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Interventricular conduction disorders after orthotopic heart transplantation: risk factors and clinical relevance

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Abstract

Background: Causes and significance of interventricular conduction disorders (IVCDs) after orthotopic heart transplantation (OHT) are still unknown.

Methods: We retrospectively researched the presence of IVCDs in 240 patients who underwent bicaval OHT in three time periods: at day 1, after 1 year, and after 3 years from OHT. To evaluate the impact of the surgical technique, a control population treated with biatrial anastomosis was used.

Results: The most common IVCD was right bundle branch block (RBBB). Its presence at day 1 correlated with transpulmonary gradient before OHT. Its presence after 1 year and its development correlated with a 1-month acute rejection score≥2 (p = .050 and p = .006). The incidence of RBBB was higher in the biatrial control population (40.7% vs 23.8%, p < .001).

Conclusions: RBBB is the most common IVCD. Its presence can be explained by a susceptibility of the right branch to heart positioning, pressure overload, and acute rejection. IVCDs do not affect prognosis.

KEYWORDS

clinical, clinical noninvasive techniques—electrocardiography, electrophysiology—conduction disturbances

Transplanted hearts are electrophysiologically unique: they lack external innervation and have altered electrophysiologic substrate from graft ischemia during transplantation and from acute and chronic rejection. There are two techniques of graft anastomosis. The biatrial technique, developed by Shumway and Lower (Shumway, Lower, & Stofer, 1966), results in an abnormally enlarged atrial cavity and distorted atrial geometry. It is often complicated by bradycardia attributed to an obligatory right atrial incision with possible injury of the donor heart sinus node (Cantillon et al., 2009). The bicaval technique, introduced in 1989, preserves the integrity of the right atrium and its sinus node by connecting the recipient pulmonary veins cuffs and the vena cava to the donor heart separately (Miniati & Robbins, 2001). The anastomosis leads to a posterior rotation on the long axis of the heart on the transverse plan, more evident with biatrial anastomosis. Both surgical techniques do not directly damage the subhisian conduction system. Nevertheless, interventricular conduction disorders (IVCDs) are often present after orthotopic heart transplantation (OHT) and can evolve, modify, or disappear over time; predisposing factors, evolution over time, and clinical significance are not yet fully understood and previous studies have contradictory results (Pickham et al., 2014; Golshayan et al., 1998; Marcus, Hoang, Hunt, Chun, & Lee, 2006; Osa et al., 2000). In particular, right bundle branch block (RBBB) is known as the most common electrocardiographic abnormality in heart transplant recipients (Golshayan et al., 1998). Several studies associated different factors with this finding, but its cause and significance remain unknown (Marcus et al., 2006; Osa et al., 2000).

The aim of this study is to evaluate incidence and risk factors of IVCDs in OHT performed with bicaval anastomosis, to research causes and pattern of development and to assess if they have any prognostic value.

1 | METHODS

We retrospectively reviewed a population of patients who underwent OHT in our Cardio-Surgery center, between 1995 and 2003, with bicaval anatomosis. We collected the following parameters:

1. Donors: age, gender, body mass index (BMI), blood group
2. Recipients: age, gender, BMI, blood group, data of right heart catheterization performed before transplantation
3. OHT: time of graft ischemia, graft anastomosis, graft recipient mismatch of blood groups and of gender, ECG and ECG monitoring before hospital discharge.
4. Five-year follow-up: clinical status, ECG, Holter ECG, presence of acute graft rejection, presence and severity of cardiac allograft vasculopathy (CAV), pacemaker (PM) implantation, 5-year mortality.

The presence of IVCDs was classified into three time periods:

1. at day 1 after OHT
2. 1 year from OHT
3. 3 years from OHT till the last follow-up.

For the evaluation of acute graft rejection, endomyocardial biopsies results were reviewed. Endomyocardial biopsies were executed (guided by echocardiography from right internal jugular vein) in the apical septum of the right ventricle (to minimize the risk of conduction tissue damage), with this standard protocol: every week in the first month after OHT, every 2 weeks till the third month, every month till the first year, or when clinically indicated. The histological rejection grading of 1990 was used, according to guidelines of the International Society for Heart and Lung Transplantation (ISHLT) (Billingham et al., 1990); the histological grade of rejection was converted into points (grade 0 = 0, grade 1A = 1, grade 1B = 2, grade 2 = 3, grade 3A = 4, grade 3B = 5, grade 4 = 6) to calculate a rejection score (RS) as the mean of the points of rejection, at 1 month and 1 year from OHT. One-month RS was used as a marker of early acute rejection. For the research of CAV, coronary angiographies were evaluated. The standardized nomenclature of ISHLT (Mehra et al., 2010) was used to classify CAV severity. Finally, to evaluate the impact of the surgical technique on IVCD, we considered a comparable control population of 150 heart recipients, transplanted in our Cardiac Surgery Center between 1985 and 1994 with biatrial anastomosis. The study protocol conforms the ethical guidelines of the 1975 Declaration of Helsinki.

