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SCIENTIFIC INVESTIGATIONS

Exercise capacity and comorbidities in patients with obstructive sleep apnea

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Study Objectives: There are few studies evaluating (1) exercise capacity as assessed by the 6-minute walking distance (6MWD) test in large populations with obstructive sleep apnea (OSA); and (2) correlations with patients' comorbidities.

Methods: This study presents a cluster analysis performed on the data of 1,228 patients. Severity of exercise limitation was defined on the basis of 6MWD.

Results: Sixty-one percent showed exercise limitation (29.2% and 31.9% mild and severe exercise limitation, respectively). About 60% and 40% of patients were included in cluster 1 (CL1) and 2 (CL2), respectively. CL1 included younger patients with high prevalence of apneas, desaturations, and hypertension with better exercise tolerance. CL2 included older patients, all with chronic obstructive pulmonary disease (COPD), high prevalence of chronic respiratory failure (CRF), fewer apneas but severe mean desaturation, daytime hypoxemia, more severe exercise limitation, and exercise-induced desaturations. Only CRF and COPD significantly ($P < .001$) correlated with 6MWD < 85% of predicted value. 6MWD correlated positively with apnea-hypopnea index, oxygen desaturation index, nocturnal pulse oxygen saturation (SpO_2), resting arterial oxygen tension, mean SpO_2 on exercise, and negatively with age, body mass index, time spent during night with SpO_2 < 90%, mean nocturnal desaturation, arterial carbon dioxide tension, and number of comorbidities. Patients without severe comorbidities had higher exercise capacity than those with severe comorbidities, ($P < .001$). Exercise limitation was significantly worse in OSA severity class I when compared to other classes ($P < .001$).

Conclusions: A large number of patients with OSA experience exercise limitation. Older age, comorbidities such as COPD and CRF, OSA severity class I, severe mean nocturnal desaturation, and daytime hypoxemia are associated with worse exercise tolerance.

Keywords: chronic respiratory failure, COPD, exercise test, 6-minute walking distance

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Patients with obstructive sleep apnea have reduced maximal aerobic capacity, which can be associated with increased cardiovascular risks and reduced survival. Most studies of exercise capacity in patients with obstructive sleep apnea were performed in relatively small sample sizes and did not include patients with comorbidities known to reduce exercise tolerance.

Study Impact: We evaluated exercise capacity in a large cohort of patients, as assessed by the 6-minute walking distance test, and tested whether patients could be included in different clusters explaining differences in exercise capacity. We found that a high percentage of patients with obstructive sleep apnea had exercise limitation. Older age, comorbidities such as chronic obstructive pulmonary disease and chronic respiratory failure, obstructive sleep apnea severity class I, severe mean nocturnal desaturation and daytime hypoxemia were associated with worse exercise tolerance.

INTRODUCTION

The estimated prevalence of obstructive sleep apnea (OSA) is 13% in males and 6% in females.[1,2] Patients with OSA have reduced maximal aerobic capacity, which can be associated with increased cardiovascular risks and reduced survival.[3] Most of studies of exercise capacity in OSA patients were performed in relatively small sample sizes, the largest accounting 111 patients[4,5] and did not include patients with comorbidities known to reduce exercise tolerance.[3] Furthermore, there are few studies on large OSA populations evaluating exercise capacity by means of the 6-minute walking distance (6MWD) test and the correlations with comorbidities.[6] However, further research is necessary to explore the relationships between physical activity, exercise, and OSA and to examine the synergic efficacy of exercise and gold standard therapy of continuous positive airway pressure (CPAP).

Therefore, the aims of this study in a large cohort of patients were to evaluate exercise capacity, as assessed by the 6MWD; to test whether patients could be included in different clusters explaining differences in exercise capacity; and to investigate the correlations between sleep characteristics and exercise capacity.

METHODS

The protocol was approved by the Ethical Committee of the Istituti Clinici Scientifici (ICS) Maugeri, Pavia, Italy (CEC 2239 October 9, 2018). All patients provided informed consent for the scientific use of their data.

Study participants

This retrospective study was conducted on prospectively collected data of a database available from January 1, 2015 to December, 31, 2018 of outpatients and inpatients with OSA of 12 Institutes of ICS Maugeri, referral centers for pulmonary rehabilitation, diagnosis, and management of OSA including CPAP, and care of patients with chronic OSA.[7–9] Patients in stable condition undergoing evaluation and first treatment with CPAP were included. In Italy evaluation and first prescription of CPAP of patients with OSA is possible also on an in-patient basis.

