The Effect of Obstructive Sleep Apnea on 3-Year Outcomes in Patients Who Underwent Orthotopic Heart Transplantation

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Despite the well-known association between obstructive sleep apnea (OSA) and cardiovascular disease, there is a paucity of data regarding OSA in orthotopic heart transplant (OHT) recipients and its effect on clinical outcomes. Hence, we sought to determine the association between OSA, as detected by polysomnography, and late graft dysfunction (LGD) after OHT. In this retrospective review of consecutive OHT recipients from 2012 to 2014 at our center, we examined LGD, i.e., graft failure >1 year after OHT, through competing risks analysis. Due to small sample size and event counts, as well as preliminary testing which revealed statistically similar demographics and outcomes, we pooled patients who had treated OSA with those who had no OSA. Of 146 patients, 29 (20%) had untreated OSA, i.e., OSA without use of continuous positive airway pressure therapy, at the time of transplantation. Patients with untreated OSA were significantly older, heavier, and more likely to have baseline hypertension than those with treated/no OSA. Although there were no differences between groups in regard to short-term complications of acute kidney injury, cardiac allograft vasculopathy, or primary graft dysfunction, there were significant differences in the occurrence of LGD. Those with untreated OSA were at 3 times the risk of developing LGD than those with treated/no OSA (hazard ratio 3.2; 95% confidence interval 1.3 to 7.9; p = 0.01). Because OSA is a common co-morbidity of OHT patients and because patients with untreated OSA have an elevated risk of LGD, screening for and treating OSA should occur during the OHT selection period. **(Am J Cardiol 2019;124:51−54)**

Apart from the well-understood risks of rejection and infection, patients with orthotopic heart transplant (OHT) may develop graft dysfunction in the years after OHT, referred to as late graft dysfunction (LGD).[1] However, mechanisms of LGD are not well understood and risk factors for LGD have not been well delineated.[2] Obstructive sleep apnea (OSA) is caused by upper airway collapse during inspiration and is accompanied by lack of airflow and strenuous breathing effort.[3,4] OSA has a well-known association with a variety of cardiovascular disease conditions,[3,5−8] including heart failure.[9,10] OSA prevalence has been reported to be as high as 19% in patients with cardiac disease, yet has largely been overlooked as a co-morbidity for OHT candidates.[6] Although it is possible that all transplant candidates are screened for OSA (and treated, if indicated), there are no uniform guidelines, and reported screening rates for OSA are inconsistent.[4,11,12] Most importantly, the effect of OSA on clinical outcomes for these patients has not been reported. Hence, the purpose of our study is to elucidate the extent to which OSA plays a role in LGD.

Methods

This was a retrospective analysis of medical records and was approved by the Institutional Review Board of Baylor University Medical Center, Dallas, Texas with a waiver of informed consent. We reviewed charts of consecutive adult OHT recipients at the Annette C. and Harold C. Simmons Transplant Institute from November 2012 to August 2014, a timeframe representative of our center's current transplantation volume, and providing sufficiently long follow-up. Exclusion criteria consisted of heart organ re-transplantation, simultaneous multiorgan transplantation, and pure central sleep apnea (given the lack of evidence for treatment efficacy in central sleep apnea using continuous positive airway pressure [CPAP]).

Data extracted from records included patient demographics, polysomnography before transplantation, CPAP utilization, cardiac allograft vasculopathy (CAV) burden, LGD, and survival. Additionally, we extracted co-morbidities including renal disease, diabetes mellitus, hypertension, and cytomegalovirus (CMV). Documented co-morbidities were defined as having a current diagnosis or receiving treatment for that disease. Patients with viral load counts >1,000, with or without clinical symptoms, were treated for CMV. CAV was graded using intravascular ultrasound on a 5-point scale: 0 (0 mm), 1 (up to 0.3 mm), 2 (0.3 to 0.5 and <180° of

