Sleep Medicine Reviews 18 (2014) 399–404

Contents lists available at ScienceDirect

Sleep Medicine Reviews

journal homepage: www.elsevier.com/locate/smrv

CLINICAL REVIEW

Cardiovascular implications of obstructive sleep apnea associated with the presence of a patent foramen ovale

Subrata Kar*

Division of Cardiovascular Medicine, University of Missouri-Columbia School of Medicine, 5 Hospital Drive, Columbia, MO 65212, USA

ARTICLE INFO

Article history:
Received 25 May 2013
Received in revised form
29 January 2014
Accepted 5 February 2014
Available online 13 February 2014

Keywords:
Patent foramen ovale
Obstructive sleep apnea
Cardiovascular disease
Stroke
Percutaneous closure

SUMMARY

Patent foramen ovale (PFO) is a common congenital cardiac abnormality of the atrial septum which occurs in 25% of the population. It allows communication between the right and left atrium enabling right to left shunting of deoxygenated blood (after birth) which may be linked to strokes or transient ischemic attacks. PFO may also have an association with obstructive sleep apnea (OSA).

OSA is a common medical condition occurring in 9% of adult males and 4% of adult females. It may increase the risk of cardiovascular disease. OSA causes intermittent hypoxia from episodes of apnea and hypopnea during sleep. Consequently, hypoxic pulmonary vasoconstriction ensues which produces an increased right atrial pressure which may generate a right to left shunt during apneic episodes promoting the occurrence of thromboembolic events. The existence of a PFO may be higher in patients with OSA. The presence of a PFO and OSA may increase the risk of stroke. In this review, the association of PFO and OSA is described along with their implications for cardiovascular disease. The relevant literature and treatment options are discussed to elaborate on the significance of the associated pathology.

Introduction

Patent foramen ovale (PFO) is a common congenital cardiac anatomical variant of the atrial septum which occurs in 25% of the population [1,2]. A PFO allows communication between the right and left atrium enabling right to left shunting of oxygenated blood in utero, thereby, bypassing the high resistance fetal pulmonary circulation [3]. After birth, the rise in the left atrial pressure with a decline in the right atrial pressure and pulmonary vascular resistance enables closure of the PFO [2,3]. PFO closure is initially functional and by the first or second year of life it becomes anatomically sealed in most children. The size of PFOs increases with age while the prevalence decreases with age [3]. PFOs may be linked to strokes, transient ischemic attacks (TIAs), migraines, systemic embolism, or decompression illness [1,3,4]. Furthermore, PFO may have an association with obstructive sleep apnea (OSA) [1].

OSA is a common medical condition occurring in 9% of adult males and 4% of adult females [3]. OSA may occur in 5–15% of the middle-aged population and may increase the risk of cardiovascular disease [5]. OSA causes nocturnal repetitive collapse of the pharyngeal airway which causes a decrease or cessation of airflow [3]. Intermittent hypoxia caused by an obstructive event during sleep induces hypoxic pulmonary vasoconstriction which increases the pulmonary vascular resistance and also produces an increased right atrial pressure. Thus, a right to left shunt is produced which may provide the nidus for systemic embolization [3]. In this review, the association of PFO and OSA is described along with their implications for cardiovascular disease. The relevant literature, clinical research, and case reports are also discussed to elaborate on their associated effects and treatment options.

Definition and prevalence of PFOs

A PFO is a normal communication between the right and the left atria which occurs during fetal development [6]. PFO remains as an embryological remnant of the fetal circulation derived from incomplete fusion of the septum primum and secundum [7]. PFOs are found in 20–34% of the population and its prevalence decreases with age [6]. Most PFOs are benign and shunting is normally not present during rest [7]. However, voluntary maneuvers such as coughing, Valsalva, singing, coitus, or weight-lifting increases the right to left shunting via a PFO [7]. Consequently, thrombi or air may enter the arterial circulation, thereby, inducing a stroke or TIA. Moreover, cryptogenic strokes may occur more often in patients with PFOs compared with the general population (approximately

* Tel.: +1 (573) 882 2296; fax: +1 (573) 882 7743.
E-mail addresses: karsu@health.missouri.edu, skar762@aim.com.

http://dx.doi.org/10.1016/j.smrv.2014.02.002
1087-0792/

Abbreviations

AHI	apnea–hypopnea index
BIPAP	bilevel positive airway pressure
CLOSURE I trial	evaluation of the STARFlex septal closure system in patients with a stroke or TIA due to the possible passage of a clot of unknown origin through a patent foramen ovale
CPAP	continuous positive airway pressure
OSA	obstructive sleep apnea
PC-trial	clinical trial comparing percutaneous closure of patent foramen ovale using the Amplatzer PFO occluder with medical treatment in patients with cryptogenic embolism
PFO	patent foramen ovale
TIA	transient ischemic attack
RESPECT trial	randomized evaluation of recurrent stroke comparing PFO closure to established current standard of care treatment
UPPP	uvulopalatopharyngoplasty

50–60% vs. 20–25%) [2]. However, no studies have unequivocally linked PFOs to cryptogenic strokes.

Percutaneous PFO closure

Data on the benefits of PFO closure remains controversial. Common reasons for which closure may be considered include cryptogenic stroke (greater than one embolic episode or PFO combined with an atrial septal aneurysm), hypoxia due to right to left intra-cardiac shunting, or major decompression illness in professional divers [1]. Factors which may increase the risk of cryptogenic stroke with PFOs include atrial septal aneurysm, recurrent cryptogenic stroke, large PFO, Chiari network, pulmonary embolism, and prothrombotic states [1].