Clinical definitions

OSA was defined on the basis of home or in-hospital polysomnography for outpatients and inpatients, respectively. According to the *International Classification of Sleep Disorders*,[10] OSA was defined as the presence of 5 or more obstructive respiratory events (apnea, hypopnea or respiratory effort-related arousal) per hour of sleep plus daytime or nighttime symptoms of OSA; alternatively, as the presence of 15 or more obstructive respiratory events per hour of sleep. The severity of OSA was defined according to guidelines (class I, apnea-hypopnea index [AHI] 5–15; class II, AHI > 15 to < 30; and class III, AHI > 30 events/h respectively).[10]

Comorbidities were defined according to the International Classification of Disease, Ninth Revision code. Reported comorbidities were confirmed by assessment of clinical and functional records and of currently prescribed drugs. In brief: hypertension and diabetes were defined according to the patients' clinical history and drug use; chronic obstructive pulmonary disease (COPD) according to the Global Strategy for Prevention, Diagnosis and Management of COPD (GOLD) guidelines[11]; overlap syndrome by the association of OSA with COPD[12]; chronic respiratory failure (CRF) by the prescription of long-term oxygen therapy (LTOT)[13]; chronic heart failure, valvulopathy, and ischemic heart disease were defined according to the clinical history, drug use, and echocardiography when available[14]; metabolic syndrome was diagnosed by at least three conditions including large waist, high triglyceride level, reduced "good" or high-density lipoprotein cholesterol, increased arterial blood pressure, and elevated fasting blood sugar.[15] Patients with associated oncologic comorbidities, orthopedic limitations, and neurologic and neuromuscular diseases were excluded.

Measurements

The following data were reported: demographics (age, sex), anthropometrics (body mass index [BMI][16]), Epworth Sleepiness Scale score,[17] and reported number and diagnosis of comorbidities according to the Cumulative Illness Rating Scale.[18]

As part of the evaluation protocol sleep and arterial blood gas assessments were performed. Standard sleep evaluation was performed with home respiratory polygraphy or in-hospital full polysomnography analyzed and scored according to accepted guidelines.[10] Pulsed oxygen saturation (SpO_2) and rate, nasal flow, thoracic-abdominal movements, and body position were monitored in all cases. Arterial blood gases were assessed on samples from the radial artery with the patients breathing air or oxygen in the sitting position for at least 1 hour. Patients under LTOT were assessed under their prescribed usual inspiratory oxygen fraction (FiO_2). Data on arterial blood gases were available in 920 patients.

According to our clinical protocol, within 2 months of a sleep study, exercise tolerance was assessed by means of the 6MWD, according to accepted technical standards,[19] regardless of the presence of any self-reported complaint of dyspnea or exercise limitation. Patients under LTOT performed the test under their prescribed usual FiO_2. At the beginning and at the end of walking, self-reported sensations of dyspnea and leg fatigue were assessed, but not reported in the database, by means of a modified Borg scale.[20] Predicted values were according to the Enright equation.[21] The lower limit of normality (LLN) was defined as the value at fifth percentile of 6MWD in Enright's study sample by the following calculations: male = 6MWD predicted value – 153; female = 6MWD predicted value – 139.[21] Patients were defined as having (1) no exercise limitation: 6MWD ≥ 85% of predicted value; (2) mild limitation: 6MWD < 85% of predicted value and ≥ LLN; and (3) severe limitation: 6MWD < LLN. Exercise–induced desaturation was defined as a 4% drop in SpO_2 to < 90% during the test.[19]

Statistical analysis

Descriptive statistics are reported as mean, standard deviation, and median for continuous variables and as numbers (n) and percentage frequency (%) for discrete variables. Percentage frequency of excluded patients among centers was calculated. For continuous variables, the differences between groups (patients with versus without severe comorbidities as COPD, CRF, chronic heart failure, diabetes, and ischemic disease) and among OSA severity classes[10] were evaluated by analysis of variance and, if Fisher exact test was significant, a *post hoc* evaluation with Bonferroni correction was performed using the *t* test. For discrete variables, differences between groups and subgroups were evaluated by chi-square analysis (Pearson chi-square test). The correlations between the demographic, anthropometric, clinical, physiological, and sleep variables and 6MWD were studied by Spearman correlation evaluation. We evaluated the risk of walk < 85% of predicted 6MWD value by odds ratio analysis using as dependent variables all baseline characteristics and presence/absence of comorbidities.