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vessel circumference), 3 (0.3 to 0.5 and ≥180° of vessel circumference), 4 (>0.5 mm).[13] Cellular rejection was defined according to the International Society for Heart and Lung Transplantation guidelines after cardiac biopsy. At our center, all patients who underwent OHT are routinely screened for sleep apnea, whereas polysomnography is conducted only on those who screen positive for sleep apnea based on STOP-BANG criteria.[14] Due to small sample size and event counts of treated OSA (n = 26, LGD events = 3), as well as preliminary testing which revealed statistically similar demographics and outcomes, we pooled patients who had treated OSA with those who had no OSA. Compliance with CPAP was based on patient self-reporting and examinations of symptoms. Evaluations for sleep apnea and compliance were conducted throughout the follow-up period. Graft failure was defined either as having clinical symptoms consistent with graft dysfunction with cardiac index <2.0 L/min/m^2 by right heart catheterization (Fick or thermo-dilution methods), or as having left ventricular ejection fraction <50% by echocardiogram. LGD was defined as graft failure not attributable to biopsy-proven rejection and occurring >1 year after heart transplantation. Although there is not a universal definition for LGD, we are not the first to use this 1-year cutoff.[15,16] After 1 year, the risk of graft dysfunction secondary to rejection decreases dramatically. Charts were reviewed for up to 3 years of follow-up.

Patient characteristics were compared based on OSA status (untreated OSA, i.e., OSA without use of CPAP therapy, vs treated/no OSA). Patients who refused treatment or failed to comply with therapy were analyzed with the untreated group. Differences in patient characteristics and clinical outcomes between the groups were assessed through Wilcoxon rank sum, chi-square, or Fisher's exact tests, as appropriate. We additionally considered 3-year LGD as a time-to-event variable by performing a competing risks analysis using the Fine and Gray method to account for the competing risk of death.[17,18] Continuous variables are presented as mean ± standard deviation or median [quartile 1, quartile 3], if skewed. Categorical variables are presented as frequency (percentage). Hypothesis testing was performed using a 2-sided alternative and a type I error rate of 5%. All analyses were conducted in SAS 9.4 (SAS Institute, Cary, North Carolina).

Table 1
Baseline characteristics of heart transplantation recipients (n = 146)

Variable	Obstructive sleep apnea		p value
	Untreated (n = 29)	Treated or none (n = 117*)	
Men	20 (69%)	90 (82%)	0.37
Age (years)	63 [59, 67]	59 [53, 65]	0.005
Race/ethnicity:			0.14
Asian	0	2 (2%)	
Black	10 (35%)	21 (18%)	
Hispanic/Latino	0	9 (8%)	
White	19 (66%)	85 (73%)	
Body mass index (kg/m^2)	31 [27, 34]	28 [25, 30]	0.003
Listing status:			0.70
1A	10 (35%)	44 (38%)	
1B	17 (59%)	60 (51%)	
2	2 (7%)	13 (11%)	
Diabetes mellitus	10 (35%)	41 (35%)	0.95
Hypertension	24 (83%)	67 (57%)	0.01
Hemodialysis	0 (0%)	1 (1%)	1.00
Serum creatinine (mg/dl)	1.4 [1.2, 1.6]	1.2 [1.0, 1.5]	0.07
Total ischemia time (min)	209 ± 63	228 ± 66	0.17
Donor age (years)	35 ± 12	33 ± 12	0.64
Male donor†	10 (34%)	55 (47%)	0.11

* Twenty-six with treated obstructive sleep apnea, 91 without obstructive sleep apnea.
† Missing 1 for untreated OSA group.

There were 146 transplant recipients who met criteria for this analysis, 29 (20%) of whom had untreated OSA at the time of OHT. Patients with untreated OSA were significantly older, heavier, and more likely to have baseline hypertension than those with treated/no OSA (Table 1). However, there were no differences in the complications of acute kidney injury, CAV, or 1-year mortality (p = 0.77, 0.19, 0.74, respectively; Table 2). The rate of treated CMV infection did not differ based on OSA groups (p = 0.56), nor did the rate of antibody-mediated rejection (p = 1.0).

