REVIEW

Patent foramen ovale and obstructive sleep apnoea: From pathophysiology to diagnosis of a potentially dangerous association

Foramen ovale perméable et syndrome d’apnées obstructives du sommeil : de la physiopathologie au diagnostic d’une association potentiellement dangereuse

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Summary Patent foramen ovale and obstructive sleep apnoea are frequently encountered in the general population. Owing to their prevalence, they may coexist fortuitously; however, the prevalence of patent foramen ovale seems to be higher in patients with obstructive sleep apnoea. We have reviewed the epidemiological data, pathophysiology, and the diagnostic and therapeutic options for both patent foramen ovale and obstructive sleep apnoea. We focus on the interesting pathophysiological links that could explain a potential association between both pathologies and their implications, especially on the risk of stroke.

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MOTS CLÉS
Foramen ovale perméable

Résumé Le foramen ovale perméable et le syndrome d’apnées obstructives du sommeil sont fréquemment rencontrés dans la population générale. En raison de leur prévalence, ils peuvent coexister fortuitement mais la prévalence du foramen ovale perméable semble néanmoins être

Abbreviations: AHA, American Heart Association; AHI, apnoea-hypopnoea index; ASA, atrial septal aneurysm; CI, confidence interval; CPAP, continuous positive airway pressure; ESO, European Stroke Organisation; FDA, Food and Drug Administration; HR, hazard ratio; OR, odds ratio; OSA, obstructive sleep apnoea; PFO, patent foramen ovale; POS, platypnoea and orthodeoxia syndrome; TIA, transient ischaemic attack; TOE, transeosophageal echocardiography; TTE, transthoracic echocardiography.

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Background

PFO and OSA, both of which are common in the general population, have mostly been studied separately. During the past decade, several studies suggesting an association between PFO and OSA have been published. Our aim is to provide clinicians with a review of all the available data concerning this potential association.

First, we will define PFO and OSA, and summarize the available epidemiological data. The diagnostic criteria and the techniques of detection are discussed. We will then focus on the interesting potential pathophysiological links between PFO and OSA, which should encourage recognition of this association. The specific case of stroke is discussed as a potential dangerous consequence of this association. We conclude with the clinical implications and possible future treatment strategies.

Patent foramen ovale: definition and epidemiology

PFO is an embryological remnant of the foetal circulation caused by incomplete fusion of the septum primum and secundum. This valve-like opening represents the most frequent interatrial communication. The prevalence of PFO is estimated to be 10–30%. The prevalence of PFO in the general population is 20.2% during the ninth and tenth decades [6]. However, the size of the foramen tends to increase with age, suggesting that small PFO may seal with time [6].

In most cases, PFO remains asymptomatic, but it may also have important clinical consequences. No specific symptoms, other than the POS in severe cases, are directly related to PFO, but when right atrial pressure exceeds left atrial pressure (e.g., Valsalva), right-to-left shunting may occur, allowing venoarterial ("paradoxical") systemic embolization and passage of deoxygenated blood in the left atrium.

Patent foramen ovale and associated diseases

Despite numerous studies, a direct relationship between paradoxical embolization through PFO and stroke remains difficult to prove. A meta-analysis of case-control studies in patients with otherwise unexplained ("cryptogenic") stroke showed, in 2000, that PFO was more prevalent in such patients, particularly in the young [8]. Another more recent study extended this observation to patients > 55 years of age who suffered stroke (28.3% vs 11.9%; P < 0.001) [9].

It has not, however, been possible to show that patients who have never had a stroke are at increased risk for a first event in the presence of a PFO and/or an ASA [2,3,10]. This may be due to the low relative stroke risk of a PFO compared with other stroke risk factors. Larger cohorts with longer follow-up would therefore be required to show such a correlation [11]. The risk of recurrence after a cryptogenic stroke is also lower than after cardiac embolism (e.g., atrial fibrillation) or after stroke due to large artery atherosclerosis. Moreover, it has been difficult to prove that patients with a PFO and otherwise cryptogenic stroke have an increased recurrence risk [12]. The risk of recurrence after cryptogenic stroke might even be the same as in a patient without PFO. Finally, the presence of an ASA, a large right-to-left shunt, and the coexistence of prothrombotic states seems to increase the association between PFO and cryptogenic stroke, but this has not been uniformly proven [13–18].

