Obstructive Sleep Apnea can be Provocative for Right-to-Left Shunting Through a Patent Foramen Ovale

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Study Objectives: Under particular conditions, a patent foramen ovale (PFO) can potentially give rise to ischemic stroke by means of paradoxical embolization, due to right-to-left shunt. Our study aimed to evaluate the presence of right-to-left shunt in patients with obstructive sleep apnea syndrome (OSAS) and diagnosed PFO during sleep.
Design and Setting: Assessment of provocative-only PFO and concomitant OSAS. Evaluation of right-to-left shunting during sleep by means of transcranial doppler with contrast medium injected in the cubital vein.
Participants: 10 consecutive patients affected by PFO detectable only under Valsalva maneuver during wakefulness and affected by OSAS (mean age 52.8 ± 10.7 years).
Interventions: Patients underwent transcranial doppler with injection of agitated saline solution mixed with air during normal breathing and during periods of apnea/hypopnea in nocturnal sleep.

Measurements and Results: Right-to-left shunt was present in 9 patients out of 10 and appeared during obstructive apneas longer than 17 seconds. In 1 out of 10 patients, only hypopneas occurred and no right-to-left shunt could be shown. The number of microembolic signals detected during periods of nocturnal apnea was positively correlated with the number detected during Valsalva maneuver in wakefulness (p<0.0001).
Conclusions: In the nocturnal sleep period, right-to-left shunt can occur during single obstructive apneas in patients with OSAS and concomitant presence of PFO. This can be a risk factor for cerebrovascular diseases. This risk could probably increase proportionally to the respiratory disturbance index of these patients.
Key words: hypoxemia, intracardiac shunting, right-to-left shunt, obstructive sleep apnea, OSAS, patent foramen ovale, apnea length, transcranial Doppler sonography, stroke.

INTRODUCTION

PATENT FORAMEN OVALE (PFO) IS THE MOST FREQUENT INTERATRIAL COMMUNICATION. The prevalence of PFO varies from about 10% to 35% of the general population, as described by studies with identification by autopsy, right-heart catheterization, or transesophageal echocardiography.[1-6] In subjects with ischemic stroke, prevalence of PFO is approximately 20% to 54%,[7-10] reaching 47% to 77%[11-15] if only patients with cryptogenic ischemic stroke are studied.

It is thought that a PFO can potentially give rise to ischemic stroke by means of paradoxical embolization,[13,16] and it is considered a major cause of stroke in young people.[16,17] Because of its valvelike nature, PFO may permit right-to-left shunting as the result of a transient, instantaneous pressure gradient between the right and the left atrium during the cardiac cycle.[18,19] However, shunting is not common in basal conditions (ie, "at rest shunting PFO"). In fact, the maximum level of shunting is usually reached during provocative maneuvers, which increase right cardiac chamber pressure, like Valsalva maneuver (i.e. "provocative-only shunting PFO"). Some everyday life events—like coughing, playing sports, lifting heavy weights, and playing breath instruments—may act as a provocative maneuver and may allow a right to left shunting through a usually silent PFO. However Valsalva maneuver is considered the gold standard for the evaluation of provocative-only shunting PFO.[20]

Transient right-sided pressure elevation occurs also during obstructive sleep apneas. Several studies have investigated hemodynamic changes associated with repetitive obstructive sleep apneas. The key observation is a rise in systemic and pulmonary arterial pressure from the beginning of the apnea to the immediate postapneic segment.[21] Sleepapnea effects on intrathoracic hemodynamics could be compared with those of a sequence of several repetitive Müller maneuvers alternated with Valsalva maneuvers at the end of the obstructive part of the "apnea complex."[22,23]

In Shanoudy et al's study, patients with obstructive sleep apnea syndrome (OSAS) a higher prevalence of PFO (69% vs 17% in the control sample) was found.[24] In the same study a significant hypoxemia after Valsalva maneuver in patients with OSAS and PFO was also found. According to these authors, the hypothesis of a right-to-left shunting during apnea could emphasize the well-known feature of oscillating blood oxygen saturation pattern occurring during sleep in patients with OSAS.

