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Discontinuing Amiodarone Treatment Prior to Heart Transplantation Lowers Incidence of Severe Primary Graft Dysfunction

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Abstract

Background—Recent studies have shown an increased incidence of primary graft dysfunction (PGD) in patients treated with amiodarone prior to orthotopic heart transplant (OHT). We hypothesized that discontinuation of amiodarone before OHT may lower the incidence of severe PGD.

Methods—This was a single-center retrospective study of 381 adult OHT recipients between January 2010 and June 2017. Within six months prior to OHT, 197 did not receive amiodarone (Group 1), 142 continued amiodarone to OHT (Group 2), and 42 had amiodarone treatment discontinued before OHT (Group 3).

Results—53 (13.9%) participants developed severe PGD, 13 (6.6%) of which were in Group 1, 36 (25.4%) were in Group 2, and 4 (9.5%) were in Group 3 (p-value < 0.001). Multivariable analysis revealed continued amiodarone treatment to OHT (Group 2; OR, 3.70; 95% CI, 1.26–10.88; p = 0.018) to be an independent risk factor for the development of severe PGD when Group 1 served as the reference group. Moreover, patients in Group 3 had no difference in the risk of severe PGD (OR = 0.416, 95% CI = 0.08–2.15; p-value = 0.296).

Conclusion—We found that discontinuing amiodarone treatment prior to OHT resulted a lower incidence of severe PGD.

Keywords

primary graft dysfunction; amiodarone; orthotopic heart transplantation; heart failure

Introduction

Primary graft dysfunction (PGD) remains the leading cause of mortality in patients post-orthotopic heart transplantation (OHT).¹ Total incidence of PGD has been found to be 7.4%, with a 30-day and 1-year mortality of 30% and 34.6%, respectively.² Previous study of PGD was difficult because of different multi-center definitions, however a 2014 consensus conference on PGD by the International Society for Heart and Lung Transplantation (ISHLT) helped to establish a common definition. Severe PGD was defined as the as dependence on mechanical circulatory support within 24 hours after completion of the cardiac transplant surgery.² Risk factors that have been identified for severe PGD originate from donor, recipient, and surgical procedural characteristics, including donor age, donor cause of death, recipient age, recipient mechanical support, recipient congenital heart disease as etiology, operative ischemic time, and donor-to-recipient mismatch.²

Concern for amiodarone use prior to OHT has been growing within the past two decades. Amiodarone is a class III anti-arrhythmic drug that also has some properties of classes I, II, and IV anti-arrhythmic drugs, and has long been considered the antiarrhythmic drug of choice for ventricular tachyarrhythmias, especially in patients with end-stage heart failure.^{3,4} The serum elimination half-life of amiodarone has been found to range from 21–120 days.^{5–9} Adverse effects of amiodarone treatment are well-documented, with gastrointestinal, neurologic, pulmonary, and thyroid toxicity among the most significant.^{3,4} Nevertheless, amiodarone remains one of the most prescribed antiarrhythmic drugs in the United States.¹⁰

Recently our group showed that amiodarone use prior to OHT is independently associated with increased incidence of PGD and in-hospital mortality, and that this relationship is associated in a dose-dependent manner.¹¹ Based on these results, we have attempted to decrease or discontinue amiodarone treatment in patients waiting OHT. In this study, we examine how the discontinuation of amiodarone treatment before OHT affects patient outcomes, particularly the incidence of severe PGD.

Methods

Patient Cohort

We retrospectively reviewed all patients who underwent OHT at Columbia University Medical Center from January 2010 through June 2017 (n = 392 recipients). Eleven patients were excluded due to incomplete identifying information. Of the remaining 381 patients, within six months prior to OHT, 197 did not receive amiodarone (Group 1), 142 received amiodarone and continued to OHT (Group 2), and 42 received amiodarone and did not continue to OHT (Group 3). The Columbia University Irving Medical Center Institutional Review Board approved this study.

