Patent foramen ovale: a novel cardiovascular risk factor in patients with sleep disordered breathing and high altitude dwellers?

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Summary

Diseases associated with chronic hypoxaemia are a leading cause of morbidity and mortality in Western countries. Epidemiological data indicate that cardiovascular diseases contribute substantially to this problem, but the underlying mechanisms are incompletely understood. Sleep disordered breathing and high altitude exposure are frequent conditions associated with hypoxaemia. Recent evidence suggests that in these conditions the concomitant presence of a patent foramen ovale plays an important pathogenic role. For example, in patients with obstructive sleep apnoea the presence of a patent foramen ovale is associated with more severe sleep disordered breathing, nocturnal oxygen desaturation, generalised endothelial dysfunction and arterial hypertension. After patent foramen ovale closure, both sleep disordered breathing and cardiovascular phenotype improve, suggesting the existence of a possible causal link. During short-term high altitude exposure, the presence of a patent foramen ovale, by aggravating altitude-induced hypoxaemia, facilitates exaggerated pulmonary hypertension. Interestingly, there is increasing evidence showing that in high-altitude dwellers a patent foramen ovale also alters the cardiovascular phenotype. In this article we will summarise recent evidence demonstrating how a patent foramen ovale alters the cardiovascular phenotype and increases cardiovascular risk in patients with sleep disordered breathing and high-altitude dwellers.

Key words: patent foramen ovale; obstructive sleep apnoea; arterial hypertension; hypoxaemia; high altitude; endothelial dysfunction; pulmonary hypertension

Introduction

Diseases associated with chronic hypoxaemia are a leading cause of morbidity and mortality in Western countries and epidemiological data suggest that cardiovascular diseases substantially contribute to this problem, but the underlying mechanisms are poorly understood. Sleep disordered breathing (SDB, with a reported prevalence of 5–49% in the general population) [1, 2] is an important example illustrating this problem, since there is abundant evidence that it is associated with an increased prevalence of arterial hypertension, stroke, myocardial ischaemia, heart failure, arrhythmia and pulmonary hypertension [3, 4]. Recent data suggest that in patients with SDB, the concomitant presence of a patent foramen ovale (PFO) may contribute to increased cardiovascular risk.

High-altitude-induced hypoxaemia is another important example of this problem, with >120 million persons worldwide who live at high altitude and are chronically exposed to hypoxia. Studies of high-altitude populations, and in particular of maladapted subgroups, provide important insight into underlying mechanisms involved in the pathogenesis of hypoxaemia-related disease in general. Recent experimental evidence suggests that at high altitude, the presence of patent PFO, by aggravating altitude-induced hypoxaemia, may contribute to cardiovascular morbidity in these populations. Here, we will review recent evidence demonstrating how PFO alters the cardiovascular phenotype in patients with SDB and high-altitude dwellers and then show how its closure may represent a possibility to reduce cardiovascular risk in these patients.

Sleep disordered breathing, definition and epidemiology

The term “sleep disordered breathing” (SDB) is used to describe four distinct pathological patterns of breathing: obstructive sleep apnoea (OSA), central sleep apnoea (CSA) sleep-related hyperventilation disorders and sleep-related hypoxaemia disorder. In this review, we focus on the first two disorders. OSA is a very frequent condition characterised by intermittent upper airway obstruction causing a reduction (hypopnoea) or cessation (apnoea) of inspiratory airflow leading to intermittent hypoxaemia. During apnoea/hypopnoea respiratory efforts are present in OSA, and the episode generally ends in arousal. CSA is much less frequent than OSA, since it accounts for <1% of all cases of SDB in the general population [5]. In CSA, by definition, there is no respiratory effort during hypopnoea