Until a few years ago transesophageal echocardiography with contrast medium, which is a semiinvasive technique, was the only reliable tool with sufficient sensitivity and specificity for the evaluation of right-to-left shunt due to the presence of PFO. A number of studies[14,25-29] have recently shown that contrast-enhanced transcranial Doppler (TcD) examination of the middle cerebral artery is highly sensitive and specific compared with contrast transesophageal echocardiography to detect right-to-left shunt. Contrast TcD presently in use is a noninvasive and safe technique that does not cause patient discomfort[25,28] and seems to be suitable for use during spontaneous sleep. In our study, we used this technique to investigate the presence of intracardiac shunting of venous blood through a usually silent PFO during obstructive apnea events in sleep.

PATIENTS AND METHODS

Study sample

A population of 78 patients affected by moderate to severe OSAS were tested for the presence of PFO. We studied 10 consecutive patients out of this population (mean age 52.8 ± 10.7 years)—7 males and 3 females—who had provocative-only shunting PFO (right-to-left shunt

Disclosure Statement
Nothing to disclose

only during Valsalva maneuver) and satisfied the following including criteria.

Patients with prior myocardial infarction, unstable angina, or decompensated congestive heart failure within 3 months prior to the study or patients with an active infectious pulmonary process, prior pulmonary embolism, or pulmonary infarction were excluded. Furthermore, patients were also excluded if either stenosis of extracranial arteries or blood-flow-velocity alterations of intracranial arteries were found on bilateral Doppler sonography.

Inclusion criteria were a respiratory disturbance index (RDI), greater than 15 (Table 1), accompanied by > 4% fall of SaO_2 with respect to wakefulness recorded baseline SaO_2, and presence of "provocative-only" PFO.

Before performing examinations, we obtained all subjects' informed consent according to the Helsinki declaration. In Table 1 the clinical characteristics of these patients are summarized.

Diagnosis of OSAS

The presence of OSAS was assessed by means of standard nocturnal polysomnography, which included electroencephalogram, electrooculograms, submental and anterior tibial electromyograms, measurements of oronasal airflow, chest wall and abdominal excursions, oxygen saturation, and single-lead electrocardiogram.

Polysomnograms were scored following the standard sleep-staging criteria.[30] Respiratory events were scored manually by one single expert. The criterion to define an obstructive apnea was a complete or almost complete cessation of airflow (at least >80% of baseline airflow amplitude), as measured by the amplitude of the thermocouple signal, lasting 10 seconds and associated with a 4% decrease in SaO_2. The criterion to define hypopnea was a clear reduction in the amplitude of the thermocouple signal to below 50% of the amplitude of baseline breathing for 10 seconds and associated with a 4% decrease in SaO_2. On the grounds of these conservative criteria the number of apneas and hypopneas per hour (respiratory disturbance index, RDI) was computed. We included in the study only patients who showed an RDI >15 (mean 60 ± 22).

PFO assessment

In all patients, the presence of right-to-left shunt was diagnosed by means of TcD (Multidop DWL, Sipplingen, Germany) with injection of contrast medium. The machine employed a 64-point fast Fourier transform analysis and used a graded color scale to display the intensity of the Doppler signal received. Every examination was recorded on-line onto the hard disk and was analyzed off-line.

The basic principle is that a gaseous contrast medium injected into a peripheral vein is expired at the pulmonary level in physiologic condition. In the presence of a PFO, microbubbles pass from the right to the left circulation during the cardiac cycle and enter the systemic circulation; the microbubbles can thus be recorded by transcranial Doppler in the middle cerebral artery as microembolic signals. Performance criteria of contrast TcD for the diagnosis of right-to-left shunt followed recommendations put forth at the consensus conference held in Venice in April 1999 at the 4th Meeting of the European Society of Neurosonology and Cerebral Hemodynamics.[20] With the patient in supine position, blood flow from the middle cerebral artery was recorded bilaterally and simultaneously to increase sensitivity[31] by two transcranial pulsed-wave 2 MHz ultrasound probes fixed to the patient's head at the level of the temporal bone window. An intravenous Daflon catheter (#18) was inserted into the cubital vein and was connected to a 250 mL bottle of physiologic solution by means of a flexible tube to maintain venous access for the duration of TcD. Two 20 mL syringes were prepared: one containing 9 mL of physiologic solution and the other containing 1 mL of air. By means of a three-way stopcock, the contents of both syringes were rapidly mixed until a homogeneous solution was obtained (ie the contrast medium). The contrast medium was rapidly injected (<5 seconds) in bolus form with the patient at rest, (session A) during physiologic respiration. The examination was subsequently repeated with maximal magnitude Valsalva maneuver, (session B). In session B, 5 seconds after the injection of the contrast medium, the examiner ordered the patient to begin Valsalva maneuver (VM). The overall Valsalva maneuver duration was 10 seconds. The patients were trained in advance to perform the VM and the efficacy of the Valsalva maneuver in magnitude and consistence for the 10 seconds was ascertained beforehand through the reduction of the systolic flow velocity on the middle cerebral artery by at least on third.