Definition of PGD

The PGD consensus statement by the ISHLT committee was used to retrospectively determine the diagnosis and degree of PGD by evaluating patients' clinical, echocardiographic, and hemodynamic data within 24 hours after heart transplantation.¹ The new grading system defines severe PGD as the requirement of mechanical circulatory support except for intraaortic balloon pump. At our center all patients with severe PGD were managed with extracorporeal membrane oxygenation (ECMO).

Data collection and follow-up

Detailed recipient characteristics including demographics, concomitant drug therapy, wait list time and status, as well as ventricular assist device history was obtained from the institutional electronic medical record as well as from the United Network for Organ Sharing (UNOS) registry. Donor data was obtained from Donornet/UNOS. Donor-recipient predicted heart mass (PHM) was calculated according to previously described equations for size match in heart transplantation from Kransdorf et al.¹²

The follow-up examinations were completed on 12/11/2019, and the follow-up duration was from 914 days to 3622 days (median, 2458 days; interquartile range, 1668 – 3037 days). Clinical follow-up was completed in 100% of patients.

Statistical Analysis

Continuous variables are presented as mean $\pm$ standard deviation and comparisons between groups were made using the one-way anova test. Non-normally distributed continuous variables are presented with the median and inter-quartile range and comparisons between groups were made using the Kruskal-Wallis H test. Categorical variables are presented as number and percent, and comparisons between groups were made using a chi-squared test or Fischer's exact test, as appropriate.

Logistic regression analysis was used to identify univariable and multivariable preoperative risk factors for severe PGD and are presented with odds ratios (ORs) and 95% confidence intervals (95% CIs). Variables that were significant ($p = 0.05$) on univariate analysis were identified for multivariate analysis. The presence of a ventricular assist device (VAD) was chosen for multivariate analysis because it was statistically significant on univariate analysis. The duration of VAD use was not used in multivariate analysis because its odds ratio was not clinically significant and due to collinearity with the presence of a VAD categorical variable. Amiodarone treatment group participation was used in multivariate analysis, with Group 1 serving as the reference group. Six-month cumulative amiodarone use and intraoperative packed red blood cells were also used for multivariate analysis due to their statistical significance on univariate analysis.

Long-term survival was plotted by Kaplan-Meier curves and curves were compared using the log-rank test. All tests were 2-sided with a significance value $\alpha = 0.05$. All analysis was performed on Stata/IC 15.0 software (StataCorp).

Results

Recipient pre-operative characteristics

Table 1 summarizes the recipient pre-operative characteristics. The presence of a ventricular assist device (VAD; p-value = 0.009), type of VAD (p-value = 0.002), the duration of VAD placement (p-value = 0.005), recipient creatinine (p-value = 0.001), cumulative amiodarone dose among Groups 2 and 3 (p-value = 0.001), initial UNOS status at listing (p-value = 0.021), and the transplant waiting time (p-value = 0.004) were statistically significant between the three groups. Group 1 had the largest number of patients on LVAD and BiVAD. Group 2 had longest duration of VAD support, total waiting time, and the highest creatinine level among the three groups. Group 3 was more likely to have VAD use prior to OHT with shorter VAD duration and total waiting time for OHT.

Donor and peri-operative characteristics

Table 2 summarizes the donor and peri-operative characteristics. The donor gender (p-value = 0.005), donor cause of death (p-value = 0.011), donor left ventricular ejection fraction (p-value = 0.014), and cardio-pulmonary bypass time (p-value = <0.001) were statistically significant between the three groups. Group 3 displayed the lowest left ventricular ejection fraction. There were no significant differences in gender and weight mismatch.

Adverse Events in Group 3 After Amiodarone Discontinuation

Of the 42 patients in Group 3, the median time from discontinuation of amiodarone to OHT date was 74 days (IQR, 38–137 days). Furthermore, 12 (28.6%) were readmitted due to non-arrhythmic causes; 1 (2.4%) patient was readmitted due to new onset atrial fibrillation after amiodarone discontinuation.