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or apnoea, and CSA is generally associated with chronic heart failure or found during high-altitude exposure. The prevalence of SDB has generally been estimated to be between 5 and 15% [2]. However, recent data suggest that its prevalence in the general population may be much higher (23.4% in women and 49.7% in men), a fact related to the increased sensitivity of current recording techniques and scoring criteria [1]. The main symptoms of OSA are snoring, excessive daytime sleepiness, morning headaches, daytime fatigue and concentration difficulties. Clinical findings often associated with OSA include obesity, enlarged neck circumference, retrognathia and nasal obstruction [4]. Diagnosis of OSA requires sleep recording demonstrating >5 episodes of apnoea or hypopnoea per hour of sleep, and its severity is assessed with the apnoea/hypopnoea index (AHI: mild 3–15; moderate 15–30; severe >30 events/h) [6, 7].

Sleep disordered breathing as a cardiovascular risk factor

Systemic circulation
SDB-induced intermittent oxygen desaturation, decreased intrathoracic pressure [8] and arousals have been shown to trigger sympathetic activation [9], increase oxidative stress [10, 11], decrease plasma nitric oxide bioavailability [12] and induce inflammation [13, 14], alterations that all may contribute to endothelial dysfunction [15, 16]. In line with this concept, OSA patients without any traditional cardiovascular risk factor have been shown to display systemic endothelial dysfunction [17]. Endothelial dysfunction is the first step in the development of arteriosclerosis. In line with this concept, OSA patients show signs of arteriosclerosis, including increased coronary artery calcium, arterial stiffness and carotid intima-media thickness [18–20], that are thought to contribute to increased cardiovascular mortality and morbidity in these patients. In OSA desaturation/oxygenation sequences follow a typical pattern and are thought to trigger sympathetic activation, oxidative stress and inflammation, which, in turn, cause cardiovascular disease and increase cardiovascular risk (fig. 1). Several cardiovascular diseases are associated with OSA (fig. 1). Among these diseases, arterial hyperten-

Pulmonary circulation
Hypoxaemia induced by sleep disordered breathing causes haemodynamic and structural alterations of the pulmonary circulation. Hypoxaemia-induced pulmonary vasoconstriction increases precapillary pulmonary artery pressure [33]. Negative intrathoracic pressure during apnoea increases right ventricular preload and pulmonary blood flow by increasing venous return, [34], and increases pulmonary venous pressure by reducing left ventricular compliance (via an increase in left ventricular transmural pressure) [35]. Moreover, as detailed above, intermittent hypoxaemia promotes inflammation, sympathetic activation and oxidative stress, which, in turn, cause pulmonary endothelial dysfunction [36, 37] and vascular remodelling [38], which ultimately may lead to persistent pulmonary hypertension [3].

Patent foramen ovale, definition and epidemiology
Patent foramen ovale (PFO) is an embryological remnant characterised by insufficient postnatal adhesion of the cardiac atrial septum primum and secundum. The gold standard diagnostic test is transoesophageal echocardiography. In the general population, the prevalence of PFO is estimated to be approximately 25% [39]. PFO has been suggested to play a pathogenic role in various conditions, such as decompression illness, migraine, transient global amnesia, platypnoea orthodoxia, high-altitude pulmonary oedema, cerebrovascular ischaemia, paradoxical emboli during air travel [40] and OSA [41–45]. The prevalence of PFO has been found to be increased in patients with OSA; Shanoudy et al. reported a prevalence of PFO of 67% (vs 17% in controls) [46] whereas Beelke et al. found a prevalence of 27% (vs 15% in controls) [47].