The criterion for PFO diagnosis was the recording of at least one clear, reproducible, microembolic signal, excluding any kind of artifactual origin of the signal, within 20 seconds of the injection.[20,28] The appearance of microembolic signals is characterized by a typical visible and audible (click, chirp, whistle) short-duration high-intensity signal within the Doppler flow spectrum, thus allowing the recording of the time of appearance of the first microembolic signal.[29,32] The time window applied (20 seconds) is widely used[20] and is considered as evidence of right-to-left shunting at the atrial level, ruling out the recording of pulmonary shunts.[20,26] However, one single study reported shorter passage times from the cubital injection site to the middle cerebral artery through an intracardiac shunt (11 seconds) with respect to pulmonary passage (14 seconds).[31]

For every session, the number of microembolic signals was recorded, counted by a specific tool of the software package of TcD (Multidop

Table 1—General characteristics of the sample and number of injections during the three respiratory conditions.

Sub.	Age (yrs.)	Sex	BMI	RDI	PSG for diagnosis of OSAS				Wakefulness session (Valsalva maneuver)		Sleep session		
					Mean Apnea length (sec.)	SaO2 (%) lowest during sleep	SaO2 (%) baseline (wake)		Latency (sec)	Nr. MS	Nr. of injection during… Normal breathing	Hypopnea	Apnea
1	52	F	34	48	34	63	94		7	8	2	8	0
2	61	M	29	76	15	54	93		7	5	1	1	7
3	60	M	30	54	27	60	95		5	20	2	2	6
4	40	M	34	80	41	41	97		7	6	1	1	7
5	30	M	27	91	33	86	97		7	25	2	0	8
6	55	M	27	39	35	79	95		5	15	1	1	7
7	67	M	27	18	23	89	98		7	3	1	1	7
8	52	M	35	60	38	37	95		5	3	2	1	7
9	53	F	35	55	45	64	94		6	35	1	1	7
10	58	F	33	80	25	86	96		8	2	2	0	6
Mean	53		31	60	32	66	95		6	12	Total 15	16	62

Sub, subject; *BMI*, Body Mass Index; *RDI*, Respiratory disturbance Index [# (apnea + hypopnea)/hour]; *SaO*2, arterial oxygen saturation; *MS*, microembolic signals

DWL, Sipplingen, Germany), and the latency were collected separately. Latency was defined as the time from the start of the injection to the recording of the first microembolic signal.

The recording of microembolic signals in basal conditions (session A) accounted for a PFO with at rest shunt, while PFO with provocative-only shunt was defined on the basis of the recording of microembolic signals only with Valsalva maneuver (session B). Extents of right-to-left shunt were classified as no right-to-left shunt (0 microembolic signals), low-grade shunt (1-10 microembolic signals), medium-grade shunt (11-20 microembolic signals), high-grade shunt (>20 microembolic signals) and without curtain effect or with curtain effect (ie the microembolic signals were so numerous as to be no longer distinguishable separately). The number of microembolic signals recorded in the Valsalva condition are listed in Table 1.

Sleep studies

The 10 patients underwent a nocturnal polysomnographic session with parallel TcD recording (Figure 1).

To avoid sleep disturbance by TcD recording, the probes used during the sleep studies were two flat transcranial pulsed-wave 2 MHz ultrasound probes, which were attached bilaterally to the patient's head and held in position by a special probe-holder belt. In each patient, a maximum of 10 injections of contrast medium was made in three respiratory conditions (normal breath, hypopnea, and apnea) with at least a 5-minute time interval between each injection (Table 1). Injection start was noted on the polysomnographic record by means of a separate marker channel, allowing exact analysis of the moment of injection and hence of latency. Methods and criteria for right-to-left shunt recognition were the same as in the wake session.