Incidence of severe PGD

Of all, 53 (13.9%) developed severe PGD. Incidence of severe PGD was significantly different among the groups: 13 (6.6%) in Group 1, 36 (25.4%) in Group 2, and 4 (9.5%) in Group 3 (Figure 1, p<0.001).

Risk factor for severe PGD

Univariate variables are listed in Table 3. Upon univariable analysis, the presence of a VAD, intraoperative packed red blood cell (pRBC) administration, amiodarone treatment group participation, and six-month cumulative amiodarone dose were chosen for multivariate analysis. Multivariate analysis revealed the intraoperative administration of pRBC (per 1000mL; OR, 3.16; 95% CI, 2.18–4.57; p < 0.001) and participation in amiodarone treatment Group 2 (OR, 3.70; 95% CI, 1.26–10.88; p = 0.018) as independent risk factors for the development of severe PGD. Presence of a VAD, cumulative amiodarone dose, and participation in amiodarone treatment Group 3 were not statistically significant predictors for the development of severe PGD.

Early and Long-term survival

The median hospital stay among all groups was 20 days (IQR, 15–31 days). The median hospital stay was 19 days (IQR, 15–29 days), 22 days (IQR, 16–33 days), and 18.5 days (IQR, 14–24 days) in Group 1, Group 2, and Group 3, respectively ($p=0.015$). Overall in-hospital mortality occurred in 21 patients (5.51%). In-hospital mortality was not statistically different among amiodarone treatment groups: 8 (4.06%) in Group 1, 12 (8.45%) in Group 2, and 1 (2.38%) in Group 3 ($p=0.192$).

One-year survival was 92% in Group 1, 88% in Group 2, and 95% in Group 3 among the three groups, respectively ($p=0.245$). Four-year survival was 81% in Group 1, 83% in Group 2, and 91% in Group 3 ($p=0.433$). Likewise, two- and three-year survival among amiodarone treatment groups were not statistically significant ($p=0.111$ and $p=0.393$, respectively). When the three groups were compared 1:1, no difference in survival was observed at one-year or three-years post-transplant when a log-rank test was performed (Figure 2).

Discussion

Our study had two key findings. First, we found that patients who were treated with amiodarone and continued that treatment to transplantation (Group 2) had a greater odds of developing severe PGD compared to patients who received no amiodarone treatment within six months of OHT (Group 1). These results match prior findings from our group.¹¹ Second, we found that patients who had discontinued amiodarone treatment prior to transplantation (Group 3) had no significant difference in their odds of developing severe PGD after OHT compared to patients who received no amiodarone treatment prior to OHT (Group 1). These findings suggest that discontinuing amiodarone may mitigate the risk of severe primary graft dysfunction.

There were no differences observed of in-hospital mortality or in one-year, two-year, three-year or four-year survival between groups in our study. The data evaluating the effect of amiodarone on mortality and the development of PGD after OHT remains mixed. One study found an increase in the incidence of PGD but no significant difference in 30-day or 1-year post-transplantation survival¹³ while another study found pre-OHT amiodarone treatment not to be associated with increased mortality after OHT.¹⁴ Conversely, a separate group found pre-OHT amiodarone treatment to have a higher incidence of 1-year mortality but no significant incidence of early graft failure.¹⁵ Finally, a recent meta-analysis of pre-amiodarone exposure found no increase in mortality in OHT recipients.¹⁶

There are several potential explanations for the similar mortality rates between groups despite the higher rate of PGD in Group 2. First, overall rates of in-hospital mortality were surprisingly low, which limits our power to assess for between group differences. Second, we aggressively manage severe PGD with early initiation of ECMO, a strategy which has shown to improve outcomes in these critically ill patients. Despite the lack of association with severe PGD and mortality in our experience, ECMO support can lead to potentially devastating complications such as stroke, bleeding, infection, and renal failure. We therefore feel that even if discontinuing amiodarone prior to transplant doesn't reduce mortality, it is

still worthwhile to avoid the need for ECMO after transplant given the potential for these devastating complications.

