Daytime Sleepiness and Driving Performance in Patients with Obstructive Sleep Apnea: Comparison of the MSLT, the MWT, and a Simulated Driving Task

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Study Objectives: To test the reliability of a driving-simulation test for the objective measurement of daytime alertness compared with the Multiple Sleep Latency Test (MSLT) and with the Maintenance of Wakefulness Test (MWT), and to test the ability to drive safely, in comparison with on-road history, in the clinical setting of untreated severe obstructive sleep apnea.

Design: N/A.

Setting: Sleep laboratory.

Patients or Participants: Twenty-four patients with severe obstructive sleep apnea and reported daytime sleepiness varying in severity (as measured by the Epworth Sleepiness Scale).

Interventions: N/A.

Measurements and Results: Patients underwent MSLT and MWT coupled with 4 sessions of driving-simulation test on 2 different days randomly distributed 1 week apart. Simulated-driving performance (in terms of lane-position variability and crash occurrence) was correlated with sleep latency on the MSLT and more significantly on the MWT, showing a predictive validity toward the detection of sleepy versus alert patients with obstructive sleep apnea. In addition, patients reporting excessive daytime sleepiness or a history of car crashes showed poorer performances on the driving simulator.

Conclusions: A simulated driving test is a suitable tool for objective measurement of daytime alertness in patients with obstructive sleep apnea. Further studies are needed to clarify the association between simulated-driving performance and on-road crash risk of patients with sleep disordered breathing.

Keywords: MSLT, MWT, driving simulation test, obstructive sleep apnea syndrome, excessive daytime sleepiness, car accident

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OBSTRUCTIVE SLEEP APNEA SYNDROME (OSAS) IS CHARACTERIZED BY DISTURBED NOCTURNAL SLEEP AND DAYTIME CONSEQUENCES, MAINLY EXCESSIVE daytime sleepiness (EDS). It affects from 2% to 4.4% (women) and from 4% to 11% (men) of the middle-aged population according to current diagnostic criteria and epidemiologic data.[1,2] OSAS is associated with increased mortality, acting as an independent risk factor for heart and cerebrovascular events and for the proneness to traffic crashes.[3-5] Drivers with OSAS are at 2 to 3 times increased risk of being involved in motor vehicle crashes, but neither disease severity nor sleepiness is consistently correlated with crash risk.[6] Sleepiness is a multidimensional entity that integrates qualitatively different facets: the sleep propensity in active or passive situations and the subjective perceptual component.[7] The intensity of sleepiness could range from the normal expression of the need for sleep (ie, innate behavior) to the main symptom of severe medical and neurologic disturbances.

The measurement of sleepiness reflects its complexity, with several objective and subjective tools available. Objectively, the Multiple Sleep Latency Test (MSLT) and the Maintenance of Wakefulness Test (MWT) are the gold standards for the detection of EDS in the clinical practice of sleep medicine.[1,8] The MSLT provides a measure of sleep propensity in a quiet appropriate situation (lying on a bed in a dark room), assuming that the more the sleep latency is reduced, the greater the subject's need for sleep. In the MSLT setting, sleepiness is equivalent to the ability to sleep, disregarding the potential occurrence of high "sleep ability" even in absence of any confirmatory sign of sleepiness (ie, in normal conditions).[9] The MWT evaluates subjects' ability to maintain wakefulness in a quiet boring, situation (sitting on a comfortable chair in a semidark room). In the MWT setting, sleepiness corresponds to alertness, in terms of capability to stay awake in a soporific (but somewhat uncommon for everyday life) condition. Moreover, the reported wide variability of MSLT and MWT sleep latencies in the normal population clearly overlaps with findings in medical disorders characterized by EDS.[10-13] Normative data include a mean sleep latency (to the first epoch of sleep) of 10.4 (± 4.3) minutes on the MSLT and of 30.4 (± 11.2) minutes on the MWT. Therefore, the range of normal falls between 1.8 and 19 minutes and between 8 and 40 minutes, respectively for MSLT and MWT (using the 2 SD from the mean to identify 95% of the normal values).[8,10-13] According to international criteria, the MSLT and MWT are the objective tools exploring different features of sleepiness. They are recommended for different clinical purposes from diagnosis confirmation (eg, MSLT) to the evaluation of therapeutic efficacy (eg, MWT), in association with subjective trait sleepiness assessment using the Epworth Sleepiness Scale (ESS).[1,8,14]

Driving is a complex psychomotor task that requires an adequate level of alertness to interact efficiently with the road environment but, in parallel, involves several perceptual, motor, and cognitive processes. The recent awareness of sleepiness-related crashes is mirrored by the medicolegal aspects concerning fitness to drive and consequent physicians' referral of patients with medical conditions.[15] Concerning individual ability to drive safely, sleepiness-related crashes can result from falling asleep while driving or from more subtle phenomena, such as inattention or

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other minor cognitive impairments (eg, risk perception or decision making) ascribed to drowsiness itself. Moreover, sleepiness perception while driving in the real traffic environment is a key factor for accident prevention because it can alert drivers to use countermeasures (eg, stop driving, drink caffeine beverages) to avoid car crashes.[16] Several studies have confirmed the negative impact of sleepiness on driving performance, as measured by driving simulator or on-road testing.[17] Driving performance evaluation should consider the complexity of the task (that requires efficient cognitive and neurobehavioral functioning, apart from vigilance itself) and the contributory role of fatigue-related effects. Fatigue differs from sleepiness, being a cumulative disinclination toward effort that can lead to reduced performance efficiency and resolves with rest (while sleepiness resolves with sleep).[18,19] Even if the ability to perform in a simulated driving test could not be translated into real fitness to drive, Philip and coworkers demonstrated that the driving impairment after sleep restriction (measured by means of inappropriate line crossing of the vehicle) is qualitatively comparable in real driving and driving simulators but of higher amplitude under simulated conditions.[20]