Clusters were identified by the Partitioning Around Medoids (PAM) method, on a matrix of Gower distances between subjects using a subset of variables showing missing data fraction < 30%. The optimal number of clusters to be imposed to the clustering algorithm was identified as the one guaranteeing the highest silhouette coefficient.

The nonparametric Wilcoxon rank-sum test and the Fisher exact test were applied to test the presence of statistically significant differences in terms of variables' distribution between clusters for continuous and categorical variables respectively. The distribution of variables by cluster was described by median

(25th – 75th percentiles) or by counts (frequency, %) based on their characteristics. The choice of nonparametric statistics was due to nongaussian distribution characterizing most of the continuous variables included in the analysis. The multivariate random forests classifier was applied on a subset of cases with no missing values to estimate the importance of each variable in discriminating between the two clusters.

Clustering functions are implemented in the R (www.r-project.org) package "cluster"; the random forest method implemented in the package "random forest," whereas Wilcoxon rank-sum test, Fisher exact test, and stepwise selection algorithm are implemented in the package "stats." Details on statistical methodology are described in the supplemental material.

The statistical significance was set for all statistical test to $P < .05$. All analyses were carried out using STATA software package (release 11, Stata Corp LP) except when specified.

RESULTS

The data of 2,800 patients with OSA were found. Two hundred forty patients with neurologic and neuromuscular diseases and 1,332 patients lacking the 6MWD data were excluded. **Table S1** and **Table S2** in the supplemental material show missing data and characteristics of excluded patients, respectively. Exclusion rate among centers ranged from 48% to 61% of all patients.

Data of 1,228 patients were fully available and analyzed. Demographic, anthropometric, and physiologic clinical characteristics and sleep parameters of patients included are shown in **Table 1.** Most of the patients were male and had obesity, with hypertension and COPD, of a range of ages and with daytime arterial blood gases, had high numbers of apneas and desaturations, long-time nocturnal desaturation, and exercise tolerance limitation. Only 1.5% of patients were free from any comorbidity.

OSA severity

As expected, AHI was statistically different among the OSA severity classes (8.8 ± 4.0, 22.4 ± 5.3, and 53.7 ± 17.7 events/h for class I, II, and III, respectively: $P < .001$). Exercise capacity as assessed by the 6MWD (328.2 ± 124.8, 361.0 ± 134.5, and 360.8 ± 136.4 meters for class I, II, and III, respectively, $P < .012$,) and prevalence of severe exercise limitation (46.3%, 28.7%, and 29.9% respectively, $P < .001$) were statistically worse for severity class I as compared to classes II and III. COPD was more prevalent in class I (58.3%, $P = .001$), whereas hypertension was more prevalent in class III (63.1%, $P = .001$). No difference was found for other comorbidities. For further details see also **Table S3** in the supplemental material.

Table 2 shows the distribution of clinical data and comorbidities according to the levels of exercise limitation. The patients were equally distributed in the three classes of limitation; AHI was greater in patients without exercise limitation who were mainly hypertensive and had diabetes along with metabolic syndrome. Older age, CRF, and COPD were more prevalent in patients with exercise limitation.

A total of 16 variables with missing data fraction < 30% (sex, age, BMI, AHI, oxygen desaturation index [ODI], time spent in bed with SpO_2 < 90% [T90], $PaCO_2$, PaO_2, mean SpO_2 during 6MWD, 6MWD % of predicted value, CRF, COPD, hypertension, diabetes, coronary artery disease, dyslipidemia, chronic heart failure) were used for clustering analysis as described in **Table S1**. **Table 3** shows variables' distribution by identified cluster. Out of the 1,228 patients analyzed, 740 (60.3%) were assigned to cluster 1, and 448 (39.7%) to cluster 2. Results from the random forest multivariate ranking (**Figure S1** and **Figure S2** in the supplemental material) showed that the five variables with the strongest influence on clusters definition were: (1) presence of COPD and (2) CRF, (3) T90, (4) AHI, and (5) ODI.

Table 1—Demographic, anthropometric, physiologic, and clinical characteristics of patients in the study.