1.1 | Statistical analysis

Normality was evaluated for each variable from normal distribution plots and histogram. Descriptive statistics such as proportions, means, and standard deviations and medians (25th–75th percentiles) were used to summarize the clinical data. Between-group comparisons were tested with Wilcoxon–Mann-Whitney signed rank test for continuous variables or chi-square test for categorical variables. For all the statistical tests used, a p-value<.05 was considered statistically significant. All the statistical analyses were performed with the SSI package version 17.0.

2 | RESULTS

2.1 | Study population

A total of 240 patients who underwent OHT with bicaval anastomosis were enrolled in the study. Clinical characteristics are showed in Table 1. Every patient performed an ECG at day 1 after OHT. The first detected rhythm after OHT was sinus tachycardia for the 89.2% of patients, with a mean heart rate of 113.9 ± 19.0 bpm; accelerated junctional rhythm for the 9.6% with a mean heart rate of 98.3 ± 24.4 bpm; 3 (1.2%) patients were stimulated by temporary PM for an atrioventricular (AV) dissociation, 2 of them underwent definitive PM implantation, in 1 case restore of normal AV conduction was documented.

TABLE 1 Baseline population characteristics

Characteristics	General population (n = 240)
Recipient[a]	
BMI (kg/m^2)	23.9 ± 3.9
Age (years)	55.8 ± 11.3
Gender (n, %)	
Male	191 (79.6%)
Female	49 (20.4%)
Donor[a]	
Age (years)	39.4 ± 13.9
Gender mismatch (n, %)	91 (37.9%)
Group mismatch (n, %)	29 (12.1%)
Ischemic time (min)	185.5 ± 52.8
Right heart catheterization before OHT[b]	
Mean pulmonary artery pressure (mmHg)	31.3 ± 15.6
Transpulmonary gradient (mmHg)	9.8 ± 5.7
Data of follow-up[a]	
Median rejection score	
1 month	0.5 (0.2–1.5)
1 year	1.4 (0.7–1.4)
CAV (n, %)	
0–1	214 (89.2%)
2–3	26 (10.8%)
PM implantation (n, %)	16 (6.7%)
5-year mortality (n, %)	64 (26.7%)

BMI, body mass index; CAV, cardiac allograft vasculopathy; OHT, orthotopic heart transplantation; PM, pacemaker.

[a]Data disposable for the 100% of the population.

[b]Missing data for 40 patients.

In a 5-year follow-up, a total of 16 (6.7%) patients underwent PM implantation.

2.2 | Interventricular conduction disorders

The only IVCD observed was complete right bundle branch block (RBBB) that was already present in the 23.8% (n = 57/240) of patients immediately after surgery; 13 of these RBBB resolved before hospital discharge and other 5 resolved within the first year. Of these 18 patients, 3 patients died before the third year after OHT and two presented again RBBB in the ECG 3 years after OHT. The total incidence of RBBB increased to 31.7% (n = 65/205) 1 year after OHT and to 34.2% (n = 64/187) 3 years after OHT (Table 2). A total of 40 patients who did not show RBBB at day 1 developed it in a few months. There was a significant correlation between the presence of RBBB and time from OHT (p < .001). The presence of RBBB was associated with left-anterior hemiblock in 13 cases (22.3%); no correlation was found between the presence of bifascicular block and PM implantation in the follow-up (p = .879).

We analyzed risk factors for the presence of RBBB in the three analyzed periods (Table 3). Regarding day 1 RBBB, we found a significant correlation with transpulmonary gradient (calculated as the difference between the mean pulmonary artery pressure and wedge pressure) measured during the right heart catheterization before OHT. In the comparison between patients with and without RBBB 1 year after OHT, there was an association with the presence of a 1-month RS ≥2 (p = .050), so with early acute rejection. No significant correlation was detected in the comparison between patients with and without RBBB 3 years after OHT. No correlation was found between RBBB and 5-year mortality or PM implantation in the three analyzed periods.

2.3 | Development of right bundle branch block

We observed that among patients who did not show IVCD at day 1 and survived at least 1 month from OHT (n = 222), 40 developed RBBB after a few months from OHT. Analyzing the predisposing factors for the development of RBBB, we found a correlation with early acute graft rejection: 1-month RS was superior than 2 in the 30.0% (12/40) of patients with RBBB development vs 12.6% (23/182) in the remaining population (p = .006). Also the percentage of these patients with a 1-year RS superior than 2 was higher, without statistical significance (13.5%, 5/37 vs 5.4%, 9/168, p = .075). No other correlations were found with donors and recipients data and in particular with 5-year mortality and PM implantation in the follow-up.