If amiodarone directly or indirectly harms patients undergoing heart transplantation, its mechanism of action remains unclear. Amiodarone primarily acts as a repolarization potassium channel blocker, a calcium channel blocker, as well as possessing α - and β -antagonistic properties. The drug also induces transient sinus bradycardia in heart transplant patients secondary to sinoatrial node dysfunction and autonomic denervation.^{17,18} Thus, current speculation on amiodarone's role in the development of PGD may include its negative chronotropic and inotropic characteristics.¹⁵

Amiodarone is also associated with multi-systemic toxicities, particularly on the thyroid and pulmonary systems. While the exact mechanism is poorly understood, amiodarone is thought to induce thyroid toxicity through its biochemical similarities to thyroid hormones, such as thyroxine and triiodothyronine, and the presence of iodine atoms in its central benzene ring.¹⁹ There is also speculation that amiodarone may induce a multi-factorial pulmonary toxicity. Mechanisms suggested for this process include a dysregulation of lysosomal enzymes, a maladaptive immune response of Th1 and Th2 cells, and pro-apoptotic effects on alveolar epithelial cells.²⁰ This pulmonary deterioration may result in right heart failure. Finally, amiodarone possesses an unusually long and variable half-life, which can range from 21 to 120 days^{5-9,21,22} It is extremely difficult, therefore, to gauge its compounded pharmacologic effects when used chronically.

Amiodarone may be a marker for a sicker patient population with an inherently higher risk for developing severe PGD. There were notable differences in baseline donor and recipient variables that may have influenced our findings. Patients in Group 2 had a longer duration of VAD placement, higher serum creatinine levels, a longer total waiting time for transplantation, and a longer hospital stay compared to the other treatment groups. Conversely, patients in Group 3 had a higher proportion of patients on VAD support (78.6%), and a slightly lower LVEF compared to Groups 1 and 2. Participants in Group 3 also had the highest percentage of UNOS Status 1A at time of listing (31.0%), although the differences of UNOS Status 1A at this time were not statistically different ($p=0.567$). We used regression modeling to account for these potentially confounding differences, and after adjusting for these variables, discontinuation of amiodarone prior to OHT was still associated with a lower risk of severe PGD.

Given an observed increased risk of severe PGD, the initiation and continued use of amiodarone should be cautiously considered for OHT candidates. At the same time, discontinuing amiodarone treatment in this population may be cautioned when considering the recurrence of atrial or ventricular tachyarrhythmias. In light of our findings, we now track amiodarone use in our listed patients. As patients move up the list and approach transplant, the indication and necessity of continued amiodarone use is re-evaluated, and dose reduction or discontinuation of therapy is considered when withdrawal of therapy may be clinically appropriate. This strategy appears feasible, as the incidence of readmission due to cardiac arrhythmia was minimal after withdrawal of amiodarone in our cohort. We therefore recommend that careful amiodarone dose reduction and withdrawal for listed

patients if clinically appropriate. If patients are unable to tolerate amiodarone discontinuation, other medications with shorter half-lives, such as beta-blockers, might be an alternative for these patients who are waiting for OHT.

Limitations

This study contains several limitations. First, the retrospective nature of this study is a limitation for our analysis. Second, the limited sample size of participants in Group 3 and the low number of primary endpoints (incidence of severe PGD) limited the number of variables included in the multivariate analysis. Moreover, based off of the criteria for PGD given by the ISHLT, severe PGD was the only grade of PGD that was able to be identified based off the data available. Additionally, the time of amiodarone discontinuation of participants in Group 3 varied (median = 73.5 days, IQR = 38–137 days). Given the variable and long half-life of amiodarone, it is possible that some patients who discontinued amiodarone treatment a few weeks before OHT may have continued to receive the active effects of the drug at the time of OHT, which could have influenced the development of severe PGD. However, this limitation would have biased in favor of the null hypothesis, suggesting that the magnitude of benefit from amiodarone discontinuation seen in our analysis may be a conservative estimate.