The potential correlation between migraine and PFO is also intensely debated, and illustrates the difficulty in assessing an association between PFO and another definite pathology with epidemiological studies. The prevalence of PFO in patients who have migraine with aura seemed to be higher (28–48%) than in controls [19–25]. After encouraging reports in case series indicating a potential benefit on migraine recurrence after PFO closure [26], the first randomized, prospective, sham-control trial could not confirm these effects [20].

PFO has also been implicated in decompression sickness. Divers with PFO have a higher load of small ischaemic brain lesions [27]. Also, the prevalence of PFO in divers who have already experienced a major event of decompression illness is higher than in divers who have not; and small PFO seem to present less risk of decompression illness [28,29].

Obstructive sleep apnoea: definition and epidemiology

OSA is a common sleep disorder, described as repeated closure of the upper airway during sleep. The obstruction may be due to: a decreased activity of the pharyngeal musculature; pharyngeal fat deposits; and mucosal inflammation leading to occlusion or near occlusion of the upper airway [30,31]. OSA is usually defined as more than five episodes of apnoea or hypopnoea per hour of sleep. The AHI is usually used to assess the severity of sleep apnoea (mild: 5–15; moderate: 15–30; severe > 30 events/h) [32,33]. Young et al. studied a middle-aged population and described a prevalence of OSA (AHI ≥ 5) of 9% in women and 24% in men.
Patients with sleep apnoea syndrome have AHI ≥ 5 and symptoms during the day, principally hypersomnolence due to sleep fragmentation. The prevalence of this syndrome in the study by Young et al. was 2% in women and 4% in men [34]. It is also associated with an increased incidence of hypertension, cardiovascular disease and traffic accidents [35—39]. OSA has also been reported in association with nocturnal arrhythmias and stroke [40,41]. OSA is frequently undiagnosed, leading to a substantial cardiovascular morbidity.

Obstructive sleep apnoea and risk of stroke

Case-control and cross-sectional studies have shown an association between snoring and cardiovascular disease [42,43]. An association between sleep-disordered breathing and stroke has also been evoked for many years [39,44,45]. In 2005, Arzt et al. published cross-sectional and longitudinal analyses of 1475 members of the general population [46]. They found that an AHI ≥ 20 increased the chance of stroke compared to an AHI ≤ 5 (OR 4.33, 95% CI 1.32—14.24; P = 0.02) [46]. In the prospective part of the study (n = 1189), the adjusted OR for a first-ever stroke in the subsequent 4 years in a patient with AHI ≥ 20 vs ≤ 5 was 3.08 (P = 0.12) [46]. Although the strong correlation between OSA and cardiovascular disease may in part be due to overlapping risk factors for atherosclerosis [47], there is evidence that OSA is an independent risk factor considering the potential mechanisms increasing the risk of stroke in OSA patients [41].

Several hypotheses may explain the increased risk of stroke in OSA patients [48—50]. Hypoxaemia and decreased cerebral perfusion pressure (due to increased intracranial pressure at the end of the apnoea) are considered to be determinants of cerebral nocturnal ischaemia. Haematological parameters may also play a role, such as enhanced platelet aggregation, increased viscosity, and higher fibrinogen concentration [48,50—53]. This increase in fibrinogen may decrease with CPAP [54]. Cardiac arrhythmias are more frequent in OSA patients, particularly atrial fibrillation, which is a risk factor for stroke [55,56].

Diagnosis

The prevalence of a disease is dependent of the definition and the technique of detection used [57]. The choice of the diagnostic tool and a strict protocol are crucial to diagnose PFO and OSA.

Diagnosis of patent foramen ovale

PFO is usually diagnosed with TTE or TOE, with injection of agitated saline contrast to create microbubbles. Contrast TOE is considered as the gold standard. The definition of PFO is based on echocardiographical criteria: ≥ 3 bubbles (≥ 1 according to some authors) must be observed in the left atrium within three cardiac cycles after the entry of the bubbles in the right atria. Direct visualization of bubbles passing through the PFO channel may also be considered as proof of PFO.

