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# Influence of Sleep-Disordered Breathing on Quality of Life and Exercise Capacity in Lung Transplant Recipients

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**Abstract**

The prevalence of sleep-disordered breathing (SDB) after lung transplantation (LTX) is high. It is well-established that SDB is associated with decreased health-related quality of life (HRQoL), but the impact of SDB on exercise capacity is less clear. In this study we investigated HRQoL and exercise capacity in LTX recipients with or without SDB. In addition, we also investigated associations between sleep parameters and both HRQoL and exercise capacity. There were 53 stable LTX recipients (age > 18 years, 31 males, time from LTX 9–120 months) enrolled into the study. They all underwent polysomnography examination. HRQoL was assessed using the Short Form-36 (SF-36). Exercise capacity was measured using the 6-min walk test and cardiopulmonary exercise testing (CPET). We found inverse correlations between severity of SDB and both the predicted maximal workload ($r = 0.24$, $p = 0.04$) and maximal oxygen uptake ($r = -0.26$, $p = 0.03$) during CPET. Relative oxygen uptake positively correlated with sleep efficiency ($r = 0.27$, $p = 0.03$). SF-36 scores did not differ between patients with and without SDB, and were not significantly associated with SDB parameters. In conclusion, the presence of SDB is associated with a slight reduction in maximal exercise capacity in LTX recipients, and there is no appreciable relationship between SDB and HRQoL.

**Keywords**

Cardiopulmonary exercise testing · Disordered breathing · Exercise capacity · Lung transplantation · Quality of life · Sleep

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## 1 Introduction

Lung transplantation (LTX) is an established treatment option for end-stage non-malignant pulmonary diseases. Given that patient's age at transplantation is increasing (median 55 years) and that LTX recipients are living longer, comorbidities are becoming an increasingly important aspect of long-term management in LTX recipients (Yusen et al. 2015). One such comorbidity is a sleep-disordered breathing (SDB) that has recently been reported to occur in a higher proportion of LTX recipients (63–53%) (Sommerwerck et al. 2016; Hernandez Voth et al. 2015; Naraine et al. 2009) than that in the general population (18%) (Young et al. 2002). SDB is characterized by respiratory irregularities during sleep and is independently associated with the development of hypertension, diabetes, cardiovascular morbidity and mortality (Marin et al. 2005; Shahar et al. 2001). New-onset hypertension and diabetes are common in LTX recipients as are weight gain and metabolic dysregulation, all of which are well-known contributors to the development of SDB (Yusen et al. 2015; Singer et al. 2003). It is therefore possible that SDB is a factor in the development of some post-LTX comorbidities, and the presence of SDB may predispose LTX recipients to adverse health outcomes. However, little is known about the potential association between SDB and post-LTX comorbidities.

Severe SDB is associated with poor health-related quality of life (HRQoL) that is an important determinant of subjective functional outcomes in the LTX population (Baldwin et al. 2001). Therefore, SDB may contribute to impaired HRQoL after LTX, along with the other known predictors such as bronchiolitis obliterans syndrome (BOS), transplant type, transplant indication, and age at transplantation (Seiler et al. 2016; Kugler et al. 2010; Singer et al. 2015). Functional outcomes after LTX are objectively assessed using the 6-min walk test (6MWT) and cardiopulmonary exercise testing (CPET) (Armstrong et al. 2016; Dudley and El–Chemaly 2012). Low exercise capacity suggests a greater morbidity. The influence of SDB on the exercise capacity is not well understood and the existing data are conflicting (Vanhecke et al. 2008; Rizzi et al. 2010), although there is an indication that SDB is associated with decreased exercise capacity in the general population (Ben Saad et al. 2015; Mansukhani et al. 2013). In the setting of heart failure there are several studies showing that SDB has a clinically-relevant impact on exercise capacity (Krawczyk et al. 2013), and that treatment of SDB improves cardiovascular morbidity, prognosis, quality of life, and exercise capacity (Aggarwal et al. 2014; Arzt et al. 2005).

Given that both heart failure patients and LTX recipients are chronically ill, it is possible that the effects of SDB on outcomes in LTX may be more similar to those in heart failure patients than to the effects of SDB in otherwise healthy individuals. Therefore, the hypothesis of this study was that HRQoL and exercise capacity would be diminished in LTX recipients with SDB compared to those without it.