Few studies on driving simulation in patients with OSAS have evaluated the relationship between objective sleepiness measurement and driving performance. George and coworkers found that tracking error on a divided-attention driving task correlated with MSLT sleep latencies in baseline conditions ($r = -0.42$, P value = 0.01), and both parameters were improved after the use of nasal continuous positive airway pressure therapy ($r = 0.65$, P value < 0.01).[21-23] We confirmed the correlation between MSLT sleep latencies and lane-position variability in patients with OSAS ($r = -0.47$, P value = 0.008), together with other performance parameters, using our monotonous driving simulation test.[24] Interestingly, Hack and coworkers showed a significant improvement in the driving performance of patients with OSAS on steering simulator after therapeutic nasal continuous positive airway pressure that was not correlated with changes in MWT sleep latencies, suggesting that reduced vigilance was not the single impairing factor for steering performance.[25] Recently, studies of sleep deprivation (with or without alcohol consumption) and patients with OSAS disclosed the predictive validity of the MWT toward driving performance.[26,27] Banks and coworkers showed that a modified nocturnal MWT was predictive of having a crash in a driving simulation only in a combined sleep-restriction-and-alcohol-consumption condition.[26] Sagaspe and coworkers found a higher correlation between mean sleep latency at MWT and lane-position variability on a driving simulation compared with previous MSLT studies of patients with OSAS ($r = -0.51$, P value < 0.01).[27]

The present study aimed to test the reliability of our driving-simulation test for the objective measurement of daytime alertness compared with MSLT and MWT in patients with untreated severe OSAS. Secondarily, we tested the association between subjective EDS, personal on-road history, and performance on the driving simulator.

METHODS

Patients

Twenty-four men with a definite clinical diagnosis of severe OSAS and with a valid driving license participated in the study. The diagnosis of severe OSAS was established by nocturnal portable monitoring (Embletta®-Embla Systems, Broomfield, CO) performed at the patient's home according to current practice parameters and diagnostic criteria.[1,28,29] The study was performed according to the standards of the local ethics board. All patients gave written informed consent prior to the study and were informed that all results were confidential without any legal impact regarding their driving licenses.

Exclusion criteria were other significant medical or sleep disorders and chronic use of drugs interfering with daytime alertness; alcohol abuse; consumption of more than 5 caffeinated beverages; and smoking more than 10 cigarettes per day.

Vigilance and Simulated Driving Performance Measurements

In each week before the study, patients completed a sleep diary (with total sleep time and number of awakenings per night) to exclude differences in their sleep schedule between the 2 testing days. No alcohol or caffeine or other sedative or stimulating substances were allowed during the 2 days of study.

The study was performed on 2 different days, 1 week apart, when patients underwent MSLT and MWT. Patients were randomly assigned to start with the MSLT or MWT day. Each day of the study consisted of 4 sessions of neurophysiologic evaluation (at 10:00, 12:00, 14:00, 16:00), subjective measurements of sleepiness (visual analogue scale [VAS] and Stanford Sleepiness Scale [SSS]), and a 30-minute driving-simulation task with our monotonous driving scenario performed at 11:00, 13:00, 15:00 and 17:00 (STISIM 300 Driving Simulator, Systems Technology Incorporated, Hawthorne, CA).[30] Each neurophysiologic session was interrupted after 20 minutes (for MSLT) or 40 minutes (for MWT) of continuous wakefulness or after the appearance of sustained sleep (3 consecutive 30-second epochs of non-rapid eye movement (NREM) stage 1 sleep or 1 epoch of any other sleep stage) to avoid interfering with the sleep homeostasis process.[8,10-13] The scoring examiner, blind to patients' clinical features, subsequently scored the sleep latency, identifying the first appearance of 1 and 3 consecutive epochs of NREM stage 1 sleep (or 1 epoch of any other sleep stage, "sustained sleep") in each session. Patients also completed the Italian version of the ESS[31] and a questionnaire on personal driving history and sleepiness while driving. The simulated-driving scenario together with the methodology used to train and test patients with OSAS were described in our previous work.[24]

Statistical Analysis

We analyzed global driving performance data and also grouped lane-position variability data into three 10-minute time blocks for each simulated driving session. We analyzed all data with Kruskall-Wallis nonparametric univariate analysis of variance (ANOVA) with Monte Carlo exact method ($\alpha < 0.05$ set) to exclude significant differences in driving performances at different times of day. Subsequently, mean driving performance data, together with mean sleep latency on the MSLT and MWT, mean subjective sleepiness measurements (SSS, VAS), and mean reported sleep time and awakenings were calculated for each patient's testing day.

Table 1—Clinical Characteristics of 24 Men With Severe OSAS

ID	Age	BMI	AHI	ESS	MWT 1	SusMWT	MSLT 1	SusMSLT
1	59	32.4	77	6	2.5	11.5	2.9	4.0
2	47	32.7	35	6	32.1	40.0	20.0	20.0
3	38	29.7	59	11	21.8	40.0	7.9	13.4
4	39	29.2	39	9	40.0	40.0	3.4	8.9
5	57	35.5	64	9	7.8	26.3	1.9	11.0
6	66	27.3	39	9	33.6	35.3	5.9	7.5
7	53	27.5	36	9	28.0	32.9	5.1	6.3
8	48	33.8	77	9	25.1	40.0	14.1	16.0
9	53	30.2	38	12	40.0	40.0	17.3	20.0
10	48	33.1	50	16	1.9	2.1	2.0	2.4
11	51	29.8	76	12	10.0	29.0	1.5	2.5
12	33	28.7	39	5	18.3	27.4	4.9	8.1
13	55	32.4	77	7	40.0	40.0	12.3	13.0
14	56	33.5	58	4	40.0	40.0	20.0	20.0
15	62	27.4	58	10	4.3	18.5	8.6	11.0
16	56	27.7	74	21	5.5	8.4	3.6	5.0
17	55	33.8	49	8	15.5	25.1	3.9	8.6
18	62	39.7	66	12	7.5	26.8	4.9	9.1
19	58	29.4	48	15	5.3	10.6	3.5	4.0
20	55	32.7	76	9	21.8	34.6	5.3	6.8
21	67	35.3	31	4	28.9	35.8	4.8	8.5
22	54	26.8	31	15	18.8	23.1	3.4	6.4
23	64	29.3	52	5	40.0	40.0	8.0	11.9
24	62	37.4	50	10	23.4	40.0	11.1	13.4