For every injection, we collected data about the respiratory condition (normal breathing, hypopnea, or apnea), the duration of the respiratory event (for hypopnea and apnea), the time of injection with respect to the duration of the respiratory event (first, second or third), the number of recorded microembolic signals, and their latency.

Statistical Analysis

The hypothesis that statistically significant influences on the occurrence and extent of right-to-left shunt could be exerted by gender, age, body mass index, RDI, lowest value of arterial oxygen desaturation, extent of right-to-left shunt in wakefulness, respiratory condition, length of respiratory event, and moment of injection in relation to the event was tested by means of multiple regression. When the occurrence of right-to-left shunt—which is a dichotomy—was considered as the dependent variable, the logistic regression was applied. Ordinary linear regression was used to analyze the extent of right-to-left shunt (expressed by the number of microembolic signals), restricting the analysis to the events in which the right-to-left shunt had occurred. In both cases the stepwise procedure was applied for the selection of the relevant regressors. To fur-
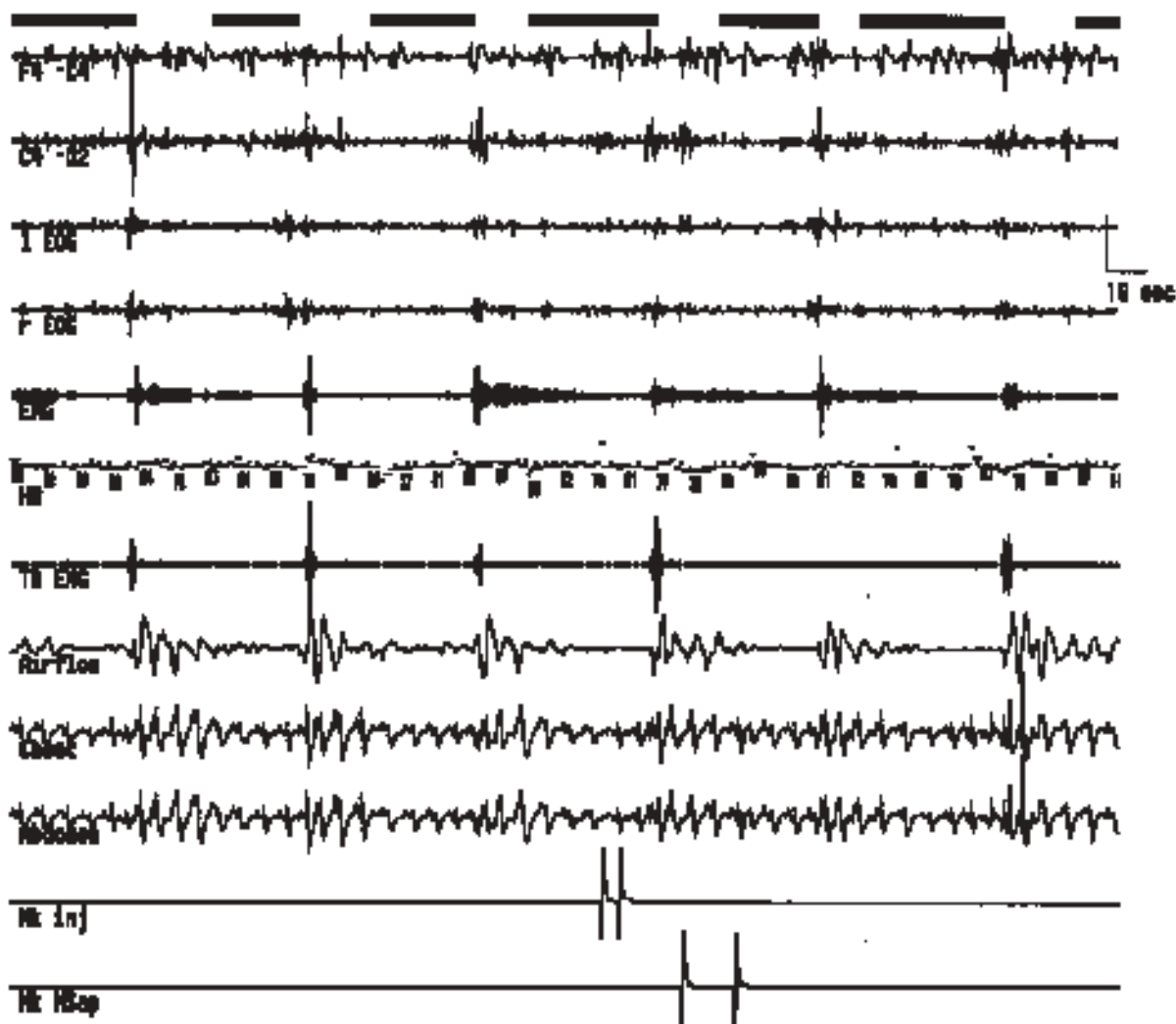
Figure 1—A 5-minute page (sleep stage 2) of time compressed polysomnographic record. From top to bottom are represented the two EEG channels (**F4-C4, C4-O2**), the two electro-oculograms (left [**l**] and right [**r**] side EOG) channels, the electromyogram (**EMG**), one channel for the heart rate (**HR**) one channel for legs' motor activity (**TB EMG**) and the three respiratory channels (**airflow**, **chest** wall and **abdominal** effort). **"Mk inj"** is the marker-channel, where begin and end of contrast medium injection are recorded. **"Mk MSap"** is the marker-channel, where the time of appearance of microembolic signals is recorded.