## 2 Methods

### 2.1 Patients and Protocol

Fifty three stable LTX recipients (age > 18 years, 31 males, time from LTX 9–120 months) were included into the study. The patients had no significant decline in forced expiratory volume in 1 s ($FEV_1$) over the last 3 months and were part of the Essen LTX follow-up program between October 2011 and September 2013. Exclusion criteria were: age < 18 years, pregnancy, symptomatic bacterial or viral infection, acute rejection, supplemental oxygen and non-invasive ventilation (NIV) due to exacerbation. Patients with any contraindication for exercise testing or cognitive impairments that limited their ability to answer the questionnaires were also excluded.

Irrespective of the presence of SDB symptoms, all subjects underwent full in-laboratory polysomnography (PSG) using a standardized 2-day protocol. A structured physical examination and an interview were performed

covering medical history and the presence of bronchiolitis obliterans syndrome. The syndrome was defined according to existing guidelines as a persistent decrease in $FEV_1$ of $\geq$20% from baseline (Estenne et al. 2002). The day before PSG, all patients completed the Short Form-36 health survey (SF-36) to assess HRQoL and they underwent submaximal (6MWT) and maximal (CPET) exercise testing.

## 2.2 Polysomnography

A full, attended PSG was performed and evaluated by trained sleep technicians according to the 2007 American Academy of Sleep Medicine standards (Iber et al. 2007). A wireless PSG system (SOMNOscreen™ plus; Somnomedics; Randesacker, Germany) was used for recording, including a thermistor to monitor oronasal airflow, pulse oximetry to measure arterial oxygen saturation ($SaO_2$), and thoracic and abdominal strain gauges to assess respiratory effort. Obstructive apneas were defined as the absence of oronasal airflow for >10 s in the presence of respiratory effort. Central apneas were identified when airflow and respiratory effort both were missing. Episodes of >10 s with a <50% reduction in airflow and a $\geq$4% decrease in $SaO_2$ were classified as hypopneas. The apnea-hypopnea index (AHI) was defined as the number of apneas and hypopneas per hour of sleep. An AHI of $\geq$10/h was considered as clinically-relevant SDB, in line with previous studies on sleep apnea prevalence in LTX patients (Sommerwerck et al. 2016; Hernandez Voth et al. 2015; Naraine et al. 2009). SDB was classified as obstructive or central, depending of the dominance of either obstructive or central events. Sleep efficiency was defined as the percentage of total sleep time divided by time in bed.

## 2.3 Health-Related Quality of Life

The German-validated version 1.0 of the SF-36 determines eight categories to assess HRQoL: physical functioning, social functioning, role functioning limited by physical problems, role functioning limited by emotional problems, mental health, vitality, pain, and general medical health. The categories can be summarized into a physical summary score and a mental summary score. Each item score is coded and transformed into a generic scale from 0 to 100 (worst to best health). German population norms for the SF-36 were used for comparative purposes (Bullinger and Kirchberger 1998).

## 2.4 Exercise Testing

Submaximal exercise capacity (6MWT) and maximal exercise capacity (CPET) were determined according to the American Thoracic Society guidelines (Brooks et al. 2003; ATS 2002). Oxygen saturation, heart rate and blood pressure were determined at beginning and end of the 6MWT. A symptom-limited incremental CPET was completed using a cycle ergometer (ZAN 600; Winkling, Austria). Oxygen saturation, heart rate, and gas exchange were measured continuously and blood pressure was measured every 3 min; blood gases were derived from the hyperemized earlobe at beginning and end of exercise as well as at maximal workload ($P_{max}$) (ABL5 Radiometer; Willich, Germany). Relative or predicted parameters were analyzed, if available, due to the fact that CPET performance is dependent on age, weight and gender. Lung function testing was performed before CPET.

## 2.5 Statistical Analysis

Differences between means were tested using the Student's t-test for normally distributed data, or the Mann–Whitney-U test or Chi-square test in case of non-normal distribution. The Kolmogorov–Smirnov test was used to test for normal distribution. Levene's test was used to assess the equality of variance in different samples. The Kruskal-Wallis test was used for non-normal distribution. Depending on normal or non-normal distribution, Spearman or Pearson's correlation analysis was performed to

identify trends in CPET, HRQoL, and SDB parameters. Multiple regressions were used to adjust for age, body mass index (BMI) and gender with forced entry selection. A p-value <0.05 was considered to be statistically significant. Statistical analysis was performed with SPSS 22.0 (SPSS Inc., Chicago, IL).