The sensitivity of microbubble assessment of PFO is increased by provocative manoeuvres such as cough [58] and voluntary Valsalva [5,59]. At the end of Valsalva strain, a transient pressure elevation inside the right-sided cardiac chambers is observed, increasing the likelihood of a right-to-left interatrial shunting. A correct Valsalva manoeuvre is crucial and the patient must receive appropriate instructions before the test. A leftward displacement of the interatrial septum indicates a higher right than left atrial pressure [60]. Increasing the number of injections, and early rather than late Valsalva, is more effective [61]. Usually, injection of contrast is performed antecubitally, but femoral injection has also been used [62].

Contrast-enhanced transcranial Doppler is also a valuable tool for PFO diagnosis, allowing noninvasive examination of the middle cerebral artery with good sensitivity and specificity. It is considered as efficient as echocardiographic techniques (evidence level type A, class II) [63]. This technique allows the examination of patients while asleep. However, it does not allow differentiation of the source of shunting (intrapulmonary or intracardiac) or provide any information on the morphology of the interatrial septum (e.g. ASA) and on other intracardiac source of embolization (e.g. thrombus) [64—68].

Diagnosis of obstructive sleep apnoea

The gold standard method for the diagnosis of OSA is polysomnography: electroencephalogram, electrocardiogram, electrooculogram, submental and tibial electromyograms, body position detector, nasal pressure recording (or an oronasal thermistor), pulse oximeter, and belts to monitor movements of the chest wall and abdomen. In some European countries, and recently in the USA, limited channel home monitoring (type III) is considered as a suitable alternative when pretest clinical suspicion of OSA is high. This type of monitoring is much cheaper and more convenient (as it can be performed at home), but is less accurate as there is no electroencephalogram.

Coexistence of patent foramen ovale and obstructive sleep apnoea

Owing to their high prevalence in the general population, it is evident that PFO and OSA may coexist fortuitously in many patients. A strict methodology is thus required to assess a potential relationship between PFO and OSA to avoid bias. The controversies observed in the studies concerning stroke and migraines are an important illustration of this problem. Two studies have specifically examined the prevalence of PFO in OSA patients. Both concluded that PFO is more frequent in patients with OSA than in controls, but with important differences in their results. The first study, conducted by Shanoudy et al., used TOE in 72 awake male patients [69]. They detected 33 PFO in 48 patients with OSA and four PFO in 24 controls (68.8% vs 16.7%; P < 0.001) [69]. In this study, mean AHI was 33.9; and mean pulmonary artery systolic pressure was higher in patients with OSA than in controls. This study also revealed that one-third of patients with OSA and PFO had a significant decrease in oxygen arterial saturation after Valsalva, suggesting that a right-to-left shunting occurred and that PFO may contribute to hypox-
Patent foramen ovale and obstructive sleep apnoea

Figure 1. Pathophysiological interactions between OSA and PFO (OSA: obstructive sleep apnoea; PFO: patent foramen ovale).

Several pathophysiological interactions exist between OSA and PFO (Fig. 1). OSA is the consequence of repetitive pharyngeal collapse while diaphragmatic efforts are maintained. At first, an obstructive apnoea may be assimilated to a Muller manoeuvre (inspiration effort against a closed upper airway), which can provoke severe negative intrathoracic pressure as low as \(-80 \text{ cm H}_2\text{O}\) [72]. If the obstruction persists, alternating sequences of Muller and Valsalva manoeuvres may be undertaken, leading to important intrathoracic pressure variations. Enhanced venous return is observed when intrathoracic pressure decreases, leading to repetitive transient pressure and volume elevation in the right heart, predisposing to right-to-left shunting [71]. Shiomi et al. undertook TTEs during the sleep of apnoeic patients, and observed a leftward shift of the interventricular septum during the apnoea in half of their patients, all presenting the lowest intrathoracic pressure during the apnoea periods [72]. This shift was correlated with a decrease in arterial blood pressure during inspiration, called a pulsus paradoxus (as described in cardiac tamponade), explained through an interdependence mechanism limiting left ventricular filling [72]. Pulsus paradoxus was more frequent in younger people who could develop more negative inspiratory oesophageal pressure [73]. Interestingly, CPAP limits the variations of intrathoracic pressure and abolishes these interdependence mechanisms and the pulsus paradoxus [72].