Conclusions

In conclusion, we found that patients who were treated with amiodarone and continued that treatment to transplantation had a greater odds of developing severe PGD compared to patients who received no amiodarone treatment. Additionally, we found discontinuing amiodarone treatment prior to transplantation returned the risk of severe PGD to the same level of patients who were not on amiodarone. These findings suggest that patients listed for OHT who are taking amiodarone should be continuously reassessed for ongoing need of antiarrhythmic therapy, and that providers should consider stopping amiodarone when it is clinically safe to do so.

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Figure 1.
Incidence of Severe PGD by amiodarone treatment groups.

Figure 2.
Four-year Kaplan-Meier survival curves after orthotopic heart transplantation (OHT).

Table 1.

Recipient pre-operative characteristics.

	Group 1	Group 2	Group 3	p-value
VARIABLE	n=197	n=142	n=42	
Age at OHT, years	52.7±12.6	55.3±10.8	56.9±10.3	0.079
Body mass index, kg/m ²	25.9±4.7	26.9±4.9	26.4±4.5	0.782
Male gender	138 (70.1)	110 (77.5)	35 (83.3)	0.111
Heart failure etiology	---	---	---	0.164
Dilated (non-ischemic)	77 (39.1)	65 (45.8)	24 (57.1)	---
Ischemic	67 (34.0)	46 (32.4)	13 (31.0)	---
Other	53 (26.9)	31 (21.8)	5 (11.9)	---
Presence of VAD	107 (54.3)	90 (63.4)	33 (78.6)	0.009
VAD Types	---	---	---	0.002
None	89 (45.2)	52 (36.6)	8 (19.1)	---
LVAD	97 (49.2)	86 (60.6)	28 (66.7)	---
RVAD	0 (0.0)	0 (0.0)	1 (2.4)	---
Total Artificial Heart	1 (0.51)	0 (0.0)	0 (0.0)	---
BiVAD	10 (5.1)	4 (2.8)	5 (11.9)	---
VAD duration, days	308 (188–447)	322 (212–723)	166 (122–289)	0.005
Creatinine, mg/dl	1.27±0.71	1.49±0.70	1.33±0.50	0.001
PVR, mmHg*min/liter	2.98±1.84	3.04±2.12	2.59±1.90	0.067
Cumulative amiodarone dose, mg	---	36600 (22800–5400)	9100 (4200–22200)	0.001
Amiodarone Washout Period - days before OHT (median, IQR)	---	---	73.5 (38–137)	---
UNOS status				
At time of listing	---	---	---	0.021
1A	41 (20.8)	19 (13.4)	13 (31.0)	---
1B	95 (48.2)	70 (49.3)	23 (54.8)	---
2	61 (31.0)	53 (37.3)	6 (14.3)	---
At time of OHT	---	---	---	0.567
1A	156 (79.2)	119 (83.8)	36 (85.7)	---
1B	38 (19.3)	23 (16.2)	6 (14.3)	---
2	3 (1.52)	0 (0.0)	0 (0.0)	---
Total waiting time for OHT, days	262 (76–583)	355 (141–622)	159 (108–293)	0.004

OHT, orthotopic heart transplant; VAD, ventricular-assist device; PVR, pulmonary vascular resistance; UNOS, united network for organ sharing

Table 2.

Donor and peri-operative characteristics.