Table 2—Number of observed right-to-left shunts by means of microembolic signal recordings with respect to the number of injections for each patient.

Number of right-to-left shunts during night sleep / Number of injections

Subject	Normal breathing	Hypopnea	Apnea
1	0/2	0/8	-
2	0/1	0/1	3/7
3	0/2	0/2	5/6
4	0/1	0/1	7/7
5	0/2	-	8/8
6	0/1	0/1	7/7
7	0/1	0/1	2/7
8	0/2	0/1	7/7
9	0/1	0/1	5/7
10	0/2	-	2/6

ther explore the relationship between the extent of spontaneous right-to-left shunting during sleep and right-to-left shunting evoked by VM during wakefulness, the maximum value of microembolic signals recorded for each subject during sleep, was related to the value recorded after VM by means of a simple linear regression.

All computations were performed using the SAS package (software version 6, SAS Inc).[33]

RESULTS

During the study night, all patients presented apneas or hypopneas with a respiratory pattern matching the diagnostic night. One patient (subject 1) presented exclusively hypopneas both during the diagnostic night and the study night (Table 2). In this patient, no right-to-left shunt could be detected. In all other patients, right-to-left shunt was detected during periods of apnea but not during hypopneas (Table 2). During apneas, right-to-left shunt could be found only for events lasting at least 17 seconds (Table 2, Figure 2). Wherever a right-to-left shunt was detected during an apnea, microembolic signals appeared within 7 seconds following apnea termination (mean: 3.9 ± 2.4 seconds).

The logistic regression applied to the occurrence of right-to-left shunt by means of the stepwise procedure, selected the respiratory condition (apnea) and the length of the respiratory event as relevant regressors and then stopped due to the complete separation of data. This reaffirmed a

threshold effect of apnea duration in activating right-to-left shunt. The stepwise procedure of the linear regression applied to the number of microembolic signals, selected the extent of right-to-left shunt (ie, the number of microembolic signals) during VM in wakefulness as the only statistically significant regressor (regression coefficient = 0.35 p<0.0001 – see table 3). Body mass index and lowest value of SaO_2 during the diagnostic night showed a trend to correlation, though they did not reach statistical significance. No other parameter significantly explained intra-subject variations in the number of microembolic signals (Table 3).

Regression analysis of the maximal microembolic signal values during sleep apneas for each subject versus the microembolic signal values during VM in wakefulness, showed a correlation between the two variables. When the intercept—which was not statistically significant—was zeroed, the regression coefficient was 0.65 (p< 0.0001) (Figure 3).

DISCUSSION

A PFO, usually hemodynamically silent, can give origin to a blood passage from right atrial circulation to left atrial circulation under particular conditions of increased arterial pressure in the pulmonary circle. The main finding is that our study demonstrates for the first time that such a condition is achieved not only during the execution of the Valsalva maneuver, but also during spontaneously occurring obstructive sleep apneas. Such a right-to-left shunt was not found, in either normal sleep breathing conditions or during hypopneas, but it occurred each time after long-lasting apneas (at least 17 sec).