Normally, blood pressure and cardiac output decrease during sleep. During an apnoea, blood pressure progressively increases and reaches its peak value after the apnoea, due to hypoxaemia, transient hypercapnia and awakening (sympathetic discharge). Pulmonary pressure also increases when hypoxaemia and hypercapnia occur [74]. Cardiac output may fall by up to 33% during the apnoea, and then increase above the baseline values when normal ventilation is restored [75]. At the beginning of the apnoea, the increase in parasympathetic tone may lead to bradyarrhythmias. After the apnoea, the increase in sympathetic tone may lead to arrhythmia like atrial fibrillation [74,76–78]. Patients with OSA conserve a higher sympathetic activity during the day than controls, which is a risk factor for developing future hypertension [36,79]. Conversely, OSA itself only plays a minor role in the development of chronic pulmonary artery hypertension compared to associated obstructive disease or chronic hypoxaemia [80].

aemia [69]. The methodology of this study was criticized, regarding patient selection and exclusion criteria [70].

In the second study, Beelke et al. studied 78 patients with OSA and 89 controls using transcranial Doppler [71]. All subjects with OSA had AHI > 10 during polysomnography, and the mean ±SD AHI was 52 ± 25 [71]. PFO was found in 21/78 patients with OSA (26.9%) versus 13/89 controls (14.6%; P < 0.05) [71]. Among patients with OSA, 85% only presented PFO during Valsalva.

Considering these two studies, it is possible to believe that the prevalence of PFO might be higher in OSA patients. However, in the second study [71], the percentage of patients with OSA and PFO (26.9%) is close to the percentage found in the general population in other epidemiological studies. The small size of these studies, the difference of patient selection, and the technique of detection is clearly insufficient to demonstrate a direct correlation between these two pathologies, and larger epidemiological studies are now required.

Moreover, these studies only show an association rather than a causal relation, and do not answer the questions of whether OSA increases the risk of PFO or whether PFO is a risk factor itself for OSA. Furthermore, no precise data on stroke before or after the diagnosis of OSA and PFO were presented in these studies.

Pathophysiological interactions between obstructive sleep apnoea and patent foramen ovale

Several pathophysiological interactions exist between OSA and PFO (Fig. 1). OSA is the consequence of repetitive pharyngeal collapse while diaphragmatic efforts are maintained. At first, an obstructive apnoea may be assimilated to a Muller manoeuvre (inspiration effort against a closed upper airway), which can provoke severe negative intrathoracic pressure as low as \(-80 \text{ cm H}_2\text{O}\) [72]. If the obstruction persists, alternating sequences of Muller and Valsalva manoeuvres may be undertaken, leading to important intrathoracic pressure variations. Enhanced venous return is observed when intrathoracic pressure decreases, leading to repetitive transient pressure and volume elevation in the right heart, predisposing to right-to-left shunting [71].
Right-to-left shunting

Left atrial pressure is normally higher than in the right atrium, but the gradient may be reversed allowing right-to-left shunting. Shunting through PFO is not frequent at rest, but may increase with voluntary manoeuvres like Valsalva or during activities of daily life (coughing, singing, sexual intercourse, weight lifting). The gradient between the atria may also be reversed in the case of OSA [69,81], severe chronic obstructive pulmonary disease [82] or pulmonary embolism [83,84]. The flow through the PFO also depends on: the size of PFO, the right ventricular function, and the function of the tricuspid valve [85].

It has been speculated that the increased prevalence of PFO in OSA patients could be attributed to recurrent elevation of pressure in the right heart observed during apnoea [69]. Beelke et al. demonstrated that obstructive apnoea itself may provoke a right-to-left shunt [81]. They studied 10 patients with OSA and PFO (which was present only during Valsalva). In nine patients, a right-to-left shunt was detected with transcranial Doppler during sleep, but only after OSAs lasting \( \geq 17 \) s [81]. This demonstrates that right-to-left shunting may occur during sufficiently long apnoeas through PFO that are 'silent' the rest of the time [81].

Hypoxaemia

In OSA, oxygen desaturation and hypoxaemia are generally attributed to the apnoeas themselves. During apnoea, alveolar ventilation is compromised, leading to transient hypoxaemia, hypercapnia and acidosis [74,76]. However, important variations of nocturnal hypoxaemia have been observed in patients with the same degree of OSA. Bradley et al. showed that desaturation was related to oxygen saturation at the beginning of the apnoea, the length of the apnoea and the lung volume at which the apnoea occurred [86]. Hypoxaemia may also accentuate the sensitivity of CO₂ chemoreceptors, increasing ventilatory instability [87]. It also increases pulmonary artery pressure due to hypoxic pulmonary vasoconstriction. Finally, hypoxaemia may play a role in oxidative stress and endothelial dysfunction, accelerating atherosclerosis [88,89]. PFO is of no clinical significance in most patients, but some patients may suffer from hypoxaemia due to the passage of deoxygenated blood from the right to the left atria. This is particularly seen in the rare cases of large PFOs, leading to POS.