	Group 1	Group 2	Group 3	p-value
VARIABLE	n=197	n=142	n=42	
Donor Characteristics				
Age at death, years	34.1±12.5	34.1±11.8	30.1±11.0	0.500
Male gender	96 (48.7)	79 (55.6)	32 (76.2)	0.005
Cause of death	---	---	---	0.011
Anoxia	61 (31.0)	42 (29.6)	9 (21.4)	---
Cerebrovascular / stroke	50 (25.4)	47 (33.1)	4 (9.5)	---
Head trauma	83 (42.1)	52 (36.6)	29 (69.1)	---
CNS tumor	2 (1.0)	1 (0.7)	0 (0.0)	---
Other	1 (0.5)	0 (0.0)	0 (0.0)	---
LVEF, %	61.5±6.2	62.1±7.7	59.5±6.1	0.014
Peri-operative Characteristics				
Ischemic time, hours	3.06±0.94	3.03±0.94	3.29±0.93	0.998
CPB time, minutes	166±48	176±64	163±42	<0.001
Cross-clamp time, minutes	91±27	88±26	92±28	0.592
Packed Red Blood Cells administered (mL)	350 (0–1000)	500 (0–1000)	600 (0–1400)	0.239
Gender mismatch (F-to-M)	18 (9.14)	13 (9.15)	5 (11.9)	0.847
Donor-to-recipient weight ratio < 0.8	7 (3.6)	6 (4.2)	1 (2.4)	0.925
Donor-to-recipient PHM ratio 0.86	32 (16.24)	28 (19.72)	2 (4.76)	0.055

CNS, central nervous system; LVEF, left ventricular ejection fraction; CPB, cardiopulmonary bypass; PHM, predicted heart mass

Table 3.

Univariable and multivariable analysis. The primary endpoint was the development of severe PGD.

VARIABLE	UNIVARIATE		MULTIVARIATE	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Recipient Characteristics				
Age at OHT, years	1.03 (1.00–1.05)	0.071	---	---
Body mass index, kg/m ²	1.06 (0.99–1.12)	0.081	---	---
Male gender	1.38 (0.68–2.80)	0.374	---	---
VAD, yes/no	2.84 (1.41–5.72)	0.003	1.43 (0.63–3.22)	0.393
VAD duration, days	1.00 (1.00–1.00)	0.007	---	---
Creatinine, mg/dl	1.17 (0.81–1.69)	0.395	---	---
PVR	1.07 (0.93–1.24)	0.333	---	---
UNOS status			---	---
At time of listing	0.99 (0.95–1.04)	0.745	---	---
At time of OHT	0.94 (0.86–1.02)	0.143	---	---
Total waiting time, days	1.00 (1.00–1.00)	0.162	---	---
Cumulative Amiodarone Dose	1.00 (1.00–1.00)	<0.001	1.00 (1.00–1.00)	0.284
Amiodarone Groups [†]				
Group 2	4.81 (2.44–9.47)	<0.001	3.70 (1.26–10.88)	0.018
Group 3	1.49 (0.46–4.82)	0.506	0.416 (0.08–2.15)	0.296
Donor Characteristics				
Age at death, years	1.00 (0.98–1.02)	0.945	---	---
Male gender	1.33 (0.74–2.41)	0.342	---	---
Cause of death	0.81 (0.58–1.14)	0.222	---	---
LVEF %	0.97 (0.93–1.02)	0.212	---	---
Peri-operative				
Ischemic time, hours	1.08 (0.79–1.47)	0.628	---	---
CPB time, minutes	1.02 (1.01–1.02)	<0.001	---	---
Cross-clamp time, minutes	1.00 (0.99–1.01)	0.598	---	---
Packed Red Blood Cells administered (1000 mL)	2.90 (2.08–4.04)	<0.001	3.16 (2.18–4.57)	<0.001
Gender mismatch (F-to-M)	1.00 (0.37–2.69)	0.997	---	---
Donor-to-recipient weight ratio < 0.8	0.47 (0.06–3.64)	0.466	---	---
Donor-to-recipient PHM ratio 0.86	1.06 (0.49–2.30)	0.880	---	---

[†]Group 1 served as the reference group.

OHT, orthotopic heart transplant; VAD, ventricular-assist device; PVR, pulmonary vascular resistance; UNOS, united network for organ sharing; LVEF, left ventricular ejection fraction; CPB, cardiopulmonary bypass; PHM, predicted heart mass