The timing of injection could be of some importance due to the impossibility of stating a priori apnea duration and, therefore, injecting too early or too late in relation to the occurrence of the maximum intraatrial pressure elevation. Such a possibility was ruled out by the nonsignificant role of the timing of injection. The occurrence of shunts was related only to the occurrence of obstructive sleep apneas of sufficient length. The minimal apnea length acted only as a permissive subject-independent threshold, while no correlation was found with the number of microembolic signals passing through the foramen. The number of microembolic signals detected during apneas is positively correlated only with the number of signals found during wakefulness in Valsalva condition. Within the limits of the assumption that the number of detectable microembolic signals can be considered as a measure of the diameter of
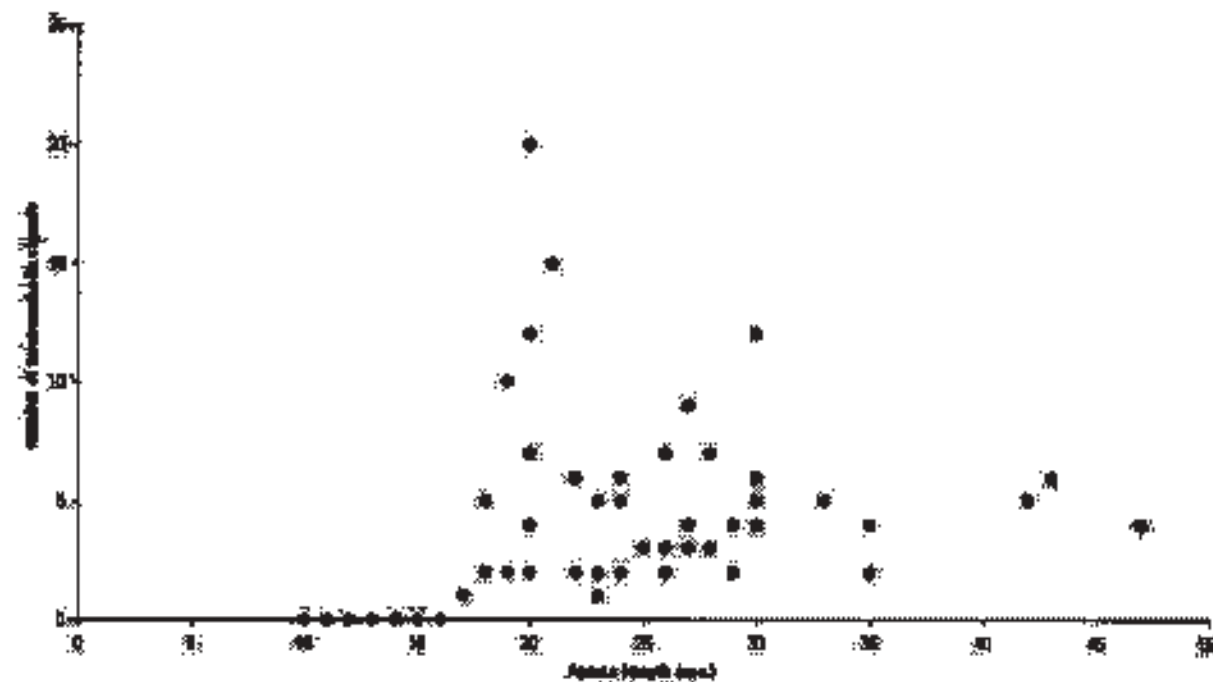
Figure 2—Scatterplot of the number of microembolic signals recorded (y-axis) after each injection given in apnea condition, as function of the apnea length (x-axis).

the foramen, the extent of the shunt during apneas seems to be correlated with the size of the PFO. On the other hand, the extent of the shunt was not significantly influenced by demographic parameters, such as age and sex, or by clinical parameters thought to be markers of the seriousness of the illness, such as RDI, mean length of apneas, or baseline SaO_2 values. However, the small number of subjects limited the sensitivity of the test for the evaluation of factors influencing intersubject variability of microembolic signals. A larger group of subjects is needed to verify the influence of the clinical and physiologic parameters on the shunt, with particular reference to the ones showing higher—though not significant—correlations, such as the BMI and lowest SaO_2.