In patients with OSA, the coexistence of a PFO may potentially worsen hypoxaemia and increase the risk of ventilatory instability. Johansson et al. have shown that right-to-left shunting through PFO may contribute to oxygen desaturation in these patients [90]. They compared 15 patients with high proportional desaturation with 15 controls with low proportional desaturation. Nine patients (60.0%) in the first group and two (13.3%) in the second group had a large PFO \( (P = 0.02) \) [90]. They concluded that oxygen desaturation occurred more frequently in OSA patients presenting a PFO, taking into account the respiratory disturbances [90].

Patent foramen ovale and obstructive sleep apnoea: a combined risk factor for stroke?

Some authors have described stroke in patients with coexisting PFO and OSA [91,92]. Ozdemir et al. studied 175 patients with cryptogenic strokes and reported that 15 (16.8%) patients with PFO woke up with stroke or TIA, which is more frequent than in patients without PFO (5%; \( P = 0.009 \)) [93]. They hypothesized that OSA could contribute to this phenomenon [93].

PFO potentially enables venoarterial embolization, and OSA predisposes patients to right-to-left shunting through the PFO. The risk of stroke could therefore be cumulative, through different mechanisms associated with PFO and OSA (Fig. 2). Some authors have already proposed that PFO should be sought in patients with OSA, in order to recommend an appropriate prevention for stroke, using pharmacological treatment or PFO closure [81].

Treatment

Treatment of patent foramen ovale

Whether to treat PFO is determined by the clinical presentation. The majority of patients with PFO will never be symptomatic, and treatment is not required. Prevention of recurrent stroke is the primary goal of PFO treatment. Treatment of hypoxaemia due to right-to-left shunting and POS are of minor importance.

A very careful work-up by stroke experts needs to be performed before implicating the PFO as a cause. Other causes are much more frequent, and certainty of causality can only rarely be established. Furthermore, the recurrence risk related to a PFO remains doubtful [12], as already mentioned. Conventional risk factors should be actively sought and treated in any stroke patients, including OSA.

If PFO is considered a probable causal factor in a TIA or stroke, and the recurrence risk is considered elevated, current possibilities to prevent PFO-related recurrences are: medical treatment with antiplatelet agents or anticoagulants, and surgical or percutaneous PFO closure. Despite numerous publications, there remains no consensus on PFO treatment and indications of percutaneous closure.

The first report of percutaneous closure of an atrial septal defect was in 1976 [94]. Since then, many different devices have been developed. In the context of previous cerebrovascular events, percutaneous closure has been described since 1992 for secondary prevention [95]. Surgical closure has also been reported in the 1990s [96,97]. As the development of percutaneous closure progressed rapidly, the number of surgical closures has declined.

Percutaneous closure is minimally invasive, has a low morbidity rate, and has a high success rate [98,99]. It allows the cessation of medication after 6 months if a high likelihood of a causal link between PFO and the cerebrovascular event has been established by stroke experts, and if other risk factors are absent. Given that the presence of an ASA in association with a PFO has been described to increase the risk of recurrent stroke compared to ASA or PFO alone in some studies, it was important to show that percutaneous closure can also treat this condition [100].
AHA guidelines state that an antiplatelet agent is recommended after non-cardioembolic ischaemic stroke (Class I, level of evidence A) [101]. After ischaemic stroke in patients with PFO, an antiplatelet agent is also recommended (Class IIa, level of evidence B) [101]. It remains unclear whether anticoagulation is superior to antiplatelet treatment in these patients [13,18], and an appropriate trial has not been performed to date. The ESO considers anticoagulation an option in stroke patients with PFO in the presence of proven deep vein thrombosis or ASA (Class IV, good clinical practice) [102].

As described above, the risk of recurrent cerebrovascular event related to a PFO probably depends on numerous other factors (concomitant ASA, size of PFO, spontaneous right-to-left shunting, recurrent strokes, hypercoagulability disorders, or vein thrombosis), which may be taken into account on an individual basis and after multidisciplinary discussion.