Table 2
Outcomes after heart transplantation

Variable	Obstructive sleep apnea		p value
	Untreated (n = 29)	Treated or none (n = 117*)	
Peak creatinine (mg/dl)	1.7 [1.2, 2.3]	1.5 [1.3, 2.0]	0.51
Acute kidney injury	14 (48%)	53 (45%)	0.77
B-type natriuretic peptide†	470 [379, 963]	723 [440, 1,289]	0.17
Treated CMV	9 (31%)	30 (26%)	0.56
Cellular rejection:‡			0.10
0R	13 (48%)	63 (58%)	
1R	10 (37%)	41 (38%)	
2R	2 (7%)	3 (3%)	
3R	2 (7%)	1 (1%)	
Antibody-mediated rejection	1 (4%)	5 (4%)	1.0
Cardiac allograft vasculopathy (by IVUS):			0.19
Grade 0	11 (42%)	41 (39%)	
Grade 1	2 (8%)	27 (26%)	
Grade 2	6 (23%)	15 (14%)	
Grade 3	1 (4%)	7 (7%)	
Grade 4	6 (23%)	14 (14%)	
1-year mortality	2 (7%)	14 (12%)	0.74
3-year outcomes:§			0.01
Late graft dysfunction (>365 days)	8 (28%)	12 (10%)	
Death	3 (10%)	19 (16%)	
Neither	17 (59%)	87 (74%)	

IVUS = intravascular ultrasound; grades: 0 (0 mm), 1 (up to 0.3 mm), 2 (0.3 to 0.5 and <180° of vessel circumference), 3 (0.3 to 0.5 and ≥180° of vessel circumference), 4 (>0.5 mm).
* Twenty-six with treated obstructive sleep apnea, 91 without obstructive sleep apnea.
† Missing 4.
‡ Missing 11.
§ If a patient died after having late graft dysfunction (LGD), he/she is counted only as having LGD. The p value is from the competing risks model.

Results

There were significant differences in the occurrence of 3-year LGD between the OSA groups (Figure 1). After accounting for death, those with untreated OSA were at approximately 3 times the risk of developing LGD compared with those with treated OSA/no OSA (hazard ratio 3.2, 95% confidence interval 1.3 to 7.9; p = 0.01). Further, patients with untreated OSA who developed LGD did so more than a year earlier than those who had treated OSA/no OSA (672 [452, 733] days vs 1,078 [732, 1,088] days post-transplant, respectively; p = 0.061). Conversely, there were no significant differences in time-to-death, for those who died (untreated OSA: 75 [57, 564] days; treated OSA/no OSA: 77 [17, 438] days, p = 0.70]).

Discussion

In this single center study of 146 OHT recipients, more than one-third of subjects had OSA. This rate is similar to other reports in patients with cardiac disease and is considerably higher than the general population.[4,11,12] Consistent with previous reports of OHT patients, untreated OSA was positively associated with age, body mass index, and hypertension.[11,12] We found a nonsignificantly lower rate of mortality and a significantly higher rate of LGD for patients with untreated OSA compared with patients with treated/no OSA.

Graft failure at any time is a deleterious clinical outcome after OHT, yet standardized schemes for diagnosis and treatment of graft failure remain contentious, with transplant centers often utilizing center-specific diagnostic criteria.[19] Although the International Society for Heart Lung Transplantation released a 2014 consensus statement regarding the definition of primary graft dysfunction after OHT, there have been no attempts to establish a unified definition for LGD.[20] A recent article from Lopez-Sainz et al defined LGD as the first hospitalization with graft dysfunction after postoperative discharge.[1]

Although idiopathic graft failure is relatively rare, diastolic dysfunction after OHT is quite common.[21] It is hypothesized to be related to preservation injury as well as elevated right- and left atrial pressures, resulting in decreased compliance of the transplanted heart.[21] In most patients, this phenomenon resolves shortly after transplant. A known link exists between OSA in both systolic and diastolic heart failure.[9] This has been postulated due to mechanisms that include mechanical, neurohumoral, inflammatory, endothelial, and oxidative effects.[9] Moreover, repetitive obstructive events are common in patients with OSA, further contributing to diastolic dysfunction. Diastolic dysfunction still present in patients at 1-year post-transplant is associated with poor outcomes.[21] It can be hypothesized that untreated OSA provides the substrate for the allograft to develop worsening diastolic dysfunction with subsequent systolic dysfunction and hemodynamic compromise leading to LGD. This is evidenced in native heart studies in which newly diagnosed OSA has been independently linked to significantly impair diastolic function and regional longitudinal strain.[22] CPAP therapy in such patients with moderate-to-severe OSA has reversed these structural and functional changes with an improvement in left ventricular ejection fraction, decrease in posterior wall thickness, and improvement in diastolic LV impairment parameters. Although a transplanted heart is a different substrate, a similar effect may provide a plausible explanation as to why we observed mitigated risk profiles in patients who were compliant with CPAP therapy when compared with untreated OSA.[23]