Clinical characteristics (age in years and body mass index [BMI in kg/m^2]) and physiologic evaluation of nocturnal respiratory disturbance (AHI, mean number of apneas and hypopneas per hour of sleep), subjective trait daytime sleepiness (Epworth Sleepiness Scale [ESS] score), objective sleepiness measured by the mean sleep latency to the first appearance of a single epoch of non-rapid eye movement [NREM] stage 1 sleep, in minutes, on the Maintenance of Wakefulness Test and Multiple Sleep Latency Test (MSLT1 and MWT1), and by the mean sleep latency to the first appearance of 3 consecutive epochs of NREM stage 1 sleep or 1 epoch of any other sleep stage (SusMSLT and SusMWT).

Mean subjective sleepiness measurements (SSS, VAS) and mean reported sleep time and number of awakenings per week and of the night before each testing day were compared with Kruskall-Wallis nonparametric univariate ANOVA ($\alpha < 0.05$ set) and correlated with Pearson and Spearman correlations ($\alpha < 0.05$ set) to exclude significant differences in subjective alertness and reported sleep on the 2 testing days. Mean driving performance data collected on the 2 different days were compared with Kruskall-Wallis nonparametric univariate ANOVA ($\alpha < 0.05$ set) and correlated with Pearson and Spearman correlations ($\alpha < 0.05$ set) to assess the reproducibility of the test versus the potential learning effect in specific tasks.

Subsequently, mean driving performance data and subjective sleepiness measurements were related to mean MSLT and MWT sleep latencies with Pearson and Spearman correlations ($\alpha < 0.05$ set).

We also divided patients into dichotomous subgroups on the basis of ESS score (higher versus lower or equal to 11), reported sleepiness while driving, history of driving crashes, and reported sleepiness-related crashes to evaluate significant differences in mean simulated driving performance parameters measured during the first day of the study for each subject with Kruskall-Wallis nonparametric univariate ANOVA ($\alpha < 0.05$ set).

Finally, we compared driving-performance results concerning primary vehicle control task (crashes, lane-position variability) with MWT results with receiver operating characteristic (ROC) curves to assess the ability of the driving simulation test to distinguish patients with EDS and those who were objectively fully alert but still had OSAS. We considered MWT (1 epoch scoring) "positive" for sleepiness if the mean sleep latency was less than 8 minutes and "positive" for full alertness if the mean sleep latency was longer that 30 minutes. The area under the ROC curves provides a measure of the performance of the driving simulation test in light of the comparison with MWT.

RESULTS

Clinical Population

The patients were a middle-aged (mean age 54 ± 8.6 years old) population of men with severe OSAS with different degrees of subjective daytime sleepiness. The mean apnea-hypopnoea index (number of apneas and hypopneas per hour of sleep) was 54.2 ± 16.2 (range 31-77), and the mean body mass index (ratio between weight in kilograms and square height in meters) was 31.5 ± 3.4 kg/m^2.

Patients complained of different degrees of subjective daytime sleepiness, evaluated with a mean ESS score of 9.7 ± 4.1 (range 4-21). Seven patients (29.2%) had an ESS score higher that 11, suggesting EDS.[14] The MSLT showed a mean sleep latency to the first epoch of sleep of 7.3 ± 5.6 minutes (range 1.5-20) and to the occurrence of sustained sleep of 10.1 ± 1.1 minutes (range 2-20). The MWT showed a mean sleep latency to the first epoch of sleep of 20.8 ± 13.7 minutes (range 1.9- 40)

Table 2—Mean Simulated Driving Performance, Subjective Sleepiness, and Reported Sleep in the 2 Different Days of the Study

	Day 1		Day 2		Pearson	Spearman
Driving performance	**Mean**	**SD**	**Mean**	**SD**	**Coefficient**	**Coefficient**
Crashes, no.	1.04	1.92	1.60	4.64	0.93[b]	0.79[b]
TTC, min.	23.54	7.63	24.85	7.50	0.81[b]	0.77[b]
DA Index	0.19	0.18	0.10	0.12	0.65[b]	0.77[b]
Reaction time, sec						
Mean	2.71	0.76	2.21	0.73	0.79[b]	0.82[b]
SD	1.13	0.25	0.96	0.33	0.62[b]	0.56[b]
Lane position, SD from the midline, m						
Overall	0.50	0.18	0.50	0.27	0.90[b]	0.89[b]
1	0.45	0.14	0.44	0.20	0.80[b]	0.80[b]
2	0.50	0.21	0.50	0.27	0.87[b]	0.88[b]
3	0.53	0.21	0.55	0.33	0.89[b]	0.88[b]
SD of speed, Km/h	13.75	3.57	12.46	5.47	0.72[b]	0.66[b]
Speeding, no.	12.65	10.28	8.27	6.42	0.37	0.47[a]
Subjective sleepiness						
SSS	2.47	0.77	2.40	0.92	0.72[b]	0.79[b]
VAS, cm	7.04	1.70	6.77	1.99	0.77[b]	0.76[b]
Reported sleep						
TST, min	362.13	116.76	384.29	90.54	0.60[b]	0.68[b]
Mean TST, min	408.55	70.13	426.74	58.30	0.89[b]	0.81[b]
Awakenings, no.	1.75	1.87	1.63	1.35	0.57[b]	0.77[b]
Mean awakenings, no.	1.68	1.23	1.55	1.12	0.86[b]	0.80[b]