TABLE 2 Incidence of right bundle branch block in the three analyzed periods

	Day 1	1 year	3 years
RBBB (n, %)	57 (23.8%)	65 (31.7%)	64 (34.2%)
No RBBB (n, %)	183 (76.2%)	140 (68.3%)	123 (65.7%)
Total patients alive (n, %)	240 (100%)	205 (100%)	187 (100%)

RBBB, right bundle branch block.

2.4 | Postsurgical right bundle branch block and graft anastomosis

It is well known in literature (Cantillon et al., 2009; Miniati & Robbins, 2001) that biatrial anastomosis is linked to a higher incidence of PM implantation due to the close proximity of the sinus node to right atrial suture line; less is known about the influence of the anastomosis technique on IVCDs. We evaluated the incidence of postsurgical RBBB in a control population of 150 heart recipients, treated with biatrial anastomosis. Comparing general features of the two populations, we observed that patients treated with biatrial anastomosis and respective donors were younger and with a shorter time of graft ischemia (Table 4). This can be due to a more rigid selection of organs and recipients in a period in which experience on OHT was limited and data on long-term outcome were lacking. The incidence of RBBB was significantly higher in the biatrial control population than in our bicaval population [61/150 (40.7%) vs 57/240 (23.8%), p < .001].

3 | DISCUSSION

As reported in other studies (Golshayan et al., 1998; Marcus et al., 2006; Leonelli, Dunn, Young, & Pacifico, 1996) RBBB resulted the most prevalent IVCD after OHT and we documented that its prevalence increased over time from OHT. The percentage of heart recipients who showed RBBB was substantially greater than that found in other populations. For example, in the Framinghan cohort the prevalence of all IVCDs was 11% in elderly men and 5% in elderly women (Kreger, Anderson, & Kannel, 1989). In the 23.8% of our patients, RBBB was already present in the first day after OHT and the most important predisposing factor for the occurrence of RBBB in these cases resulted in a pulmonary hypertension "out of proportion." So RBBB at day 1 was mainly an expression of right ventricular strain and remodeling consequent to severe heart failure, reversible only in the 23% of cases. However, the 16.7% of the total population enrolled developed RBBB later and in particular in the first months after OHT. In this group, pulmonary hypertension did not seem to be involved in the genesis of the IVCD, while early acute rejection (the calculation of 1-month RS gave us the possibility of having a clear picture of the early period after OHT) played an important role. Moreover, the association between RBBB and early acute rejection might be underestimated by our retrospective study, as endomyocardial biopsies were obviously not focused on the conduction system, which antigens are different from myocyte antigens and can themselves be targets of rejection. According to this hypothesis, some authors (Knight et al., 2010) described cases of rejection with preferential involvement of the conduction system that can be detected only with post mortem histological analysis. In literature only Osa et al. (2000) and Leonelli et al. (1996) found a relationship between RBBB and rejection, without any timing difference and defining rejection as the "number of treatable episodes." As reported in most literature (Golshayan et al., 1998; Marcus et al., 2006; Ramey et al.,

