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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.

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, transoesophageal echocardiography; TTE, transthoracic echocardiography.

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Syndrome d'apnées du sommeil ;
Accident vasculaire cérébral

plus élevée chez les patients présentant un syndrome d'apnées obstructives du sommeil. Nous passons en revue dans cet article la physiopathologie, le diagnostic et les options thérapeutiques du syndrome d'apnées obstructives du sommeil ainsi que du foramen ovale perméable. Nous mettons l'accent sur les liens physiopathologiques qui peuvent suggérer une potentielle association entre ces deux entités et leurs implications, principalement dans le risque d'accident vasculaire cérébral.

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 9.2—24.3% based on TOE [1—3], 10—18% on TTE [4,5], and 14.6—27.3% on autopsy studies [6,7]. Based on all available series, the prevalence of PFO in the general population is estimated to be 10—30%. The prevalence of PFO decreases with age, from 34.3% during the first three decades of life to 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 $\geq$ 5) of 9% inwomen and 24% in men