	Included Patients
Number	1,228
Sex, male/female, n (%)	839 (68.3)/389 (31.7)
Age, years	66.0 ± 11.4
BMI, kg/m^2	33.6 ± 7.0
BMI > 30 kg/m^2, n (%)	417 (67.3)
BMI < 19 kg/m^2, n (%)	9 (0.7)
ESS score	7.5 ± 4.9
AHI, events/h	38.3 ± 22.9
AHI central, events/h	3.8 ± 8.1
AHI mean duration, seconds	21.9 ± 6.5
ODI, events/h	36.1 ± 24.0
Night SpO_2 mean, %	90.2 ± 5.4
T90, %	34.3 ± 31.8
$PaCO_2$, mm Hg	40.0 ± 5.8
PaO_2, mm Hg	73.1 ± 10.9
6MWD, meters	356.1 ± 134.7
6MWD, % of predicted value	77.1 ± 25.1
Mean SpO_2 during 6MWD, %	93.3 ± 2.9
Mean SpO_2 reduction during 6MWD, %	2.1 ± 2.5
CIRS, no. of comorbidities	2.5 ± 1.5
Comorbidities, n (%)	
CRF	355 (28.9)
COPD	560 (45.6)
Chronic heart failure	56 (4.5)
Diabetes	302 (24.6)
Ischemic disease	196 (16.0)
Dyslipidemia	484 (39.4)
Hypertension	727 (59.2)
Metabolic syndrome	410 (33.4)
Others	141 (11.5)
None	18 (1.5)

Data are shown as mean ± standard deviation unless otherwise indicated. 6MWD = 6-minute walking distance, AHI = apnea-hypopnea index, BMI = body mass index, CIRS = Cumulative Illness Rating Scale, COPD = chronic obstructive pulmonary disease, CRF = chronic respiratory failure, ESS = Epworth Sleepiness Scale, ODI = oxygen desaturation index, $PaCO_2$ = arterial carbon dioxide tension, PaO_2 = arterial oxygen tension, SpO_2 = pulse oxygen saturation, T90 = time in bed spent with SpO_2 < 90%.

Table 2—Demographic, anthropometric, physiologic, and clinical characteristics of patients according to the three levels of exercise limitation.

	No Limitation	Mild Limitation	Severe Limitation	*P*
Number (%)	478 (38.9)	358 (29.2)	392 (31.9)	
Sex, male/female, n (%)	354 (74.1)/124 (25.9)	233 (65.1)/125 (34.9)	252 (64.3)/140 (35.7)	.003
Age, years	64.6 ± 10.7	67.5 ± 11.1	66.3 ± 12.4	.001; .001[a]
BMI, kg/m^2	33.4 ± 6.2	34.0 ± 7.1	33.4 ± 7.7	.353
BMI > 30 kg/m^2, n (%)	325 (68.0)	248 (69.5)	252 (64.3)	.280
BMI < 19 kg/m^2, n (%)	2 (0.4)	3 (0.8)	4 (1.0)	.563
ESS score	7.6 ± 4.9	7.2 ± 4.8	7.6 ± 5.3	.708
AHI, events/h	40.4 ± 22.2	37.8 ± 22.4	36.2 ± 24.0	.021; .019[b]
AHI central, events/h	4.0 ± 8.1	2.3 ± 4.9	5.3 ± 11.5	.016; .018[c]
AHI mean duration, seconds	22.1 ± 6.2	21.4 ± 6.7	21.9 ± 7.0)	.515
ODI, events/h	39.4 ± 23.3	34.8 ± 23.5	33.7 ± 24.9	.0018; .025[a]; .003[b]
Night SpO_2 mean, %	90.4 ± 5.9	90.3 ± 4.4	89.3 ± 5.0	.145
T90, %	29.5 ± 28.8	34.3 ± 31.2	40.2 ± 34.9)	< .001; <.001[b]; .034[c]
$PaCO_2$, mm Hg	39.3 ± 5.3	40.2 ± 5.4	40.8 ± 6.8	.0053; .005[b]
PaO_2, mm Hg	74.5 ± 10.4	72.9 ± 10.8	71.1 ± 11.7	.0005; < .001[b]
6MWD, meters	471.7 ± 85.9	338.9 ± 84.6	231.0 ± 95.3	< .001; < .001[a]; < .001[b]; < .001[c]
6MWD, % of predicted value	101.5 ± 12.1	75.3 ± 7.1	48.9 ± 15.1	< .001; < .001[a]; < .001[b]; < .001[c]
Mean SpO_2 during 6MWD, %	92.97 ± 3.13	93.20 ± 6.18	93.26 ± 5.6	.6530
Mean SpO_2 desaturation during 6MWD, %	1.57 ± 1.96	1.92 ± 2.22	2.41 ± 2.55	< .001; < .001[b]; .023[c]
CIRS, no. of comorbidities	2.5 ± 1.5	2.4 ± 1.4	2.5 ± 1.5	.700
Comorbidities, n (%)				
CRF	82 (17.2)	114 (31.9)	165 (42.1)	< .001
COPD	144 (30.2)	178 (49.8)	241 (61.4)	< .001
Chronic heart failure	5 (1.0)	20 (5.6)	30 (7.6)	< .001
Diabetes	134 (28.0)	83 (23.1)	86 (21.9)	.088
Ischemic disease	83 (17.4)	49 (13.6)	66 (16.4)	.335
Hypertension	338 (70.7)	198 (55.3)	191 (48.8)	< .001
Dyslipidemia	202 (42.3)	142 (39.7)	140 (35.7)	.147
Metabolic syndrome	168 (35.1)	121 (33.8)	121 (30.9)	.404
Others	94 (19.7)	40 (11.2)	7 (1.8)	< .001
None	10 (2.1)	4 (1.0)	4 (1.0)	.343