Data are reported as the mean (and standard deviation) of the results of the simulated driving performance and the subjective sleepiness and reported sleep time and awakenings from the 2 days of the study together with Pearson and Spearman correlation between testing day 1 vs day 2 (Coefficient refers to correlation coefficient; TTC, the time from the beginning of the simulation to the occurrence of the first crash; DA Index, ratio between wrong and total answers to divided-attention driving task; Reaction time is to divided attention driving task; Lane position is the standard deviation of lane position overall and in the first, second, and third 10-minute time blocks; Speeding, times exceeding the speed limit; SSS, Stanford Sleepiness Scale; VAS, visual analogue scale; TST, reported total sleep time in the night before the testing day; Mean TST, mean total sleep time in the week before the testing day; Awakenings, reported number of awakenings in the night before the testing day; Mean Awakenings, mean number of reported awakenings in the week before the testing day). [a]P Value < 0.05. [b]P Value ≤ 0.005.

and to the occurrence of sustained sleep of 29.0 ± 12 minutes (range 2.1-40). If the neurophysiologic examinations are considered as abnormal when the mean sleep latency to the first epoch of sleep was lower than 8 minutes, the MSLT would be indicative of increased sleep propensity in 70.8% (17 subjects) of the population, whereas the MWT would disclose reduced alertness in 29.2% (7 patients) of the sample (Table 1).

Reported Sleep and Sleepiness on the 2 Testing Days

Mean reported sleep time and number of awakenings per week and in the night before each testing day did not differ between the first and the second day of the study (Kruskall-Wallis test, asymptotic P value > 0.2) (Table 2).

Subjective (SSS and VAS) and objective (MSLT and MWT sleep latencies) sleepiness measurements assessed at different times on each day did not show significant circadian alertness variations (Kruskall-Wallis test, asymptotic P value > 0.05). Mean subjective sleepiness scores (SSS and VAS) did not differ on the 2 different days of the study (Kruskall-Wallis test, asymptotic P value > 0.7) (Table 2).

Finally, mean reported sleep time and awakenings, as well as mean subjective sleepiness measurements in the 2 testing days, were significantly and positively correlated (Spearman correlation coefficients > + 0.7, P value ≤ 0.005) (Table 2).

Driving Performance Data

Reproducibility of the Driving-Simulation Test and Learning Effect

The comparison between simulated driving performance data performed at different times on each day excluded significant differences for simulated driving performance parameters (Kruskall-Wallis test, asymptotic P value > 0.05). The comparison between mean simulated driving data performed in the first and second days of the study disclosed a significant improvement regarding the secondary tasks of the test but not in the primary vehicle-control task (Kruskall-Wallis test). The learning effect was clear for divided attention driving task (DADT), showing a lower mean divided attention index (ratio between wrong and total responses to DADT) on the second day (asymptotic P value = 0.011, confidence interval [CI], 0.008-0.013), together with a reduction in mean reaction times to DADT (asymptotic P value = 0.018, CI = 0.014-0.021), mean standard deviation of speed (asymptotic P value = 0.038, CI = 0.033-0.043), and a tendency to reduction of the times exceeding the speed limit (asymptotic P value = 0.16, CI = 0.15-0.17). The parameters measuring features connected to the primary vehicle-control task (mean number of crashes, mean time between the beginning of the simulation and the occurrence of the first crash, lane-position variability throughout the driving

