify recipient anti-HLA antibody production was unavailable at our center.

The frequency of HLA-A, HLA-B, and HLA-DR mismatches was similar to previous reports.[17,18] However, there was an elevated rate of highly incompatible donor/receptor pairs. There was a tendency toward association between HLA-DR mismatch and acute cellular rejection in the first 6 months after HTX. This is in line with previous studies which have suggested intensification of the immunosuppressive regimen in patients with mismatch, particularly in the case of HLA-DR.[19,20] Although the evaluation of antibody-mediated rejection was not the aim of this study, it is worth to remind the additional influence of HLA mismatches on antibody-mediated rejection episodes and the development of cardiac allograft vasculopathy. In the study by Nath et al.[21], the presence of antibodies against donor-mismatched HLA could be demonstrated in recipients with antibody-mediated rejection or cardiac allograft vasculopathy. Ho et al.[22] have also shown that the presence of HLA-specific antibodies correlates with antibody-mediated rejection, chronic allograft vasculopathy, and lower graft survival.

The logistic difficulty to perform HLA compatibility tests between donor and receptor quickly has been overcome, with cross-match testing being performed nowadays in up to 2 hours.[12,13] This study suggests that HLA-DR compatibility might be considered useful as an additional criterion to select HF patients waiting for HTX, especially when more than one candidate has the same characteristics (e.g., ABO matching, weight). In addition, when HLA-DR mismatch is detected, more intensive immunosuppressive therapy might be advised, while if mismatch is not present, therapy might be lessened, possibly reducing the incidence of complications such as infections or cancer. Nonetheless, the small patient number and short follow-up (6 months) limit conclusions about the influence of HLA mismatch on long-term prognosis after HTX and if any special intervention should be directed toward these patients. Larger, multicenter studies are needed to further evaluate this issue and strengthen the conclusions on the value of HLA matching in HTX.

5 | CONCLUSIONS

In a Brazilian population, there was a tendency toward an association between HLA-DR mismatch and acute cellular rejection after HTX. This should be further evaluated in larger studies, but may suggest that HLA compatibility testing may be useful for receptor selection or to tailor the intensity of immunosuppressive treatment.

CONFLICT OF INTEREST

None.

AUTHORS' CONTRIBUTIONS

Lígia Beatriz Chaves Espinoso Schtruk: Participated in concept, data collection, drafting article; Tereza Cristina Fellipe Guimarães: Participated in study design; Luis Cristóvão Pôrto: Participated in data analysis; Maria Cristina Caetano Kuschnir: Participated in critical revision of article; Alexandre Siciliano Colafranceschi: Participated in data collection; Paulo Moreira da Silva Filho: Participated in critical revision of article; Andrea De Lorenzo: Participated in writing of the final version of the article and critical revision of article.

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