Data are shown as mean ± standard deviation unless otherwise indicated. Limitation defined as: no = 6MWD ≥ 85% of predicted value, mild = 6MWD < 85% of predicted value and ≥ LLN, and severe = 6MWD < LLN. [a]mild versus no limitation, [b]severe versus no limitation, [c]severe versus mild limitation. 6MWD = 6-minute walking distance, AHI = apnea-hypopnea index, BMI = body mass index, CIRS = Cumulative Illness Rating Scale, COPD = chronic obstructive pulmonary disease, CRF = chronic respiratory failure, ESS = Epworth Sleepiness Scale, LLN = lower limit of normality, ODI = oxygen desaturation index, $PaCO_2$ = arterial carbon dioxide tension, PaO_2 = arterial oxygen tension, SpO_2 = pulse oxygen saturation, T90 = time in bed spent with SpO_2 < 90%.

Cluster 1 included younger patients with high number of nocturnal apneas and desaturations and high prevalence of hypertension with mild exercise limitation. Cluster 2 included older patients, all with COPD, with fewer nocturnal apneas but with more severe mean nocturnal desaturations, daytime hypoxemia, high prevalence of CRF, severe exercise limitation, and high exercise-induced desaturations. Details on cluster results are described in the supplemental material.

Figure 1 shows the distribution of levels of exercise limitation among clusters: approximately 60% of patients showed exercise limitation, 32% with severe limitation. As expected, cluster 2 included 75% of patients with exercise limitation, (44% severe) whereas cluster 1 showed exercise limitation in 49% of the cases with a lower prevalence of severe limitation (24%): all differences among clusters were statistically significant ($P < .001$).

Distance walked < 85% of predicted value was explained mainly by the presence of CRF (odds ratio: 2.871; standard error = 0.426, 95% confidence interval = 2.145–3.842; $P < .0001$) and COPD (odds ratio 2.8851; standard error = 0.365, 95% confidence interval = 2.251–3.698; $P < .001$). The few patients (7.7% of all sample) experiencing exercise-induced desaturations showed shorter 6MWD than those without (311 ± 135 versus 360 ± 134 meters, respectively: $P = .008$).

Table 3—Distribution of variables used for clustering by cluster.

Variable		CL1	CL2	*P*
Number (%)		740 (60.3)	488 (39.7)	
Sex, n (%)	Female	249 (33.7)	140 (28.7)	.069
	Male	491 (66.3)	348 (71.3)	
Age, years (range)		67 (57–74)	69 (62–75)	< .001
BMI, kg/m^2		32.7 (29.1–37.3)	32.1 (29.0–37.1)	.223
AHI, events/h		37 (23.3–57.5)	29.1 (16.3–49.0)	< .001
ODI, events/h		35.7 (20.8–55.1)	25.4 (12.2–47.0)	< .001
T90, %		19.4 (5.0–47.0)	37.4 (9.0–72.2)	< .001
$PaCO_2$, mm Hg		39 (36.2–42.0)	39 (36.4–43.0)	.208
PaO_2, mm Hg		74 (67.8–81.2)	69.9 (63.6–78.0)	< .001
Mean SpO_2 during 6MWD, %		94.1 (92.5–95.9)	92.3 (89.5–94.8)	< .001
6MWD, % of predicted value		82.0 (66.4–98.1)	71.9 (54.8–87.8)	< .001
CRF	No	570 (83.8)	211 (50.4)	< .001
	Yes	110 (16.2)	208 (49.6)	
COPD	No	624 (91.2)	7 (1.5)	< .001
	Yes	60 (8.8)	469 (98.5)	
Hypertension	No	271 (37.7)	217 (45.5)	.008
	Yes	448 (62.3)	260 (54.5)	
Diabetes	No	534 (74.4)	366 (76.9)	.337
	Yes	184 (25.6)	110 (23.1)	
Coronary artery disease	No	613 (85.0)	391 (82.5)	.259
	Yes	108 (15.0)	83 (17.5)	
Dyslipidemia	No	441 (61.3)	282 (59.4)	.506
	Yes	278 (38.7)	193 (40.6)	