TABLE 3 Comparison between patients with and without right bundle branch block

	RBBB at day 1 after OHT	No RBBB	*p*-Value
Total patients alive (*n*)	**57**	**183**	
Age (years)	56.0 ± 11.0	55.6 ± 11.5	.688
BMI (kg/m^2)	24.2 ± 3.3	23.8 ± 4.0	.453
Age of donor (years)	37.5 ± 16.0	40.0 ± 13.0	.266
Male gender (*n*, %)	43 (75.4%)	148 (80.9%)	.374
Gender mismatch (*n*, %)	21 (36.8%)	70 (38.3%)	.848
Blood group mismatch (*n*, %)	5 (8.8%)	24 (13.3%)	.360
Ischemia time (min)	187.6 ± 53.1	176.9 ± 51.2	.177
Mean artery pressure (mmHg)	33.0 (14.0–46.2)	30.0 (18.5–39.0)	.746
Transpulmonary gradient (mmHg)	13.5 (7.5–16.5)	8.0 (5.0–12.5)	.047
5-year mortality (*n*, %)	15 (26.3%)	49 (26.8%)	.945
PM implantation (*n*, %)	6 (10.5%)	10 (5.5%)	.181
	RBBB 1 year after OHT	**No RBBB**	***p* value**
Total patients alive (*n*)	**65**	**140**	
Age (years)	55.9 ± 10.8	55.3 ± 12.1	.765
BMI (kg/m^2)	23.7 ± 3.7	24.1 ± 3.8	.385
Age of donor (years)	40.5 ± 15.2	37.5 ± 13.6	.204
Male gender (*n*, %)	52 (80.0%)	111 (79.3%)	.906
Gender mismatch (*n*, %)	24 (36.9%)	52 (37.1%)	.976
Blood group mismatch (*n*, %)	4 (6.3%)	21 (15.2%)	.072
1-month RS ≥ 2 (*n*, %)	14 (21.9%)	16 (11.4%)	.050
1-year RS ≥ 2 (*n*, %)	5 (7.8%)	9 (6.4%)	.717
5-year mortality (*n*, %)	11 (16.9%)	18 (12.9%)	.437
PM implantation (*n*, %)	7 (5.0%)	6 (9.2%)	.247
	RBBB 3 years after OHT	**No RBBB**	***p* value**
Total patients alive (*n*)	**64**	**123**	
Age (years)	56.4 ± 9.6	4.5 ± 12.8	.269
BMI (kg/m^2)	24.5 ± 3.8	23.5 ± 3.8	.076
Age of donor (years)	40.0 ± 15.1	37.5 ± 13.4	.123
Male gender (*n*, %)	55 (85.9%)	95 (77.2%)	.156
Gender mismatch (*n*, %)	24 (37.5%)	45 (36.6%)	.902
Blood group mismatch (*n*, %)	4 (6.3%)	16 (13.2%)	.155
1-month RS ≥ 2 (*n*, %)	13 (20.3%)	13 (10.6%)	.068
1-year RS ≥ 2 (*n*, %)	5 (7.8%)	4 (3.3%)	.167
5-year mortality (*n*, %)	6 (9.4%)	5 (5.3%)	.418
PM implantation (*n*, %)	4 (6.3%)	7 (5.7%)	.878

BMI, body mass index; OHT, orthotopic heart transplantation; PM, pacemaker; RBBB, right bundle branch block; RS, rejection score.

2013) we did not find any correlation between RBBB and 5-year mortality or PM implantation and between bifascicular block and PM implantation. The impact of the surgical technique on the postsurgical RBBB seemed very important, as we observed a significantly higher incidence of RBBB in the younger control population treated with the biatrial technique. Both with bicaval and biatrial anastomosis the subhisian conduction system is not directly damaged; we hypothesize that heart positioning and, in particular, the posterior rotation on the long axis of the heart, more important with biatrial anastomosis, may influence the conduction through the right branch. Desouza, Joseph, Cuculich, Ewald, and Rudy (2013) with a noninvasive mapping of ventricular activation recently demonstrated a later activation of the right ventricular basal free wall post-OHT and other investigators related RBBB to heart positioning without a clear demonstration (Golshayan et al., 1998; Butman, Phibbs, Wild, & Copeland, 1990). Moreover, Sandhu, Curtiss, Follansbee, Zerbe, and Kormos (1990) noted with

TABLE 4 Comparison between patients with bicaval and biatrial anastomosis

Characteristics	Bicaval anastomosis (n = 240)	Biatrial anastomosis (n = 150)	p-Value
Recipient[a]			
BMI (kg/m^2)	23.9 ± 3.9	22.8 ± 3.5	.004
Age (years)	58.0 (52–63)	47.5 (38.7–55)	<.001
Gender (n, %)			
Male	191 (79.6%)	131 (87.3%)	.050
Female	49 (20.4%)	19 (12.7%)	
Donor[a]			
Age (years)	42.0 (27–52)	22.0 (17–35.2)	<.001
Gender mismatch (n, %)	91 (37.9%)	46 (30.7%)	.145
Group mismatch (n, %)	29 (12.1%)	14 (9.3%)	.376
Ischemic time (min)	185.5 ± 52.8	132.7 ± 47.7	<.001
RBBB (n, %)	57 (23.8%)	61 (40.7%)	<.001

BMI, body mass index; RBBB, right bundle branch block.
[a]Data disposable for the 100% of both populations.

radionuclide angiography a greater left-anterior oblique angle in heart recipients who presented RBBB. So probably the right branch can be stretched and damaged during heart positioning.

3.1 | Limits of this study

This is a retrospective study involving a large population and some information about clinical status and some ECGs might be not available especially if executed in other hospitals.

Endomyocardial biopsies were not focused on the conduction system.

We preferred to use the standardized nomenclature of ISHLT of 1990 to maintain the original rejection grading of the disposable biopsies and to avoid mistakes in the conversion with the new nomenclature.

4 | CONCLUSIONS

The presence of IVCDs in OHT is largely related to intraoperative factors and to surgical technique. RBBB is the most common IVCD and its presence can be explained by an increased susceptibility of the right branch to injury and in particular to right ventricular pressure overload, along with inflammation due to early acute rejection and to mechanical stretch due to posterior rotation. The presence of IVCDs do not affect prognosis.

CONFLICT OF INTEREST

None.

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