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# Dose-dependent association between amiodarone and severe primary graft dysfunction in orthotopic heart transplantation

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**KEYWORDS:**
primary graft dysfunction;
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**BACKGROUND:** There is growing concern regarding the association between pre-transplant amiodarone exposure and post-transplant adverse outcomes. We hypothesized that amiodarone use would be associated with the development of severe primary graft dysfunction (PGD) in a dose-dependent manner.

**METHODS:** This was a retrospective review of 269 adult orthotopic heart transplantation (OHT) recipients at our institution between 2010 and 2014. At the time of OHT, 100 were receiving amiodarone therapy (Group 1) and 169 were not (Group 2).

**RESULTS:** Pre-OHT creatinine was higher in Group 1 (1.49 ± 0.63 vs 1.27 ± 0.68 mg/dl, $p = 0.011$). At time of listing, Group 1 had higher frequency of status 2 (42.0% vs 29.0%), and Group 2 had higher frequency of status 1A (20.7% vs 8.0%; $p = 0.009$). Severe PGD (mechanical circulatory support within 24 hours post-OHT) was significantly higher in Group 1 (20.0% vs 5.3%, $p < 0.001$). Pre-OHT amiodarone use was an independent risk factor for severe PGD (odds ratio [OR], 6.05; 95% confidence interval [CI], 2.47–14.83; $p < 0.001$) and in-hospital mortality (OR, 2.88; 95% CI, 1.05–7.88; $p = 0.039$) in multivariable analysis. Each 100-mg increase in the day-of-OHT amiodarone dose (OR, 1.55; 95% CI, 1.26–1.90) and each 18,300-mg increase in the 6-month cumulative dose (OR, 1.67; 95% CI, 1.31–2.15) was associated with increased odds of developing severe PGD ($p < 0.001$ for both).

**CONCLUSIONS:** Amiodarone use pre-OHT is independently associated with increased incidence of severe PGD and in-hospital mortality and linearly associated with increased incidence of severe PGD in a dose-dependent manner.

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Primary graft dysfunction (PGD) is a significant predictor of adverse outcomes among orthotopic heart transplantation (OHT) recipients. Although variability in the definition has made it difficult to determine the exact incidence of PGD,

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single-center studies report its incidence ranging from 2.3% to 32.4%.[1–10] A pre-conference survey from the 2013 International Society for Heart and Lung Transplantation (ISHLT) consensus conference on PGD revealed an estimated incidence of 7.4% given the definition agreed on by most of the participating institutions (left ventricular ejection fraction [LVEF] $\leq$ 40%, requirement of mechanical circulatory support [MCS], and a timeframe of $<$ 24 hours). Of the 7.4% with PGD, mortality was 30% at 30 days and 34.6% at 1 year.[9]

Numerous risk factors have been suggested for PGD in studies spanning the last 2 decades. The 2 factors most frequently implicated include donor age[1,7,11–14] and ischemic time.[7,11,12,14–16] Other factors commonly associated with PGD include donor cardiac dysfunction on echocardiography,[11,14–16] donor high-dose inotropic support,[4,14,15,17] recipient pulmonary hypertension,[14,18–21] and female donor–to–male recipient mismatch.[1,11,14,22]

Recently, there has been conflicting evidence in the literature suggesting that amiodarone, a class III antiarrhythmic, may be associated with adverse outcomes among OHT recipients. Some studies have suggested that pre-OHT amiodarone use is not associated with decreased survival[23] or poorer graft function in the early post-OHT period.[24,25] Others have shown amiodarone to be significantly associated with PGD,[26] in-hospital mortality,[27,28] and decreased long-term survival.[24,29] We hypothesized that amiodarone use would be associated with the development of severe PGD (defined as the need for MCS $\leq$ 24 hours post-OHT) in a dose-dependent manner.

## Methods

The Columbia University Medical Center Institutional Review Board approved this study. The requirement of individual consent was waived.