Our study also has some constraints. The high number of monitored variables from both PSG and contrast TcD needed a complex recording technique. To prevent significant sleep disturbances during monitoring, we chose to omit esophageal pressure measurements. The absence of these data unfortunately does not allow the formulation of consistent hypotheses about hemodynamic mechanisms of shunting during obstructive sleep apnea. However, some interpretations could be extracted from literature. In previous studies, high esophageal pressure oscillations with values as low as -80cm H_2O were reported during apnea. They were associated with leftward shift of the interventricular septum and pulsus paradoxus (ie, inspiratory decrease in systolic blood pressure of 10 mm Hg or more).[22,34] Other previous findings reported an increased filling of the right ventricle during the inspiration effort against a closed upper airway, with displacement of the interventricular septum and transmission of right ventricle pressure increase to the atrial chamber.[22] Obstructive apnea starts with an inspiratory effort against a closed upper airway (ie, Müller maneuver), followed by sequences of other Müller maneuvers and, if the obstructive apnea is long enough, the likelihood of alternating sequences between Müller and Valsalva maneuver increases.[22,23] The Valsalva maneuvers, which occur in the latter part of an obstructive apnea, however, seem to give rise only to a relatively small increase in end-expiratory pleural pressure in contrast with the relatively large decrease in end-inspiratory pleural pressure (ie, Müller maneuver). However, in our study, the appearance of right-to-left shunts for apneas with a length of at least 17 seconds should not be simply correlated with the magnitude of Müller or Valsalva maneuver, per se, but

Table 3—Multiple regression analysis of the number of microemboli signals (MS) during apneas vs. possible relevant factors.

A) Parameter estimated after the procedure for stepwise selection of significant factors.

The only factor significantly correlated to the number of microembolic signals recorded during apneas was the number of microembolic signals recorded in Valsalva condition during wakefulness (**# MS during Valsalva maneuver**), which is the measure of the maximal possible extent of right-to-left shunt.

Variable	Parameter estimate	Standard error	F-value	Pr>F
Intercept	0.868	0.859	1.02	n.s.
# MS during Valsalva maneuver	0.350	0.062	32.02	<0.0001

B) Partial correlation values between the number of microemboli signals (MS) during apneas and factors excluded by the regression analysis, controlling for the only significant regressor (number of microembolic signals during Valsalva maneuver in wakefulness).

Variable	Correlation coefficient	Significance level
Single apnea length during injection	-0.013	0.933
Age	+0.143	0.350
Body mass index	+0.287	0.056
RDI	+0.048	0.751
Lowest SaO_2	-0.267	0.076
Gender	-0.067	0.661
Baseline SaO_2	-0.236	0.119
1/3 of injection	+0.113	0.460
Mean TST apnea length	-0.105	0.492

RDI, respiratory disturbance index; **SaO₂**, arterial oxygen saturation; **1/3 of injection,** the time of injection with respect to the duration of the respiratory event (first, second and third 1/3); **TST**, total sleep time.