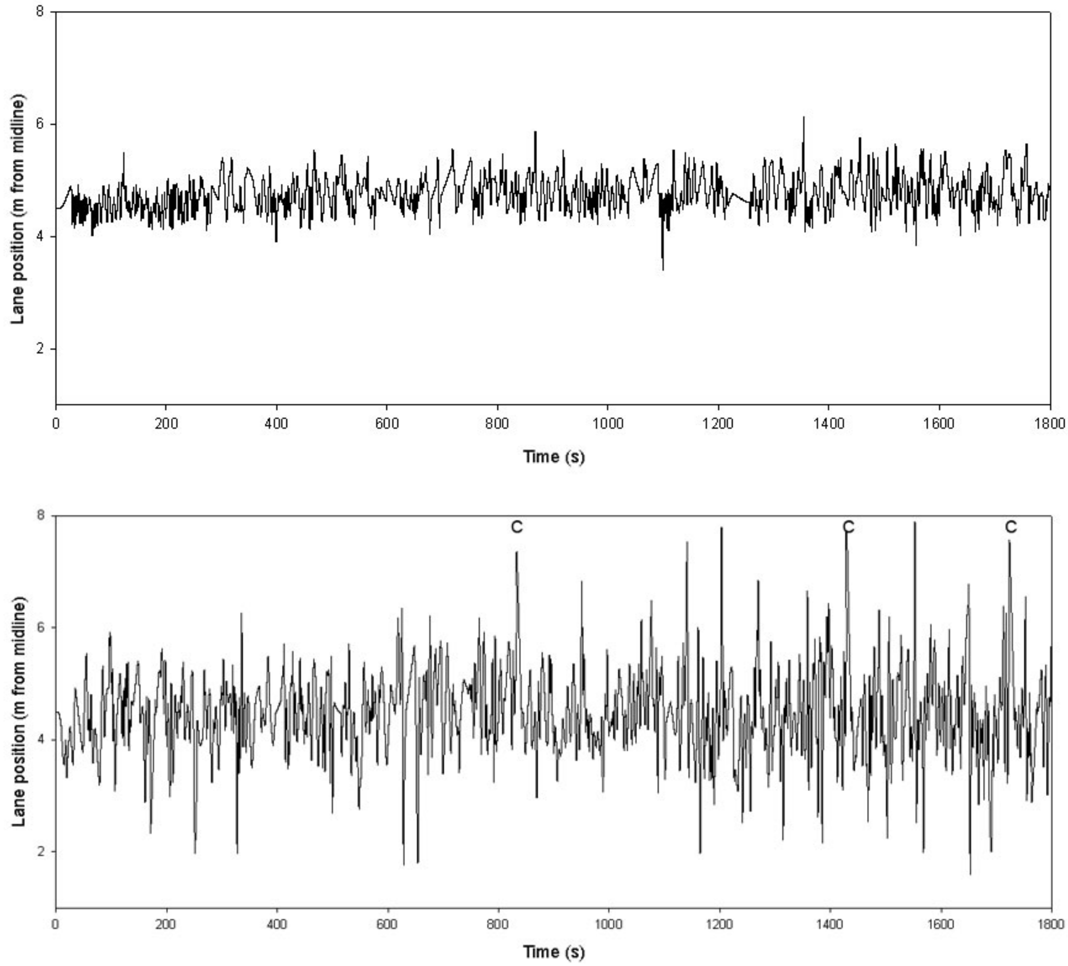

Figure 1—Example of the driving performance of a fully alert (upper part) and a sleepy (lower part) patients with obstructive sleep apnea syndrome, showing lane position and crashes (C) over time. The tracings run from left to right and represent the amount of oscillation from the midline of the simulated road over the period of 30 minutes (1800s). Note the overall worse performance of the sleepy patient with a clear deterioration over time of the steering performance associated with crash occurrence.

simulation and in the three 10-minute time blocks) did not differ on the 2 days of the study (asymptotic P value > 0.3).

Finally, mean simulated driving parameters connected to the primary vehicle-control task were strongly positively correlated between the 2 testing days (Pearson correlation coefficients > + 0.8, P value ≤ 0.005). On the contrary, mean parameters measuring secondary tasks of the driving test were less significantly correlated between the 2 testing days (Pearson's correlation coefficients > +0.6) (Table 2).

Correlations Between Simulated Driving Performance and Objective Sleepiness Measurements

We related all mean driver performance data together with mean subjective sleepiness measurements (VAS, SSS) to objective daytime sleepiness measured by the MSLT and MWT (using both the 1- and 3-epoch scoring criteria for the detection of sleep latency) via Pearson and Spearman correlations. The parameters involved in the primary vehicle-control task (number of crashes and time between the beginning of the simulation and the occurrence of the first crash and lane-position variability during the whole driving simulation and in the three 10-minute time blocks), together with subjective sleepiness measurements, were significantly correlated with MSLT and MWT results. On the other hand, some of the parameters involved in the secondary tasks of the driving test (divided attention index, mean reaction times to DADT, and mean standard deviation of the speed) correlated significantly only with MWT results.

Interestingly, the correlation coefficients of simulated driving parameters showed much higher absolute values with MWT than with MSLT and with the sustained-sleep scoring criterion compared with the single-epoch criterion in both the MWT and MSLT (Table 3).

Comparison of Simulated Driving Performance Data in Different Patients' Subgroups Based on Subjective EDS, Reported Sleepiness While Driving, Reported Car Crashes and Reported Car Crashes Subjectively Ascribed to Sleepiness

To assess the predictive validity of subjective sleepiness (as measured by ESS) and personal driving history in the past 3 years on simulated driving performance, we compared all the mean results of the simulated driving test as dependent variables, using as independent factors, subjective sleepiness (8 pa-

Table 3—Correlations Between Mean Sleep Latencies on the MSLT and MWT and Mean Driving Performance Parameters

	MSLT 1		SusMSLT		MWT 1		SusMWT	
	Pearson	Spearman	Pearson	Spearman	Pearson	Spearman	Pearson	Spearman
Crashes, no.	-0.380	-0.560[b]	-0.530[a]	-0.930[b]	-0.455[a]	-0.836[b]	-0.671[b]	-0.804[b]
TTC, min	0.483[a]	0.551[b]	0.598[b]	0.579[b]	0.732[b]	0.829[b]	0.840[b]	0.792[b]
DA Index	-0.181	-0.113	-0.325	-0.259	-0.597[b]	-0.561[b]	-0.613[b]	-0.546[a]
Mean RT, s	-0.150	-0.082	-0.253	-0.223	-0.564[b]	-0.505[a]	-0.553[b]	-0.518[a]
SD RT, s	-0.009	-0.046	-0.093	-0.142	-0.320	-0.275	-0.341	-0.298
SD Mid, m	-0.429[a]	-0.525[a]	-0.497[a]	-0.492[a]	-0.677[b]	-0.745[b]	-0.825[b]	-0.764[b]
SD1Mid, m	-0.416[a]	-0.505[a]	-0.459[a]	-0.462[a]	-0.673[b]	-0.702[b]	-0.847[b]	-0.753[b]
SD2Mid, m	-0.422[a]	-0.536[a]	-0.512[a]	-0.504[a]	-0.647[b]	-0.661[b]	-0.787[b]	-0.707[b]
SD3Mid, m	-0.439[a]	-0.561[b]	-0.502[a]	-0.528[a]	-0.634[b]	-0.717[b]	-0.797[b]	-0.755[b]
SD Speed, Km/h	-0.292	-0.291	-0.410[a]	-0.304	-0.571[b]	-0.552[b]	-0.736[b]	-0.583[b]
Speeding, no.	-0.058	-0.002	-0.070	-0.129	-0.465[a]	-0.463[a]	-0.418[a]	-0.491[a]
SSS	-0.557[b]	-0.596[b]	-0.555[b]	-0.597[b]	-0.548[a]	-0.540[a]	-0.717[b]	-0.652[b]
VAS, cm	0.523[a]	0.531[a]	0.585[b]	0.555[b]	0.585[b]	0.628[b]	0.734[b]	0.705[b]