Variables' distribution is expressed in terms of median (25th–75th percentiles) or counts (frequency, %) for continuous and categorical variables respectively. CL1 = variable's distribution in cluster 1. CL2 = variable's distribution in cluster 2. *P* = value of *P* from the Wilcoxon rank-sum test or by the Fisher exact test. 6MWD = 6-minute walking distance, AHI = apnea-hypopnea index, BMI = body mass index, COPD = chronic obstructive pulmonary disease, CRF = chronic respiratory failure, ODI = oxygen desaturation index, $PaCO_2$ = arterial carbon dioxide tension, PaO_2 = arterial oxygen tension, SpO_2 = pulse oxygen saturation, T90 = time in bed spent with SpO_2 < 90%.

Detailed results of correlation analysis are reported in **Table 4**. Age, BMI, T90, mean night SpO_2 showed the highest significant, albeit modest negative correlations, whereas levels of resting and exercise oxygenation were positively correlated with 6MWD.

Comorbidities

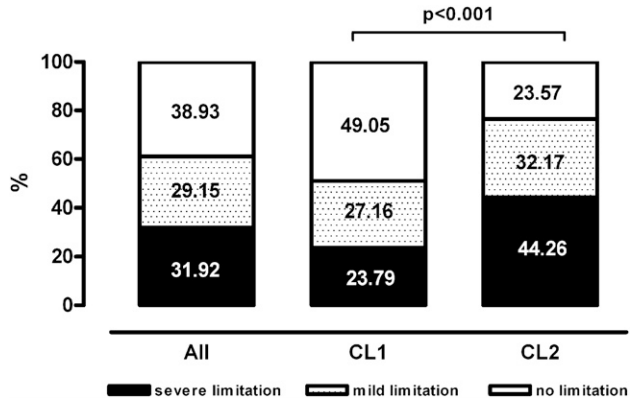
Severity of OSA was similar for patients without and with comorbidities (AHI: 39.4 ± 22.6 versus 37.6 ± 22.9 events/h, *P* = .239; and ODI: 38.0 ± 23.4 versus 35.5 ± 24.3 events/h, *P* = .126). As shown in **Table 2**, numbers of comorbidities as assessed by Cumulative Illness Rating Scale[18] were not different among levels of exercise capacity. Patients without comorbidities were significantly younger, more oxygenated, and showed higher exercise tolerance than patients with severe comorbidities (age: 60.8 ± 13.1 versus 67.9 ± 9.9 years; *P* < .001); PaO_2: 75.8 ± 11.7 versus 71.8 ± 10.4 mm Hg; *P* < .001; 6MWD: 413.1 ± 143.6 versus 338.0 ± 125.0 meters; *P* < .001, 6MWD % of predicted value: 78.8 ± 22.2 versus 75.0 ± 26.1; *P* = .02). **Figure 2** shows the distribution of levels of exercise capacity according to the presence of severe comorbidities. Approximately 65% of patients with as well as almost half patients without severe comorbidities had exercise limitation.

DISCUSSION

This study compared the exercise capacity in patients with OSA with or without common comorbidities in the largest population studied thus far, and confirms that more than 60% of patients experience exercise limitation as assessed by the 6MWD. As original findings this study adds that patients could be distributed between two clusters: one included younger patients with more severe OSA, high prevalence of hypertension, and mild exercise intolerance; the second cluster included older patients, all with COPD, with daytime, nighttime, and exercise desaturations and severe exercise limitation. Age and BMI were slightly but significantly negatively correlated with 6MWD.

The occurrence of comorbidities in our patients are those commonly reported for patients with OSA.[6,22] There is evidence that the combination of OSA and COPD, also known as overlap syndrome, is not common in the general hospital population

Figure 1—Stratification of patients with different levels of exercise limitation among clusters.