PFO and cardiovascular function in sleep disordered breathing
SDB induces vascular dysfunction, but the underlying mechanisms are incompletely understood [48]. Recent evidence suggests that the presence of a PFO may contribute to this problem [16, 49, 50]. In a prospective open-label interventional clinical trial we searched for PFO with tran-
esophageal echocardiography in 40 consecutive patients with newly diagnosed OSA [16, 50]. PFO was found in 14 OSA patients (prevalence 33%), whereas it was not detectable in the remaining 26 patients. OSA patients with PFO underwent closure, whereas patients without this problem served as controls. Conventional therapy (i.e. continuous positive airway pressure therapy) was postponed in both groups, and cardiovascular assessment was performed at baseline and at 3-month follow-up; endothelial function was assessed by use of flow mediated dilation of the brachial artery, arterial blood pressure by 24-hour ambulatory blood pressure measurement and carotid stiffness by measuring parameters of local elasticity; cardiac function and pulmonary artery pressure were evaluated with transthoracic echocardiography. At baseline, endothelial function, carotid stiffness, arterial blood pressure and cardiac function were similar in patients with and without PFO, whereas the right ventricular to right atrial pressure gradient (RV-RA gradient) was roughly 20% higher in OSA patients with PFO than in those without this problem (fig. 2, left panel) [16]. At follow-up, PFO closure significantly improved the apnoea-hypopnoea index (ΔAHHI −7.9 ± 10.4 vs +4.7 ± 13.1 events/h, p = 0.0009, PFO closure versus control) and the oxygen desaturation index (ΔODI −7.6 ± 16.6 vs +7.6 ± 17.0 events/h, p = 0.01). The number of patients with severe OSA decreased significantly after PFO closure (from 79% to 21%, p = 0.007). Figure 2 shows that these favourable effects of PFO closure on nocturnal breathing and oxygen saturation translated into improved pulmonary and systemic cardiovascular function, as evidenced by a 4-mm Hg decrease of the RV-RA pressure gradient (fig. 2, left panel) [47], a significant decrease of nocturnal systolic (−7 mm Hg) and diastolic (−3 mm Hg) blood pressure (fig. 2, right panel) together with the restoration of normal circadian blood pressure variability and improved left ventricular diastolic function [16].

In summary, these data provide the first direct experimental evidence that in patients with OSA, a PFO contributes to altered systemic and pulmonary blood pressure regulation, and altered left ventricular diastolic function. These detrimental effects appear to be related, at least in part, to a PFO-induced aggravation of SDB and nocturnal oxygen desaturation. PFO closure interrupts this vicious cycle. The significant decrease of average night-time heart rate could suggest that the favourable effects of PFO closure were related, at least in part, to a reduction of sympathetic nerve activity [16].

**PFO and cardiovascular function during acute, short-term and chronic high-altitude exposure**

There is evidence that exaggerated hypoxaemia contributes to vascular dysfunction during high-altitude exposure [51, 52], but the effects of the presence of a PFO on cardiovascular regulation has been little investigated. In mountaineers susceptible to high-altitude pulmonary edema (HAPE), patent foramen ovale was reported to be roughly four times more frequent than in participants resistant to this condition. During acute exposure to high altitude (4559 m), HAPE-susceptible participants with a large PFO had more severe hypoxaemia and higher pulmonary artery pressure than those with a small or no PFO. These findings suggest that at high altitude, a large PFO may contribute to exaggerated arterial hypoxaemia and pulmonary hypertension and, in turn, facilitate HAPE [41]. Moreover, there is direct experimental evidence in humans showing that, in addition to aggravating hypoxaemia by right-to-left shunting, PFO also aggravates hypoxaemia by impairing pulmonary gas exchange efficiency [53]. Taken together, these studies suggest that the presence of PFO, by aggravating altitude-induced hypoxaemia, facilitates exaggerated pulmonary hypertension during short-term high-altitude exposure.