Data are shown as Pearson and Spearman correlation coefficients between mean driving-performance parameters and mean sleep latencies, in minutes, on the Multiple Sleep Latency Test (MSLT) and Maintenance of Wakefulness Test (MWT), scored according to the first appearance of a single epoch of stage 1 sleep (MSLT1 and MWT1) or to the occurrence of sustained sleep—the first appearance of 3 consecutive epochs of stage 1 sleep or 1 epoch of any other sleep stage (SusMSLT and SusMWT). TTC refers to the time from the beginning of the simulation to the occurrence of the first crash; DA Index, the ratio between wrong and total answers to divided-attention driving task; RT, reaction time to divided-attention driving task; Mid, lane position; SD1-2-3-Mid, standard deviation of lane position in the first, second, and third 10-minute time blocks; Speeding, number of times exceeding the speed limit; SSS, Stanford Sleepinees Scale; VAS, visual-analog scale). [a]P Value < 0.05. [b]P Value ≤ 0.005.

tients with ESS score > 11), reported sleepiness while driving (17 patients), reported car crashes (16 patients), and reported car crashes due to sleepiness (4 patients) with Kruskall-Wallis nonparametric ANOVA. Subjective sleepiness (ESS score > 11) significantly affected simulated driving performance in terms of mean number of crashes (0.3 ± 0.1 vs 2.8 ± 2.9; asymptotic P value = 0.029, CI = 0.024-0.033), time to first car crash (26.9 ± 2.1min vs 15.5 ± 2.9 min; asymptotic P value = 0.034, CI = 0.029-0.038), lane-position variability throughout the simulation (0.4 ± 0.03 m vs 0.7 ± 0.1m; asymptotic P value = 0.011, CI = 0.009-0.014), and in the three 10-minute time blocks (0.4 ± 0.03 m vs 0.6 ± 0.04 m; 0.4 ± 0.03 m vs 0.7 ± 0.1 m; 0.4 ± 0.03 m vs 0.7 ± 0.1 m; asymptotic P value = 0.021, CI = 0.017-0.025; 0.007, CI = 0.005-0.009 and 0.021, CI = 0.017-0.025 for first, second, and third 10-minute time blocks, respectively). Reported history of car crashes in the past 3 years also affected simulated driving performance in terms of mean number of crashes (0.2 ± 0.1 vs 1.4 ± 0.6; asymptotic P value = 0.033, CI = 0.029-0.038), mean lane-position variability throughout the simulation (0.4 ± 0.03m vs 0.6 ± 0.05m; asymptotic P value = 0.024, CI = 0.020-0.028), and in the three 10-minute time blocks (0.3 ± 0.03 m vs 0.5 ± 0.04 m; 0.4 ± 0.03 m vs 0.6 ± 0.05 m; 0.4 ± 0.03 m vs 0.6 ± 0.05 m; asymptotic P value = 0.037, CI = 0.032-0.042; 0.021, CI = 0.017-0.025; 0.011, CI = 0.008-0.013). Reported sleepiness while driving and reported sleepiness-related crashes did not affect driving simulated performance (excluding sleepiness-related crashes on mean lane position variability in the third 10-minute time block with 0.5 ± 0.1 m vs 0.8 ± 0.3 m; asymptotic P value = 0.018, CI = 0.014-0.021). Interestingly, none of the investigated factors (ESS score, reported sleepiness while driving, reported car crashes, and sleepiness-related crashes) showed any significant impact on the secondary tasks of the driving simulation (answers to DADT, mean and SD of reaction times to DADT, mean and SD of speed and times exceeding the speed limits).

ROC Curves of Driving Simulated Performance vs MWT Results

To test the suitability of simulated driving performance for the objective evaluation of alertness, we compared single mean driving parameters measuring the primary vehicle-control task (number of crashes, lane-position variability across the whole simulation and in the three 10-minute time blocks) with the mean sleep latency on the MWT. We considered MWT "positive" for EDS in 7 patients (mean sleep latency ≤ 8 min), and for full alertness in 7 patients (mean sleep latency > 30 min). A graphic display of lane position and crash occurrence over time of an alert and a sleepy patient is depicted in Figure 1 (upper and lower part, respectively). The deterioration over time of the steering performance by means of mean lane-position variability in the three 10-minute time blocks is shown in Figure 2.

When considering the ability of the driving simulated test to detect sleepy subjects in comparison with the MWT, all the driving parameters explored were significant with an area under the ROC curves of 0.870 (± 0.076 SEM, P value = 0.005) for crashes, 0.958 (± 0.044 SEM, P value = 0.001) for lane-position variability throughout the simulation, and 0.966 (± 0.037 SEM, P value = 0.0004), 0.924 (± 0.058 SEM, P value = 0.001), and 0.966 (± 0.037 SEM, P value = 0.0004) for lane-position variability, respectively, in the first, second, and third 10-minute time blocks (Figure 3A). When considering the ability of the driving test to detect fully alert subjects on the MWT, the majority of the parameters were again significant with an area under the ROC curves of 0.920 (± 0.057 SEM, P value = 0.001) for crashes, 0.798 (± 0.093 SEM, P value = 0.024) for lane-position variability throughout the simulation, and 0.811 (± 0.088 SEM, P value = 0.019), 0.752 (± 0.101 SEM, P value

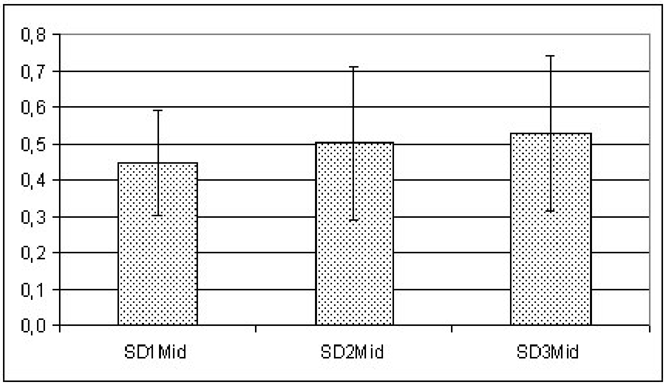

Figure 2—Mean lane position variability (and standard deviation) in the three 10-minute time blocks of the simulated driving test of 24 patients with obstructive sleep apnea syndrome. An overall deterioration over time of the tracking performance is represented by the progressive increase of lane-position variability. SD1-2-3-Mid refers to the standard deviation of lane position in the first, second, and third 10-minute time blocks.