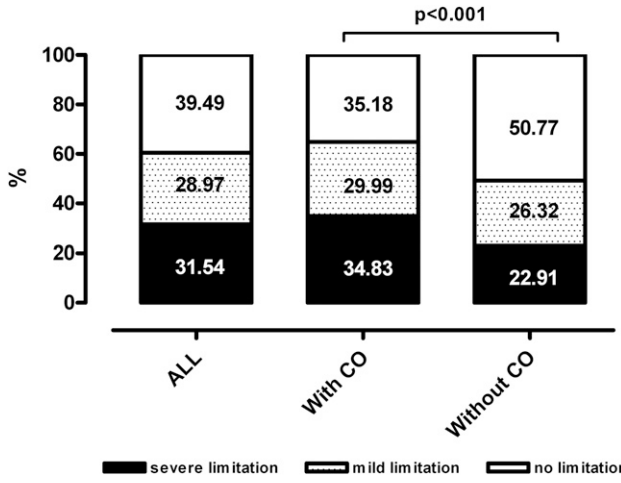
Limitation defined as: no = 6MWD ≥ 85% of predicted value, mild = 6MWD < 85% of predicted value and ≥ LLN, and severe = 6MWD < LLN. 6MWD = 6-minute walking distance, CL1 = cluster 1, CL2 = cluster 2, LLN = lower limit of normality.

Table 4—Significant correlations (Spearman correlation) between 6MWD and patients' characteristics.

	Rho	*P*
Age	−.4535	< .001
BMI	−.1825	< .001
AHI	.0825	.0039
ODI	.0998	.0008
Night SpO_2 mean	.1981	< .001
T90	−.2016	< .001
PaO_2	.2809	< .001
$PaCO_2$	−.1560	< .001
Comorbidities	−.1085	< .001
Mean SpO_2 on 6MWD	.2267	< .001

6MWD = 6-minute walking distance, AHI = apnea-hypopnea index, BMI = body mass index, ODI = oxygen desaturation index, $PaCO_2$ = arterial carbon dioxide tension, PaO_2 = arterial oxygen tension, SpO_2 = pulse oxygen saturation, T90 = time in bed spent with SpO_2 < 90%.

Figure 2—Stratification of patients with different levels of exercise limitation according to the presence of comorbidities.



Limitation defined as: no = 6MWD ≥ 85% of predicted value, mild = 6MWD < 85% of predicted value and ≥ LLN, and severe = 6MWD < LLN. 6MWD = 6-minute walking distance, CO = comorbidities, LLN = lower limit of normality.

(1.0% to 3.6%), whereas it is highly prevalent in patients with either OSA (7.6% to 55.7%) or COPD (2.9% to 65.9%). Our data analysis showed that 45.6% of our patients with OSA had a diagnosis of COPD and the cluster analysis showed that exercise limitation was explained by the presence of CRF and COPD. Overlap syndrome is associated with more frequent cardiovascular morbidity, poorer health-related quality of life, more frequent acute exacerbations of COPD, and increased medical costs.[2] Patients with overlap syndrome also have been shown to have lower night mean SpO_2, longer T90, and worse sleep quality than patients with OSA only.[2,22] Our results seem to confirm longer T90 but not worse ODI or night SpO_2 mean, whereas no data are available for sleep quality.

In our study exercise capacity was assessed by the 6MWD. Assessment of peak oxygen consumption (V'_{O2peak}) during the cardiopulmonary exercise test is considered the gold standard for evaluation of exercise capacity.[3,4] However the cardiopulmonary exercise test requires human and organizational resources and may be unavailable in many real-life conditions. The 6MWD is an accepted tool for evaluation of submaximal exercise capacity in patients with cardiorespiratory diseases and is useful for studies on large populations.[19,23] A systematic review found that mean V'_{O2peak} was significantly lower (89.9% of predicted value) in patients with OSA than in control patients. This reduction was larger in patients without obesity.[3] In our study the mean 6MWD in patients with OSA without severe comorbidities was 81.5% of predicted value, consistent with the reported values of mean V'_{O2peak},[3] and showed significant differences according to the associated comorbidities. Therefore, we are confident that the 6MWD we used in our study was sensitive enough to evaluate exercise capacity in these patients.

The effect of OSA on exercise tolerance is still discussed. Previous studies have given conflicting results, some[24–29] but not all[30–32] showing reduction in cardiorespiratory fitness. The reasons for exercise limitation in patients with OSA are not clear. Studies have reported different physiologic adaptations during exercise such as excessive blood pressure, delayed heart rate recovery, chronotropic incompetence, and respiratory and skeletal muscle changes.[4,25,28,33,34] These studies report data without evaluation of the effect of comorbidities; therefore, our study contributes to clarify this issue in a very large population. In our study approximately 65% of patients with as well as almost half patients without severe comorbidities experienced exercise limitation.