Interestingly, there is increasing evidence to suggest that a PFO also alters the cardiovascular phenotype during long-term high-altitude exposure. For example, in a recent study, we searched for PFO with esophageal echocardiography in healthy high-altitude dwellers and patients with chronic mountain sickness who were born and had been permanently living between 3600 and 4000 m [54]. The prevalence of PFO in these high-altitude dwellers was 32% (18/57 participants) and thus did not differ from the prevalence reported at low altitude. Importantly, however, the presence of PFO in high altitude dwellers was associated with right ventricular enlargement at rest (p <0.01, fig. 3, left panel), and exaggerated pulmonary hypertension (fig. 3, right panel) and right ventricular dysfunction during mild exercise [54]. In line with these findings, in a subsequent study we found that in high-altitude dwellers suffering from SDB, pulmonary artery pressure was significantly

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**Figure 2**

Pulmonary artery pressure and systolic night-time blood pressure in obstructive sleep apnoea (OSA) patients with or without patent foramen ovale (PFO). Effects of PFO closure. Pulmonary artery pressure (right-ventricular to right-atrial [RV-RA] systolic pressure gradient) is significantly higher in OSA patients with PFO than in OSA patients without PFO (no PFO) at baseline and significantly decreases after PFO closure at follow-up (left panel). Systolic night-time blood pressure (BP) significantly decreases after PFO closure at follow-up (right panel).

**Figure 3**

Right ventricular (RV) basal diameter and right-ventricular to right-atrial (RV-RA) systolic pressure gradient in high-altitude dwellers with (+) or without (−) patent foramen ovale (PFO). High-altitude dwellers with PFO display RV enlargement (left panel) and higher pulmonary artery pressure (right panel) compared with high-altitude dwellers without PFO.
higher in patients with PFO than in those without it [49].
Finally, preliminary data (Rexhaj et al., not published) sug-
gest that in high-altitude dwellers, the presence of a PFO is
associated with systemic vascular dysfunction.
In summary, these data suggest that in high-altitude dwell-
ers the presence of a PFO is associated with systemic and
pulmonary vascular dysfunction. In the pulmonary circu-
lation, this vascular dysfunction leads to increased pul-
monary artery pressure and right heart dysfunction. Further
studies need to examine whether in high-altitude dwellers
systemic vascular dysfunction associated with a PFO in-
creases the prevalence of cardiovascular endpoints in the
systemic circulation [16, 49].

Effects of a PFO on arterial oxygenation in patients with sleep disordered breathing at low and high altitude

In patients with OSA at low altitude, the presence of PFO
is associated with a marked increase of both the frequency
and severity of nocturnal oxygen desaturation [16, 53, 56].
In high-altitude dwellers (3600 m), the presence of PFO
is associated with more severe SDB and nocturnal hypox-
aemia [49]. Taken together, these data suggest that in SDB,
the presence of a PFO puts these patients at risk for more
severe nocturnal hypoxaemia. This could be related, at
least in part, to right-to-left shunting across a PFO, as evi-
denced by invasive haemodynamic measurements in healthy
humans, demonstrating that during the onset of simulated
OSA, in response to the steep decline in intrathoracic pres-
sure, right atrial pressure exceeds left atrial pressure (fig.
4) [57]. Accordingly, Schäfer et al. found that in OSA
patients, during apnoea the pulmonary artery pressure in-
creased by about 10 mm Hg; the main contributors to this
response were hypoxaemia, mechanical factors and an in-
crease in negative intrathoracic pressure [58].

Is there a direct causal link between sleep disordered breathing and PFO?