Regarding percutaneous closure, the indications are very restrictive in the USA. The FDA accepted percutaneous closure when medical treatment failed for secondary prevention of stroke, i.e. after a recurrent stroke [103]. The AHA guidelines edited in 2006 stated that insufficient data were available to propose PFO closure after a first stroke (Class IIb, level of evidence C) [101]. Nowadays, occluders are available under an FDA-approved investigational device exemption. The ESO considers endovascular closure an option in patients with cryptogenic stroke and high-risk PFO, for instance with concomitant ASA (Class IV, GCP) [102]. The results of the CLOSURE I trial were presented at the AHA late-breaking clinical trial session (AJ Furlan et al. Chicago, IL, 15 November 2010). Closure I is a prospective, multicentre, randomized controlled trial comparing PFO closure with best medical therapy involving 909 patients < 60 years of age with a cryptogenic stroke or a TIA and a PFO. Of these, 447 patients had percutaneous PFO closure with STARFlex and 462 received optimal medical treatment. Two years after randomization, no difference was observed between the two groups in terms of stroke and TIA. The incidence of stroke was 12 (3.1%) in the PFO closure group versus 13 (3.4%) in the medically treated group ($P = 0.77$), whereas TIA was observed in 13 (3.3%) and 17 (4.6%) patients, respectively, in each group ($P = 0.39$). Thirteen major complications (3.2%) were reported after PFO closure whereas none were reported with medical treatment ($P < 0.001$). This first study failed to demonstrate superiority of PFO closure over medical treatment in preventing stroke or TIA recurrence. More importantly, a higher rate of complications was observed in the device group.

Other ongoing randomized studies are currently investigating the role of device closure in the prevention of cryptogenic stroke and TIA recurrence (CLOSE, PC-trial, RESPECT). Of note, the recurrence rate of stroke in patients with previous cryptogenic stroke is low on medical therapy. This may partially explain the negative results of CLOSURE I as more patients and a longer follow-up may have been needed to reach a sufficient power of analysis.

**Treatment of obstructive sleep apnoea**

Conservative treatment (e.g. weight loss and discontinuation of alcohol and sedatives) is recommended to all OSA patients and may, in some individuals, be sufficient to treat the disease. However, CPAP is the treatment of choice for OSA. Therapies must be based on the symptoms of the patient (daytime somnolence), the severity of OSA (AHI) and the presence of cardiovascular comorbidities [104]. A recent observational study with a mean follow-up of 10.1 years showed that the risk of fatal and nonfatal cardiovascular events was increased in men with severe OSA (AHI > 30).
or with an AHI of 5–30 and daytime sleepiness compared to controls [37]. This study also demonstrated that treatment with CPAP reduced the risk of cardiovascular events in severe OSA patients. This should encourage more clinicians to recognize OSA, and to propose appropriate treatment that may decrease mortality [104,105].

CPAP decreases fluctuations of intrathoracic pressure and restores a normal venous return during sleep, allowing a decrease of right-to-left shunting through PFO. Treatment with CPAP also attenuates nocturnal and daytime sympathetic activity and decreases systemic blood pressure and pulmonary pressure (Table 1) [79,106]. Becker et al. followed apnoeic patients efficiently treated with CPAP, and observed a reduction in blood pressure during the day and the night [106].

A recent prospective study by Martinez-Garcia et al. showed that long-term CPAP treatment in patients with moderate to severe OSA (AHI ≥ 20) who suffered from ischaemic stroke is associated with a reduction in mortality [107]. They compared the clinical evolution of 68 patients with AHI ≥ 20 who did not tolerate CPAP to 70 patients with AHI < 20 and to 28 patients with AHI > 20 who tolerated CPAP. The patients with AHI > 20 who did not tolerate CPAP had a higher risk of mortality compared with the other two groups (HR 2.69, 95%CI 1.32–5.61; P = 0.009) and HR 1.58, 95%CI 1.01–2.49; P = 0.04, respectively [107]. These studies confirm that effective treatment of OSA may improve prognosis of patients, particularly those with previous stroke.