### Patient cohort

For this retrospective cohort analysis, 276 adults who underwent OHT at Columbia University Medical Center between 2010 and 2014 were identified. Seven patients were excluded because of limited medical record availability. Of the remaining 269 patients, 100 were receiving amiodarone therapy at the time of OHT (Group 1), and 169 were not receiving amiodarone (Group 2). For Group 1, day-of-OHT and 6-month cumulative amiodarone doses were recorded. The initial dose at study entry and subsequent dose adjustments during the collection period were tallied. The exact date of a dose change was not documented in 13 patients, so we assumed it was changed on the median between the dates of the 2 notes containing discrepant doses. Finally, the 25 patients who received amiodarone therapy in the 6 months before OHT but who stopped before OHT were given a 6-month cumulative dose of 0 mg (i.e., they were included in Group 2). Two sensitivity analyses were conducted to address the unique situation of these 25 patients—one using the patients' actual 6-month cumulative doses (instead of 0 mg) and one with these patients removed from the analysis.

Data were gathered from electronic medical records and the United Network for Organ Sharing (UNOS) database as of June 17, 2016. Recipient data included age, body mass index, gender, heart failure etiology, presence of ventricular assist device (VAD), VAD duration, creatinine, pulmonary vascular resistance, UNOS status at the time of listing and time of OHT, and total waiting time. Donor data included age, gender, cause of death, LVEF, and presence of inotropes. Peri-operative data included ischemic time, cardiopulmonary bypass time, cross-clamp time, female-to-male gender mismatch, and donor-to-recipient weight ratio of $<$ 0.8. Data were missing for 24 patients (8.9%) from pulmonary vascular resistance, 2 (0.7%) from donor inotropes, 4 (1.5%) from ischemic time, 1 (0.3%) from cross-clamp time, and 3 (1.1%) from VAD duration.

The study primary end point was severe PGD, defined as the need for MCS $\leq$ 24 hours after OHT.[9] Secondary end points included hospital length of stay, in-hospital mortality, and 4-year survival.

### Statistical analysis

Continuous variables are presented as mean $\pm$ standard deviation, and comparisons between the groups were made using *t*-tests. The median and interquartile range is presented for non-normally distributed continuous variables, and comparisons were made using the Mann-Whitney test. Categoric variables are presented as frequency and percent, and comparisons were made using the chi-square test and Fisher's exact test, where appropriate. Binary logistic regression was used for multivariable analysis to generate odds ratios (ORs) and 95% confidence intervals (95% CIs). Linearity of continuous predictors (i.e., day-of OHT dose and 6-month cumulative dose) was first examined by dividing the sample into a priori defined sub-groups by the value of their covariate of interest, with the cut points chosen to break the sample into roughly equal parts.

Rates of PGD in each group were visually inspected to see whether they corresponded with a dose–response type relationship. For this visual inspection, the day-of-OHT dose was categorized as 0 mg, 1 to 399 mg, and $\geq$ 400 mg and the 6-month cumulative dose as 0 mg, 1 to 30,000 mg, 30,001 to 60,000 mg, and $>$ 60,000 mg. Once linearity was confirmed, the original continuous predictors were used in the logistic models. Covariates adjusted for in the multivariable model were chosen for their clinical significance and because each fell below a significance threshold of 0.2 for predicting the respective outcome. Long-term survival was plotted by Kaplan-Meier curves, which were generated in Stata 12.1 software (StataCorp LP), and the curves were compared using the log-rank test. All tests were 2-sided with an $\alpha = 0.05$. All analyses were performed on SPSS 24 software (IBM Corp.).

## Results

### Recipient pre-operative characteristics

Table 1 summarizes the recipient pre-operative characteristics. Pre-OHT creatinine was 1.49 $\pm$ 0.63 mg/dl for Group 1 and 1.27 $\pm$ 0.68 mg/dl for Group 2 ($p = 0.011$). UNOS status at the time of listing was significantly different between the 2 groups ($p = 0.009$), with more Status 2 in Group 1 and more Status 1A in Group 2. The frequency of bridging with VAD was similar in both groups ($p = 0.717$).

### Donor and peri-operative characteristics

Donor characteristics and peri-operative variables are reported in Table 2. Donor characteristics did not differ