= 0.057), and 0.815 (± 0.089 SEM, P value = 0.017) for lane-position variability, respectively, in the three 10-minute time blocks (Figure 3B).

DISCUSSION

We measured the daytime sleepiness of 30 patients with severe OSAS with concurrent (objective and subjective) methodologies to test the reliability of our simulated driving test to detect EDS. Our key findings are (1) the reproducibility of the driving test across time; (2) the stronger correlations between simulated driving performance and the ability to maintain wakefulness (MWT), compared with the propensity to fall asleep (MSLT); (3) the suitability of our simulated driving test to predict MWT results indicative of full alertness or impaired vigilance; and (4) the association of subjective EDS (ESS score > 11) and reported history of traffic crashes, with significantly lower performances on the driving simulator.

The current medicolegal problem concerning the fitness to drive of sleepy subjects, together with the ascertained relevance of sleepiness-related crashes, has led to an urgent need to identify objective tools suitable for detecting patients' ability to drive. To our knowledge, 6 studies have analyzed the correlations between simulated driving performance of patients with OSAS and MSLT or MWT results, and our study was the first to consider both MSLT and MWT simultaneously with driving simulation.[21-25,27] Reports of subjective sleepiness have obviously been disregarded because most subjects could bias their report fearing that their driving license would be revoked, irrespective of the real danger to themselves and others.

The MSLT showed a high sleep propensity (mean sleep latency < 8 min) in 71% of the population, according to international diagnostic criteria, whereas the MWT was indicative of an inability to stay awake (mean sleep latency < 8 min) in 29% of the patients, according to current practice parameters for its clinical use.[1,8] In parallel, our simulated driving test proved to be reproducible on several occasions over time without suffering from learning effect for the primary vehicle-control task

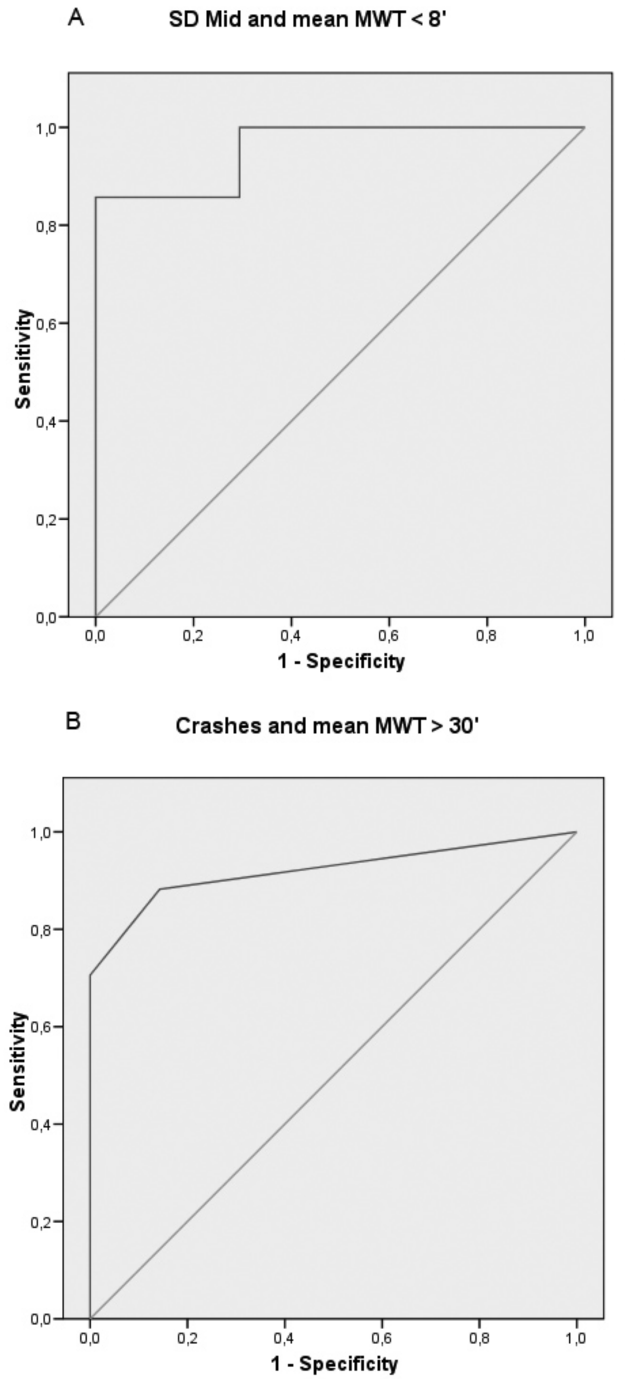

Figure 3—Receiver operating characteristic (ROC) curves between mean lane-position variability and short sleep latency on the Maintenance of Wakefulness Test (MWT) (A) and between the mean number of crashes and long sleep latency on the MWT (B). The ROC curve in **A** shows the true-positive rate (sleep latency on the MWT < 8 minutes and high lane-position variability) vs the false-positive rate (sleep latency on the MWT < 8 minutes without subjects having high lane-position variability) of the mean sleep latency on the MWT and the mean standard deviation of lane position for each patient. The ROC curve in **B** shows the true-positive rate (sleep latency on the MWT > 30 minutes and the absence of a driving-simulator crash) vs false-positive rate (sleep latency on the MWT > 30 minutes with the subjects having crashed) of the mean MWT sleep latency and the mean crash number for each patient.

(crashes, lane-position variability). The stability of the driving test (together with subjective sleepiness measures) proved that patients were in a comparable alertness condition on the 2 days of the study and that the discrepancy between MSLT and MWT results reflected complementary aspects of daytime sleepiness measured by the 2 tests themselves.[1,8] Interestingly, our simulation measured, in parallel, different aspects of drivers' conditions: driving performance was stable over time for the primary vehicle-control task (number and time to crash, lane-position variability), probably reflecting intrinsic drivers' features, whereas it showed a significant learning effect on secondary tasks (speed limits, DADT) that were clearly influenced by the cognition of the driving test itself. Driving is a complex task that necessarily requires alertness as a sine qua non for efficient sensorimotor interaction with the simulated environment.