## 3 Results

The overall prevalence of SDB was 53% (28/53). Patient demographic and clinical characteristics at baseline in patients with and without SDB are shown in Table 1. Patients with SDB had a significantly higher BMI ($p < 0.05$), and were significantly more likely to have undergone LTX for chronic obstructive pulmonary disease (COPD) ($p < 0.001$).

The majority of patients were PSG-naïve and were not being treated with NIV. However, 15 patients had been prescribed NIV-treatment before enrolment in the study; indications were previously-diagnosed SDB (n = 13) and phrenic paresis (n = 2). Four patients had previously-diagnosed SDB but were not receiving NIV-treatment. Subgroup analysis showed no significant differences between NIV-naïve and NIV-treated subjects with respect to patient characteristics and outcome variables.

### 3.1 Health-Related Quality of Life

In general, the SF-36 scores of the German norm population were similar to both SDB and non-SDB patients of our LTX population (Fig. 1). A significant difference of HRQoL could be observed in only one of eight categories (general health).

### 3.2 Exercise Testing and Sleep Parameters

Overall, there was a significant inverse correlation between AHI and sleep efficiency ($r = -0.23$, $p = 0.02$). AHI, as an indicator of SDB, was significantly and inversely correlated with the percentage of predicted maximal workload ($\%P_{max}PRED$) and relative maximal workload ($relativeP_{max}$). Age, BMI, and gender were also significantly associated with AHI (Table 2). Based on the significant associations documented

**Table 1** Patient demographic and clinical characteristics at baseline in lung transplant recipients with and without sleep-disordered breathing

| | Lung transplant recipients | | |
|---|---|---|---|
| | without SDB (n = 25) | with SDB (n = 28) | p |
| Age, years | 52 ± 12 | 57 ± 7 | NS |
| Males, n (%) | 11 (44) | 20 (71) | <0.05 |
| AHI, per hour | 4.6 ± 2.7 | 32.4 ± 23.1 | <0.0001 |
| Body mass index, kg/m$^2$ | 24.1 ± 4.76 | 26.9 ± 3.6 | <0.05 |
| OSA | | 24 (86) | |
| CSA | | 4 (14) | |
| COPD, n (%) | 7 (28) | 17 (61) | <0.05 |
| IPF, n (%) | 6 (24) | 8 (29) | <0.05 |
| Time since LTX, months | 53 ± 28 | 51 ± 31 | NS |
| BOS status, n (%) | | | |
| 0 | 16 (64) | 16 (57) | NS |
| ≥1 | 9 (36) | 12 (43) | NS |
| $FEV_1$, % best | 73 ± 25 | 76 ± 21 | NS |

Values are means ±SD or number (%) of patients

*SDB* sleep-disordered breathing, *AHI* apnea-hypopnea index, *OSA* obstructive sleep apnea, *CSA* central sleep apnea, *IPF* idiopathic pulmonary fibrosis, *LTX* lung transplantation, *COPD* chronic obstructive lung disease, *BOS* bronchiolitis obliterans syndrome, *NS* not significant