One possibility could be that SDB induces/reopens a PFO,
i.e. SDB-induced exaggerated nocturnal hypoxaemia dur-
ing apnoea/hypopnoea triggers pulmonary vasoconstric-
tion, elevates pulmonary artery pressure and increases right
atrial pressure above left atrial pressure, which, in turn,
promotes PFO. The increased prevalence of PFO in pa-
tients with chronic obstructive pulmonary disease could
be consistent with this hypothesis [59]. Alternatively, and
more probably, a PFO appears to have an exacerbating ef-
fect on phasic breathing in OSA. The crucial element in
this context is short episodes of atrial right-to-left shunt
with ensuing episodes of hypoxaemia, which aggravate
the already disturbed central breathing regulation in OSA.
The initiating incident in the cascade of phasic breathing in
OSA is the first apnoea in the context of muscular relaxa-
tion during rapid eye movement sleep. Rising arterial
pressure of carbon dioxide (PCO₂) in the context of this apnoea
induces breathing efforts against the closed glottis, which
briefly elevate right atrial pressure above left atrial pressure
and leads to shunting of deoxygenated blood to the system-
atic side in the presence of a PFO. Hypoxaemia impairs en-
dothelial function in the pulmonary and in the systemic cir-
culation, and it acts as a central respiratory stimulant that
influences PCO₂ steerred respiratory regulation differently
from other stimulants. Hypoxaemia lowers the eupnoic
PCO₂ level in the context of hyperventilation without con-
comitant reduction in the apnoic PCO₂ threshold, thus
destabilising the system and rendering it more prone to
ensuing apnoic phases [50, 60]. In line with this hypo-
thesis, circumstantial evidence suggested that PFO closure
may improve symptoms and SDB in patients with OSA
[61–63]. This concept is markedly strengthened by a recent
prospective study showing that PFO closure in OSA pa-
tients improved SDB and nocturnal oxygenation, and sig-
nificantly decreased the number of patients suffering from
severe OSA from 79 to 21% [16, 50].

These data show a pathophysiological interaction between
OSA and PFO, where right-to-left shunting across a PFO
aggravates SDB and nocturnal oxygen desaturation, lead-
ing to more severe cardiovascular alterations, as evidenced
by the improvement of both SDB and cardiovascular phen-
o-type after PFO closure in patients with OSA. These data
strongly suggest that PFO represents a novel cardiovascular
risk factor in patients with sleep disordered breathing
(and high-altitude dwellers). If confirmed in larger pro-
spective randomised studies, PFO closure in SDB may
emerge as a valid alternative to conventional therapy for
decreasing the cardiovascular risk (and, by attenuating no-
turnal oxygen desaturation, possibly also for attenuating
clinical symptoms), particularly in patients who are intoler-
ant of nocturnal ventilatory and/or dental device treatment.

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References


Figure 1
Pathophysiologival relationship between obstructive sleep apnoea (OSA) and cardiovascular diseases. OSA is characterised by intermittent hypoxaemia, arousals and intrathoracic pressure swings inducing sympathetic activation, exaggerated oxidative stress and chronic inflammation leading to systemic and pulmonary endothelial dysfunction, the first step in the development of generalised arteriosclerosis and pulmonary hypertension.

Figure 2
Pulmonary artery pressure and systolic night-time blood pressure in obstructive sleep apnoea (OSA) patients with or without patent foramen ovale (PFO). Effects of PFO closure. Pulmonary artery pressure (right-ventricular to right-atrial [RV-RA] systolic pressure gradient) is significantly higher in OSA patients with PFO than in OSA patients without PFO (no PFO) at baseline and significantly decreases after PFO closure at follow-up (left panel). Systolic night-time blood pressure (BP) significantly decreases after PFO closure at follow-up (right panel).
**Figure 3**
Right ventricular (RV) basal diameter and right-ventricular to right-atrial (RV-RA) systolic pressure gradient in high-altitude dwellers with (+) or without (-) patent foramen ovale (PFO). High-altitude dwellers with PFO display RV enlargement (left panel) and higher pulmonary artery pressure (right panel) compared with high-altitude dwellers without PFO.

**Figure 4**
Pathophysiological link between obstructive sleep apnoea (OSA) and patent foramen ovale (PFO). OSA is characterised by intermittent hypoxaemia that causes hypoxic pulmonary vasoconstriction and increases pulmonary vascular resistance. During apnoea/hypopnoea the patient expires or inspires against the collapsed upper airways producing intrathoracic pressure swings. Augmented pulmonary vascular resistance and intrathoracic pressure swings increase right atrial (RA) pressure over left atrial pressure. The presence of a PFO allows right-to-left shunting which further exacerbates hypoxaemia, thereby completing a vicious circle.