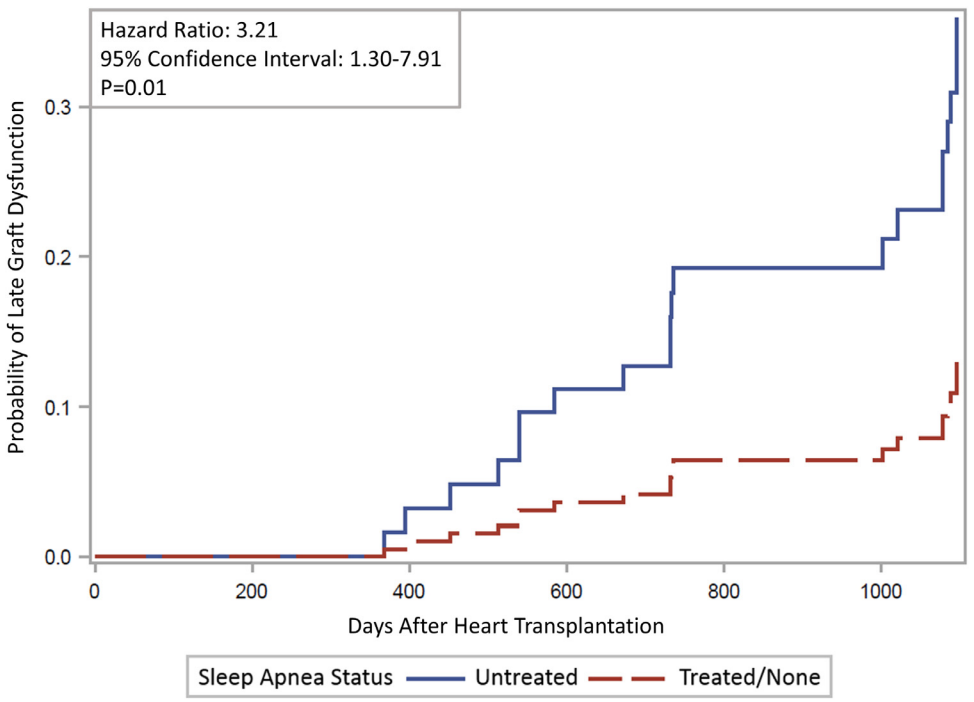

Figure 1. Cumulative incidence functions by sleep apnea group (untreated obstructive sleep apnea vs treated obstructive sleep apnea/no obstructive sleep apnea).

Further, there were no differences between the groups in terms of acute cellular rejection, antibody-mediated rejection, or CAV. CMV infection has been associated with more risk for solid organ graft rejection and even with valganciclovir prophylactic treatment graft loss remains a considerable concern.[24] In our study, there was no difference in rates of treated CMV infections, nor was CMV associated with LGD (in a separate competing risks analysis for the outcome of LGD, using CMV as a covariate yielded a p value = 0.27).

This study has limitations inherent to those of any small, retrospective, single center study. As such, the generalizability of our results may be compromised. Only patients who screened positive for sleep apnea based on the screening questionnaire underwent polysomnography. Hence, it is possible that patients could have underreported symptoms on the screening questionnaire and remained undiagnosed with sleep apnea and/or OSA. Another potential limitation is that compliance with CPAP was based solely on patients' verbal self-report; however, this is reflective of generally acceptable clinical practice. Polysomnography was not performed serially, so we did not have the ability to utilize it as a time-varying covariate. Further, patients' OSA was not graded based on the apnea-hypopnea index. We do not know the mechanism of LGD and there were too few instances of LGD to perform adjusted analyses.

In conclusion, untreated OSA was highly prevalent in this study of OHT recipients. Our results indicate that untreated OSA may be a contributing factor to LGD, particularly in the absence of proved rejection. To our knowledge, this study is the first to reveal an increased risk of LGD in patients with untreated OSA.

Disclosures

The authors have no conflicts of interest to disclose.

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