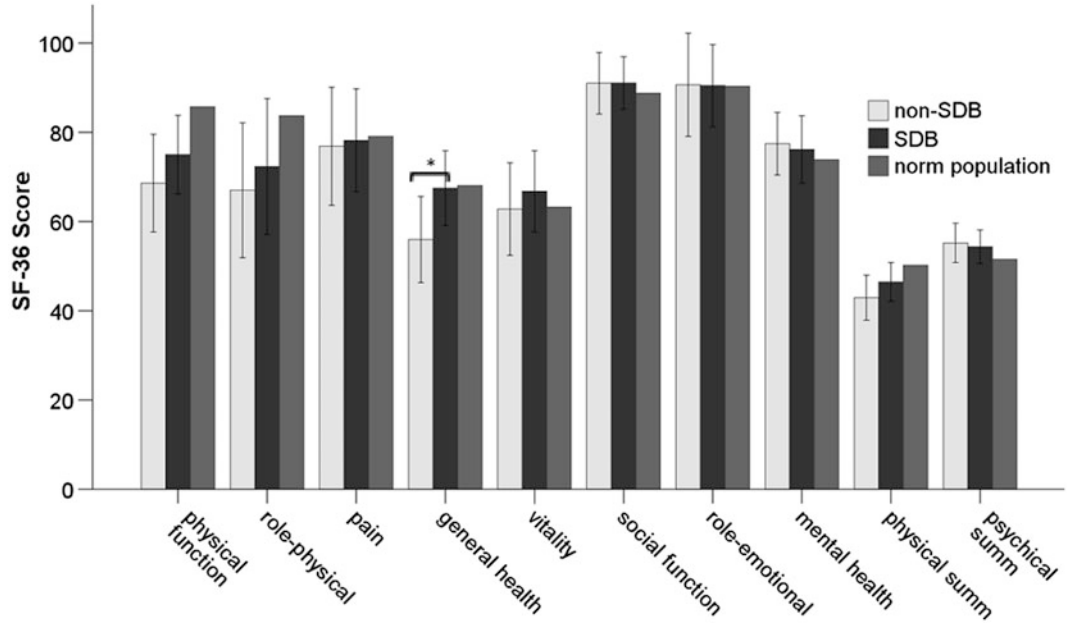


**Fig. 1** Comparison of Short Form-36 (SF-36) scores between lung transplant recipients with (n = 28) and without (n = 25) sleep-disordered breathing (SDB) and the population norm for Germany; *p < 0.05 for the comparison between patients with and without SDB. Scores on a scale from 0 to 100, indicating worst to best health

**Table 2** Correlations between exercise testing and sleep parameters in lung transplant recipients (n = 53)

| | | Correlation with AHI | | Correlation with sleep efficiency | |
|---|---|---|---|---|---|
| | Value | *r* | p | *r* | p |
| BMI, kg/m$^2$ | 26 ± 4 | 0.40 | 0.002 | −0.02 | 0.45 |
| Age, years | 55 ± 10 | 0.33 | 0.01 | −0.08 | 0.30 |
| Males, n (%) | 31 (58) | 0.34 | 0.01 | −0.18 | 0.10 |
| CPET results | | | | | |
| %$P_{maxPRED}$, % | 49.0 ± 14.5 | −0.24 | 0.04 | 0.19 | 0.09 |
| Relative $P_{max}$, W/kg | 1.0 ± 0.4 | −0.30 | 0.02 | 0.20 | 0.08 |
| Relative $VO_{2max}$, mL/min/kg | 14.6 ± 4.2 | −0.26 | 0.03 | 0.27 | 0.03 |
| %$HR_{maxPRED}$, % | 74 ± 10 | −0.02 | 0.44 | −0.02 | 0.44 |
| Oxygen pulse, mL/min/kg | 8.8 ± 2.6 | 0.24 | 0.04 | 0.07 | 0.31 |
| 6MWD, m | 513 ± 112 | 0.07 | 0.31 | 0.16 | 0.12 |
| $FEV_1$, % predicted | 75 ± 23 | 0.14 | 0.16 | 0.10 | 0.24 |
| $FEV_1$, % best | 80 ± 16 | 0.04 | 0.40 | 0.31 | 0.01 |
| VC, % predicted | 89 ± 22 | 0.07 | 0.32 | −0.004 | 0.49 |
| Systolic BP, mmHg | 121 ± 11 | −0.04 | 0.40 | −0.14 | 0.17 |
| Diastolic BP, mmHg | 71 ± 7 | 0.13 | 0.17 | 0.02 | 0.44 |

Values are means ±SD or number (%)

*AHI* apnea-hypopnea index, *BMI* body mass index, *CPET* cardiopulmonary exercise testing, *%$P_{maxPRED}$* percentage of predicted maximal work rate, *relative $P_{max}$* maximal workload relative to weight, *relative $VO_{2max}$* maximal oxygen uptake relative to weight, *%$HR_{max}$* percentage of predicted maximal heart rate (220-age), *6MWD* six-minute walk distance, *$FEV_1$* forced expiratory volume in 1 s, *VC* vital capacity, *BP* blood pressure, *r* one-tailed Pearson's correlation coefficient

in this study, LTX recipients with a high AHI and low sleep efficiency had a significantly lower relative maximal oxygen uptake ($VO_{2max}$).

In multivariate analysis adjusted for age, BMI and gender, only $VO_{2max}$ remained significantly associated with sleep efficiency ($r^2 = 0.49$). In this model, a 10% increase in sleep efficiency was associated with a 0.8 mL/min/kg increase in $VO_{2max}$, independent of age, BMI and gender ($p = 0.01$). There were no significant associations between 6-min walk distance and SDB parameters (Table 2). CPET was limited mainly by leg fatigue.