Severe exercise limitation was more prevalent in patients in the mildest OSA severity class I than those in more severe classes II and III, and we found only modest, albeit significant relationships between severity of OSA and 6MWD. Furthermore, patients with high numbers of nocturnal apneas and desaturations were included in cluster 1. Alameri et al[24] found

no correlations between the 6MWD and the severity of OSA or other polysomnographic parameters. Beitler et al[26] found that AHI alone explained 16.1% of the variability observed in percent predicted V'_{O2peak}. We also found a negative relationship between BMI and 6MWD. A study by Rizzi et al[28] suggests that obesity alone and sex, when associated with diabetes but not OSA, influence cardiorespiratory function on exercise.

The goal of our study was not to evaluate the effect of OSA on physical activity. At what extent does the observed reduced exercise capacity translate in physical activity? A systematic review reported that the mean number of daily steps across studies was lower than the recommended threshold of 10,000 daily steps and exercise training is associated with improved outcomes.[34] It is plausible that patients with OSA are neither physically capable nor psychologically motivated to exercise, in part due to daytime sleepiness and fatigue, which reduce the stimulus and time for physical activity. Insufficient physical activity on the other hand is probably associated with the risk factors contributing to OSA, such as obesity and metabolic syndrome, and increases OSA severity.[4]

Clinical implications

These results have clinical implications. The reduced exercise capacity and the influence of comorbidities highlights the importance of careful clinical history and of exercise training and suggests also that the 6MWD may be used in routine evaluation of exercise capacity of these patients.

Continuous positive airway pressure remains the first-line therapy for OSA; however, it has limited effect on cardiometabolic risk factors and body weight and a few observational studies have shown that patients treated with CPAP do not increase spontaneous levels of physical activity.[2] Exercise training not only reduces the severity of OSA and improves daytime symptoms of sleepiness, but also significantly improves exercise capacity.[6,35–37] These results might be even more evident in patients with those comorbidities assessed in our study due to the recognized effect of exercise training in those conditions.[38,39]

Limitations of the study

Our study has limitations. Although as all retrospective analyses of large populations our study describes the real life of health services, it is missing data such as that for arterial blood gases, and is affected by a huge number of exclusions. Despite the lack of data of 6MWD of excluded patients due to organizational and not to clinical reasons, and severity of OSA was not different between included and excluded patients, we cannot exclude that these exclusions might have affected the findings in a significant way. Therefore, our data must be interpreted with caution.

We did not study a control population; however, we are confident that the comparison with predicted values of 6MWD allowed an unbiased evaluation of results.

Given the modality of data recording (according to the International Classification of Diseases, Ninth Revision) we were unable to score the severity of comorbidities such as COPD or heart failure. Furthermore, the reported comorbidity occurrence must not be considered as "prevalence," because patients did not undergo specific diagnostic tests. However, the reported comorbidity occurrence was defined also by evaluation of patients' clinical records and documentation of drug consumption.

CONCLUSIONS

This study in a vast population shows that exercise capacity is impaired in a large percentage of patients with OSA. The reduction in exercise capacity and more severe exercise desaturation is more evident in older patients, with severe mean nocturnal desaturations and daytime hypoxemia and with associated comorbidities such as COPD and CRF and in OSA severity class I. 6MWD may be used to characterize patients and to evaluate the effects of treatment.

ABBREVIATIONS

6MWD, 6-minute walking distance
AHI, apnea-hypopneas index
BMI, body mass index
COPD, chronic obstructive pulmonary diseases
CPAP, continuous positive airway pressure
CRF, chronic respiratory failure
LTOT, long-term oxygen therapy
ODI, oxygen desaturation index
OSA, obstructive sleep apnea
SpO_2, pulse oxygen saturation
T90, total sleep time spent with $SpO_2 < 90\%$

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DISCLOSURE STATEMENT

All authors approved the definitive version of the manuscript and declare that questions related to the accuracy or integrity of any part of it have been appropriately investigated and resolved. MV has full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Work for this study was performed at Istituti Clinici Scientifici Maugeri IRCCS. This work was supported by the "Ricerca Corrente" Funding scheme of the Ministry of Health, Italy. The authors report no conflicts of interest.