### Perspectives of treatment in cases of coexistence of patent foramen ovale and obstructive sleep apnoea

A case of spectacular improvement of OSA after closure of PFO has been described by Silver et al. [108]. A 51-year-old man admitted for a cryptogenic stroke had a PFO closure. His AHI dropped from 189 (181 apnoeas and 8 hypopnoea) to 19 apnoeas/hour after closure. The patient also reported a significant improvement in his symptoms of daytime somnolence. No weight loss or medication changes were noted [108].

Agnoletti et al. reported another case of a 42-year-old man with severe OSA with AHI of 44 and spontaneous right-to-left shunting through PFO seen with TOE [109]. This patient was initially treated with CPAP, which improved his AHI to 3, but the patient still had fatigue, dyspnoea, and desaturation on exertion. Finally, percutaneous closure of the PFO was performed, allowing complete resolution of symptoms [109]. Pinet and Orehek reported a case of a patient with severe OSA (AHI 82) and right-to-left shunting through a PFO [110]. The shunt was demonstrated by transcranial Doppler and confirmed with TOE. After 1 week of CPAP, his AHI dropped to 3. Further transcranial Doppler analysis did not show any passage of microbubbles during normal breathing, suggesting the absence of shunt at rest. Shunt was nevertheless still present during Valsalva [110].

Some assumptions can be made from these few anecdotal cases. First, percutaneous closure of PFO decreases the passage of deoxygenated blood in the left atria. This limits intermittent hypoxaemia and the risk of periodic breathing that may aggravate OSA. Passage of neurohumoral mediators through PFO triggering OSA has also been evoked, but has never been proven. Secondarily, CPAP limits the variation of intrathoracic pressure and diminishes hypoxaemia and arterial pulmonary pressure, thus decreasing right-to-left shunting.

### Summary and conclusions

Despite variations in different studies, the prevalence of PFO in the general population may be considered as high (10–30%). With a prevalence of 9% in women and 24% in men, OSA is also a common disorder. It is thus easy to suggest that numerous patients present both PFO and OSA. Actual available epidemiological data are insufficient to demonstrate a correlation between PFO and OSA, but suggest an increase of prevalence of PFO in OSA patients.

PFO is usually asymptomatic and OSA also remains frequently undiagnosed. This explains the fact that the association of both of these pathologies is poorly known and little studied. Only one very recently published review has addressed this question [111].

OSA and PFO have both been independently suspected to increase the risk of stroke, but their association has never been specifically studied. Even though PFO remains asymptomatic in most cases, right-to-left shunting may favour paradoxical systemic embolization and is considered as a potential risk factor for stroke. OSA also confers an increased incidence of hypertension, nocturnal arrhythmias and haematological disturbances, thus increasing the risk of stroke and cardiovascular morbidity. OSA leads itself to desaturation and hypoxaemia, which may be aggravated by PFO due to right-to-left shunting. Right-to-left shunting through the PFO is favoured by elevation of pressure in the right atrium created by apnoeas and is reinforced by hypoxic pulmonary vasoconstriction. Therefore, it is possible to hypothesise that the association of PFO and OSA might create a cumulative risk for stroke, and that PFO may be an aggravating factor in OSA, increasing the risk of periodic breathing.

In the future, large epidemiological studies should assess the association of PFO and OSA in patients to determine their risk of stroke. The role of PFO closure in these patients should also be studied to determine its efficiency in preventing stroke. In our opinion, a thorough investigation of OSA should be performed in patients with PFO who have suffered from stroke in order to decide on the appropriate prevention. We are not advocating investigation of PFO in all OSA patients.

### Table 1  Effects of continuous positive airway pressure (CPAP).

<table>
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<tr>
<th>Effect</th>
<th>Description</th>
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<tbody>
<tr>
<td>Decrease of fluctuations of intrathoracic pressure</td>
<td>Restoration of venous return</td>
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<tr>
<td>Abolishment of interdependence mechanisms and pulsus paradoxus</td>
<td>Reduction in blood pressure during the day and night</td>
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<tr>
<td>Attenuation of sympathetic activity</td>
<td>Reduction of pulmonary artery pressure during apnoea</td>
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<tr>
<td>Reduction in blood pressure during the day and night</td>
<td>Improvement of endothelial dysfunction</td>
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patients, except for those who have presented with a stroke or a TIA.

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P.M.: clinical trials: co-investigator of the ROPE study and member of data safety and monitoring board of the CLOSE study.
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