The significant correlations of simulated driving parameters with objective daytime sleep latencies on the MSLT and MWT confirmed the relationship between simulated driving ability and vigilance, as has already been suggested in previous studies.[21-25,27] In particular, the stronger relationship between driving performance and the MWT results, compared with the MSLT results, suggests that the real condition permitting driving was closer to the ability to maintain alertness than to the proneness to fall asleep. This finding was in line with the current clinical use of MWT that is highly recommended to "assess an individual's ability to remain awake when his or her inability to remain awake constitutes a public or personal safety issue."[8] The efficacy of the MWT as a good predictor of alertness was also confirmed in a paradigmatic example of 2 aviators safely returned to flying duty despite pathologic MSLT results.[32]

Subsequently, we explored the relationships between different simulated driving parameters measuring primary vehicle control and vigilance for the detection of unquestionable EDS (mean MWT sleep latency < 8 min) and full alertness (mean MWT sleep latency > 30 min) in patients with OSAS using ROC curves analysis. Fully alert subjects with OSAS had similar lane-position variability and crash frequency as healthy subjects in normal conditions evaluated in our previous studies.[33,34] The divergent results of single driving parameters suggests that lane-position variability was more effective in the discrimination of sleepy OSAS, whereas crashes were more useful to identify fully alert patients. In this perspective, a threshold of 0.58 m for mean lane-position variability throughout the simulation would have a sensitivity of 86% with a specificity of 95% in the discrimination of patients with a mean sleep latency of less than 8 minutes on the MWT. On the other hand, a threshold of 0.12 for mean crashes (equivalent to not having a single crash in the 4 driving simulations performed during the day) would have a sensitivity of 88% with a specificity of 86% in the detection of subjects with a mean sleep latency above 30 minutes on the MWT, probably also reflecting the common "ceiling effect" of the 2 tests that finished after a specified period of time irrespective of sleep or crash occurrence.

Even if our driving simulation was suitable for the detection of impaired alertness in patients with OSAS, why should we use a driving simulation instead of the MWT? Theoretically, many reasons could justify the development of an appropriate simulated driving-performance test. Firstly, patients frequently report sleepiness while driving, a situation with external stimuli (completely different from the MWT setting). Secondly, even if patients were not able to stay awake in a boring situation, this did not automatically imply that the same impairment would appear when accomplishing a specific (even if monotonous) task.

Several studies have explored the relationship between driving simulated performance and automobile crashes in patients with OSAS, showing conflicting results.[35] Poor simulated-driving performance has been shown to be significantly (or nearly significantly) associated with increased accident rates, whereas Turkington and coworkers have identified a positive association of good tracking performance with low crash risk counterbalanced by the lack of association between poor performances and crash history in a population of 150 patients with OSAS.[36-38] Other studies have failed to find any association between on-road history and simulated driving performance.[24,39] Our approach differed from our previous study because we enrolled only patients with severe OSAS.[24] Therefore, we analyzed the driving performance of dichotomous groups of patients on the basis of reported EDS (ESS score > 11), history of road crashes, and history of sleepiness while driving or of sleepiness-related crashes. We found significantly worse simulated driving performance when patients reported EDS and history of a car crash during the last 3 years. Interestingly, the simulated performance was impaired only in the parameters connected with the primary vehicle-control task that were clearly correlated with objective daytime sleepiness, measured by means of sleep latencies on the MSLT and MWT. The association of both conditions—EDS and traffic accidents—with poorer performances on the driving simulator was of clinical relevance, even if not mirrored by an analogous association with reported sleepiness while driving or sleepiness-related crashes. We could speculate that impairment of the simulated driving performance in terms of lane-position variability was a more reliable objective measure of sleepiness than were subjective assessments and reports. In fact, our OSAS population perceived sleepiness (as proved by significant correlations between driving performance and subjective sleepiness measured by VAS and SSS, data not shown) in the laboratory setting, thus probably acting out "safe" behaviors and countermeasures to drowsy driving on the real road. The discrepancy between EDS or reported crashes and sleepiness perception while driving or sleepiness-related crashes in light of the performance on driving simulation could be interpreted as an intrinsic limitation of subjective sleepiness perception (including recall bias), mainly evident when patients were asked about the association of drowsiness to personal on-road history. Moreover, even if our patients with OSAS appeared aware of their sleepiness, we could speculate that drowsiness worsened driving performance in a subtle, not subjectively perceivable, way as mirrored by simulated driving and history of traffic crashes.

Our study had some limitations. Firstly, we performed a single nocturnal cardiorespiratory sleep study for diagnostic purposes, disregarding the potential internight variability of OSAS severity (apnea-hypopnea index). To address this shortcoming, we underline 3 points. (1) To our knowledge, there is no scientific evidence showing significant internight variability of apnea-hypopnea index in severe OSAS without positional effect (as in our patients). (2) We did not perform standard polysomnograms the nights before the 2 testing days to avoid any influence of the polysomnography setting on patients' sleep and vigilance the following day, and we relied on subjective sleep reports during the week before each testing. (3) Finally, we demonstrated that subjective sleepiness (and reported sleep) did not differ between the 2 testing days. The second limitation was that we evaluated only men. Therefore, it would be worth evaluating women with OSAS, given the reported sex difference in sleepiness perception in the general population.[7]

Our simulated driving test was suitable for objectively measuring daytime sleepiness in men with severe OSAS and for providing potentially valuable information on their fitness to drive. Further real driving studies could confirm these preliminary findings, including in women with OSAS and other medical disorders characterized by EDS.

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DISCLOSURE STATEMENT

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