Complications of PFO closure include device embolization, tamponade, and retroperitoneal bleeding which occur in 1% of cases. Air emboli may also induce transient ST elevation [1]. Long-term complications may include thrombus formation, erosion, and fistula formation [1].

Observational studies of PFO closures

A recent meta-analysis [8] of observational studies comparing percutaneous PFO closure vs. medical therapy for the prevention of recurrent neurological events after cryptogenic stroke showed the superiority of percutaneous closure compared with medical therapy in event reduction [0.8 (95% confidence interval (CI) = 0.5–1.1) vs. 5.0 (95% CI = 3.6–6.9) events/100 person-years]. The meta-analysis included 39 studies (8185 patients) evaluating transcatheter closure, 19 studies (2142 patients) of medical therapy, and 10 studies (1886 patients) comparing both medical and transcatheter closure which were included in a pooled analysis. The pooled analysis showed the incidence of recurrent neurological events/100 patients-years with transcatheter closure of 0.76 (95% CI = 0.48–1.05) compared with 4.39 (95% CI = 3.20–5.59) in the medical therapy group.

Furthermore, treatment with anticoagulants (warfarin) showed lower risk of recurrent neurological events compared with antiplatelet (aspirin or aspirin and clopidogrel) agents [2.2 (95% CI = 1.1–3.4) vs. 4.2 (95% CI = 2.9–5.4)]. Thus, this meta-analysis suggests that PFO closure may be superior to medical management for cryptogenic stroke in patients with evidence of paradoxical embolus.

A systematic review by Khairy et al. [9], also showed a reduction in recurrent neurological thromboembolism with percutaneous closure compared with medical therapy. However, direct comparisons between percutaneous and medical treatment were not provided in this review. Another systematic review by Kitsios et al. [10], compared secondary stroke prevention via PFO closure vs. medical therapy. An analysis of 52 single-arm studies, seven comparative non-randomized studies, and the evaluation of the STARFlex septal closure system in patients with a stroke or TIA due to the possible passage of a clot of unknown origin through a patent foramen ovale (CLOSURE I) trial [11] was performed. The incident rates of recurrent stroke was 0.36 events (95% CI = 0.24–0.56) per 100 person-years with transcatheter closure vs. 2.53 events (95% CI = 1.91–3.35%; $p < 0.001$) per 100 person-years with medical therapy. In observational and non-randomized studies of medical therapy (nine studies), anticoagulants were superior to antiplatelets for the prevention of stroke recurrence (incidence rates of recurrent cerebrovascular events = 0.42, 95% CI = 0.18–0.98).

Randomized controlled trials of PFO closure

The recently completed CLOSURE I trial [12] refutes the findings of the systematic review by Khairy et al. [9] and Kitsios et al. [11] The CLOSURE I trial [12] was the first prospective, multicenter, open-labeled, randomized, independently adjudicated PFO device closure trial which evaluated PFO closure with the STARFlex device (NMT Medical, Boston, Massachusetts) plus medical therapy (six months of aspirin and clopidogrel followed by 18 mo of only aspirin) compared with medical therapy alone (24 mo of warfarin or aspirin or combination therapy) in the prevention of recurrent stroke or TIA in patients with cryptogenic stroke or TIA and a PFO. A total of 909 patients (≤60 y of age) who were followed for two years showed no primary endpoint benefits from percutaneous PFO closure compared with medical therapy [447 patients (5.5%) vs. 462 patients (6.8%); $p = 0.37$] [11]. The primary endpoints were two-year incidence of stroke or TIA, all-cause mortality in 30 d, and neurological mortality 31 d to 2 y. No deaths occurred at 30 d in either group and no deaths from neurological causes occurred within the two-year follow-up in either group. However, the closure group had higher rates of major vascular procedural complications compared with medical therapy [13 (3.2%) vs. 0, $p < 0.001$] and atrial fibrillation [23 (5.7%) vs. 3 (0.7%), $p < 0.001$]. Consequently, the CLOSURE I trial [11] failed to support the benefits of PFO closure with the STARFlex septal closure system in patients with cryptogenic stroke or TIA for the prevention of recurrent stroke or TIA.

Recently, the results of the randomized evaluation of recurrent stroke comparing PFO closure to established current standard of care treatment (RESPECT trial) [13] were reported using the Amplatzer PFO occluder. The RESPECT trial [13] was a prospective, multicenter, randomized, event-driven trial evaluating whether PFO closure was superior to medical therapy (one or more antiplatelet agents or warfarin) in preventing recurrent ischemic stroke or early death. A total of 980 patients (ages of 18–60, mean age of 45.9 y) were enrolled in a 1:1 ratio of medical vs. closure therapy. Treatment exposure between the medical and closure group were unequal due to higher dropout rate in the medical group (1184 patients-years in the medical vs. 1375 patients-years in the closure group; $p = 0.009$). In the intention-to-treat cohort, nine patients in the closure group and 16 in the medical group had a recurrent stroke (hazard ratio with closure, 0.49; 95% CI of 0.22 to 1.11; $p = 0.08$). There were significant variations in the between-group differences in rates of recurrent strokes in the prespecified per-protocol cohort (six events in the closure group vs. 14 events in