## 4 Discussion

This study investigated the role of SDB in LTX recipients in terms of HRQoL and exercise capacity for the first time. The results showed that exercise capacity was reduced in LTX recipients with versus without SDB, as indicated by correlations between both AHI and sleep efficiency and CPET parameters. Interestingly, there were no differences between LTX recipients with and without SDB with respect to HRQoL.

In LTX recipients, maximal exercise capacity was inversely associated with AHI and positively associated with sleep efficiency. Correlation coefficient values of −0.24 to −0.30 and 0.19 to 0.27, respectively, indicate a relatively small association. Nevertheless, it is possible that the relationship is linear and therefore that the impact of SDB on exercise capacity increases in parallel with the severity of SDB. Overall, though, the results of this study suggest that the observed association between SDB and exercise capacity in LTX is likely to be of little clinical relevance. This is supported by the finding of no association between SDB and moderate exercise testing (6MWT), which is a good indication of activities of daily living (ATS 2002).

Existing data on the association between SDB and exercise capacity are conflicting. Several small studies could not show an association between these parameters, instead suggesting that obesity and other demographic characteristics are confounders for impaired exercise capacity in SDB (Rizzi et al. 2010). The current results may support this hypothesis because AHI correlated well with BMI, age and gender, reflecting the multifactorial causes of reduced exercise capacity in SDB. However, this study found an independent, significant association between $VO_{2max}$ and sleep efficiency on multivariate regression analyses adjusted for BMI, age and gender. Other exercise capacity parameters did not fit in the adjusted model, but a type-II error is quite possible due to the small sample size. It was for this reason that parameters corrected for weight, age and gender were primarily used in the analyses to avoid bias by confounding demographic characteristics.

Other studies have also reported a positive association for exercise capacity with sleep efficiency and a negative association with AHI in multivariate modelling (Mansukhani et al. 2013; Lin et al. 2006). Vanhecke et al. (2008) reported that $VO_{2max}$ was decreased in severe SDB, which is in agreement with the current results and supports the hypothesis that impaired exercise capacity is more relevant in severe SDB. The reasons underlying impaired exercise capacity in SDB are likely to be multifactorial. BMI, age and gender influence exercise capacity and are considered major predisposing factors for SDB (Young et al. 2002). Deregulated muscle metabolism has been suggested as a contributor to physical deconditioning in SDB (Bonanni et al. 2004). Sleep fragmentation and impaired vagal activity associated with SDB may also contribute to reduced exercise capacity (Hong and Dimsdale 2003). LTX and SDB may have synergetic effects because vagal denervation is a frequent complication after LTX and could worsen impaired vagal activity in SDB. Data from this study also suggest a peripheral muscular limitation of CPET because the main reason for terminating CPET was leg fatigue. This supports the thesis, discussed by Bartels et al. (2011) that exercise testing in post-LTX patients is limited to a greater extent by muscle dysfunction than by cardiopulmonary factors. Possible reasons for the described muscle dysfunction could be immobilization, atrophy, and deregulated muscle metabolism secondary

to the side effects of corticosteroid and immunosuppressive therapy. Taken together, the available data suggest that impaired exercise testing after LTX might be worsened in the presence of SDB but that the observed association between CPET and SDB is likely to be multifactorial in origin.

This study did not document any differences in HRQoL between LTX recipients with and without SDB. In fact, those with SDB scored slightly better in the general health category of the SF-36. This result may be an anomaly due to the small sample size and confounders such as comorbidities. When compared with population norms, LTX recipients had similar HRQoL in the emotional and mental health categories but reduced scores for the physical and general health scales. This is consistent with data from previous studies on HRQoL in LTX (Kugler et al. 2010). However, the current results differ from those in other sleep medicine studies investigating links between SDB and HRQoL, such as the Sleep Heart Health Study (Baldwin et al. 2001). In that large cohort study, the vitality scale was negatively affected even in mild-to-moderate SDB, suggesting that even mild SDB had an impact on quality of life. The impact of severe SDB on HRQoL has previously been reported to be significant. The patients enrolled in the current study predominantly had moderate SDB and there was no association between severity of SDB and HRQoL due to the small sample size. It may be possible that a study including a larger patient sample might show impaired HRQoL in LTX recipients. Another possibility is that the relationship between HRQoL and SDB differs in chronically ill patients compared with a general sleep medicine clinic population. HRQoL in SDB is strongly linked to SDB symptoms such as excessive daytime sleepiness or snoring (Baldwin et al. 2001), and it has been shown that these symptoms occur at a very low frequency in heart failure patients with central sleep apnea (Bitter et al. 2012). The observed lack of SDB symptoms in LTX recipients indicated by a normal Epworth Sleepiness Scale (Sommerwerck et al. 2016; Hernandez Voth et al. 2015; Naraine et al. 2009) adds to the body of evidence suggesting that an absence of symptoms may be a potential explanation for the lack of association between SDB and impaired HRQoL in patients with other chronic comorbidities.