with its swings of increasing and decreasing effects in pleural pressure. This could directly influence the interatrial pressure balance and, on the other side, also increase inspiratory venous return. In fact, this is suggested by a study reporting improved diagnostic accuracy in the evalua-
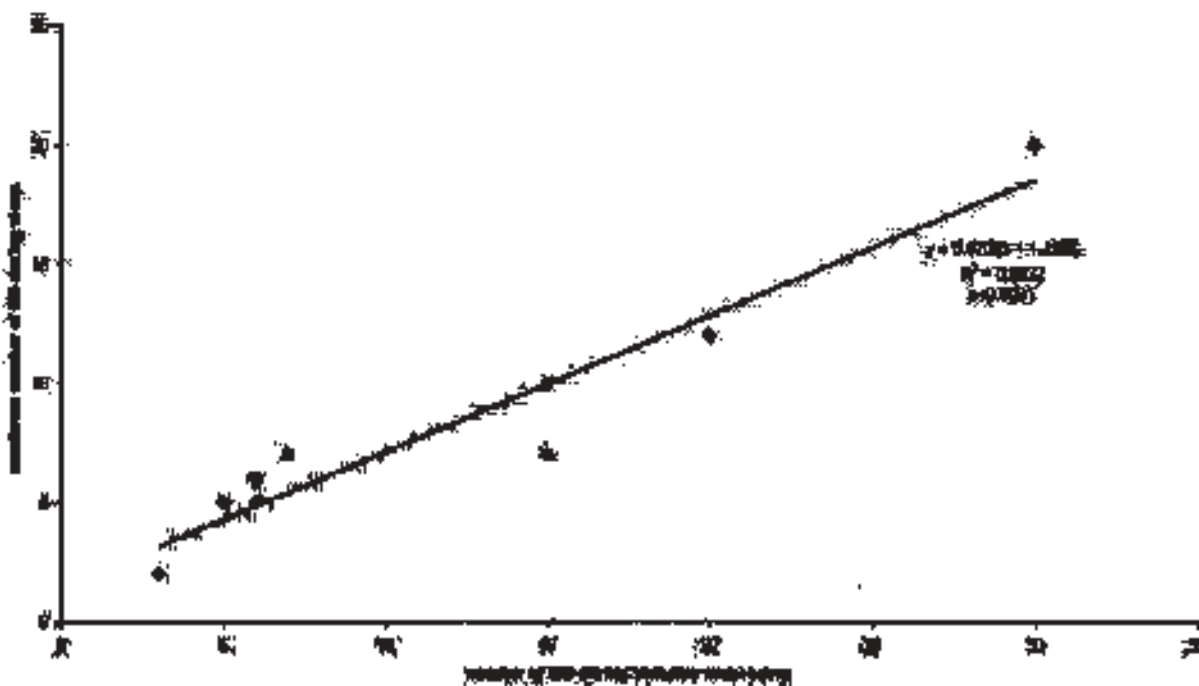
Figure 3—Scatterplot of the maximum number of microembolic signals (MS) recorded during obstructive apneas in sleep (y-axis) with respect to the number of MS recorded during Valsalva maneuver in wakefulness (x-axis). Linear regression indicates the correlation between the two variables (p<0.0001).

tion of atrial septal defects by employing a Valsalva maneuver immediately followed by a Müller maneuver to enhance the right-to-left shunt.[35] Large inspiratory increase in venous return during obstructive apnea and the persistence during wakefulness of venodilatation in OSAS patients has been demonstrated in animals and humans.[36-38]

Our research study presents only preliminary data, and our main objective was to evaluate whether the presence of a provocative-only PFO could be considered a risk factor for stroke in subjects with OSAS. In fact, enhanced risk for cerebrovascular disease in patients with OSAS with respect to normal population, was shown in previous studies.[39-41] The strong association between sleep apnea disorder and stroke is further supported by a high prevalence of OSAS (62.5%-80%) in patients with transient ischemic attack or stroke.[41] In these studies, features not related to the presence of PFO were investigated, especially hematologic features that increase whole blood viscosity[42] and that are considered responsible for the reactive polycythemia in patients with OSAS. Platelets also have an increased tendency to aggregate in the circulation,[43] thus forming microemboli.

The importance of a PFO as a risk factor for the occurrence of an ischemic stroke by means of paradoxical embolization is still a question open to debate.[44,45] Many factors, such as the size of the foramen, membrane mobility, and coexistence of embolic sources are thought to play an important role.[46-48] The importance of provocative maneuvers and of events able to increase the right chamber pressure, as a potential factor of increased risk for stroke, were stressed.[29,49,50] Some other authors[13,46] however, did not find any correlation between the occurrence of stroke and circumstances able to increase right chamber pressure in patients with provocative-only shunts.

Our data demonstrate that sleep apnea in the presence of a PFO is a condition that greatly favors the occurrence of a shunt. Consequently, the importance of the coexistence of the two conditions as an adjunctive potential risk factor should be taken into due consideration, even more in relation to the high prevalence of PFO (69%) found in patients with OSAS.[24]

Clinical practice shows that the RDI of patients with OSAS can range from 10 to more than 100 apneas per hour and a large number of apneas are often longer than 17 seconds. Hence it can be supposed that the association of both OSAS and provocative-only shunting PFO may increase the exposure time for paradoxical embolism in a quite similar way as in patients with the condition of at-rest patency in the absence of OSAS.

Therefore, in our view, a timely diagnosis of PFO in patients with OSAS could be an important measure to reduce the risk of stroke, permitting additive approaches such as surgical closure of the PFO and pharmacologic treatment.

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