Another factor that could have influenced the association between SDB and HRQoL is that this study did not differentiate between OSA and CSA, which would have meant that investigations into the relationship between SDB and HRQoL were influenced by the different characteristics of OSA and CSA. The characteristics of LTX recipients are another possible explanation for the lack of effect of SDB on HRQoL in the current study. LTX recipients are chronically ill, have a history of markedly reduced HRQoL, and a significant symptom burden compared with the general population treated at sleep clinics (Kugler et al. 2010). Given that the SF-36 is a subjective questionnaire, over-estimation of current burden based on the experience of former symptoms could have influenced the study results. In addition, comorbidities may have biased SF-36 scoring and masked any association between SDB and HRQoL. Taking all this into account, it is probably appropriate to question the reliability of the SF-36 questionnaire in the LTX setting. However, there are no specific questionnaires to assess HRQoL in LTX recipients and only a few studies have assessed the usefulness of specific HRQoL instruments such as the St. Georges Respiratory Questionnaire in the LTX setting. The SF-36 has also been previously used to assess HRQoL in LTX recipients, and the shortcoming may be in those with a combination of LTX and SDB, rather than just LTX alone. It has been recently suggested that the SF-36 captures generic data on HRQoL in LTX recipients, but that additional transplant-specific domains are also important (Singer et al. 2015).

To improve the reliability of the study results, assessments were conducted over a 48-hour period. Gold-standard methods such as full in-laboratory PSG and CPET were used. The results of CPET provide more objective data than the 6MWT which is easily influenced by patients' motivation or physician-patient interaction. There are two ways of interpreting the finding that SDB parameters were correlated with CPET assessments but not

with 6MWT. The first is that CPET is the superior method and that subjective interference masked any effects of SDB on 6MWT, and the second is that the association was only measurable in maximal exercise testing because it is relatively small and clinically insignificant compared with 6MWT, which is more relevant for the patients' activities of daily living.

This study has several limitations that need to be taken into account. The main limitation is that a proportion of the patients was not PSG-naïve and had received NIV-treatment before enrolment. NIV has been shown to have positive effects on cardiovascular risk factors such as hypertension and on exercise capacity, but does not improve metabolic syndrome (Gottlieb et al. 2014; Arzt et al. 2005). However, subgroup analysis, albeit with small patient numbers, showed that the results were similar in NIV-treated and NIV-naïve patients. Another issue is the significant heterogeneity inherent in the LTX population. Age, gender and transplant indications, as well as medication and comorbidities, may have confounded assessments of HRQoL and exercise capacity or masked possible adverse effects of SDB in LTX, so that a type-II error could have occurred. It is difficult to control these parameters, and these are common limitations in existing studies that enrolled patient groups of comparable size and characteristics. Nevertheless, a larger sample size would help to balance the influence of heterogeneous patient characteristics at baseline. The small sample size in this study also limited the ability to analyze SDB severity and to investigate the causes and consequences of SDB in LTX recipients. Further prospective studies with a larger sample size are needed to better answer these questions. The current study provides useful information for the design of such studies, such as the inclusion of maximal exercise testing.

In conclusion, the results of this study show that comorbid SDB is associated with a slight reduction in maximal exercise capacity in stable LTX recipients, but that there is no clinically-relevant association between SDB and moderate exercise capacity or HRQoL. Nevertheless, the high prevalence of SDB as a common comorbidity in LTX recipients suggests that further investigations into the clinical effects and consequences of SDB, and the role of effective SDB treatment in LTX recipients are warranted.

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**Conflicts of Interest** The authors declare no conflicts of interest in relation to this article.

**Ethical Approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the Ethics Committee of the Medical Faculty of the University of Duisburg-Essen.

**Informed Consent** Written informed consent was obtained from all individual participants included in the study.

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