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Atrial Septal Defect/Patent Foramen Ovale and Migraine Headache

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1. Introduction

Migraine headaches affect approximately 13% of US population, affecting women in a 3:1 ratio and with a 60–80% familial inheritance. Migraine is a relevant social health problem; in fact it significantly restricts the social life of those who are affected. Recently, migraine headache has been suspected to be a potential risk factor for stroke, particularly in women, smokers and for those making use of oral contraception.

Onset of migraine is usually between the ages of 20–64, with over 80% having their first episode before age 30 and tends to decrease in middle age. Migraine with aura (MA) is a variant characterized by transient neurological visual, verbal, sensory or motor symptoms that last from five to sixty minutes. MA is also known as "classic migraine" though only 25% of migraneurs experience an aura.

Increased frequency of patent foramen Ovale (PFO) in migraneurs was first reported in 1998 in a case–control study.

An increased prevalence between patent foramen Ovale (PFOs) and migraine exists but there is conflicting data of a causal relationship between these two conditions. It remains controversial whether cardiac screening and intervention provides a treatment benefit in migraneurs and is an area currently investigated for demonstrating clinical benefit of PFO closure. This topic is an intersection between the practice of primary care physicians, neurologists, and cardiologists on the best practice and management of patients with difficult to control migraines given the billions spent on physician visits and pharmacotherapy.

Several mechanisms linking PFO to migraine have been hypothesized, including humoral causes (serotonin-platelet activation, aggregation, and embolism causing cortical spreading depression) and genetic causes (autosomal dominant inheritance with incomplete penetrance). The presence of a right to left shunt (RLS) may be the most potent trigger of migraine attacks with or without aura, and researchers have speculated that a large RLS may contribute to the high risk of ischemic stroke in migraneurs with PFO.

Diagnostic Modalities to evaluate the presence or absence of PFO in the migraine patients are another controversial subject. Mostly agree that the Trans –thoracic echocardiography is

less sensitive test particularly in adolescents and adults. Trans- Esophageal and Intra-Cardiac Echocardiography carry more reliability in detecting left to right shunt. Recently Trans-Cranial Doppler has been postulated as more accurate test to detect the right to left shunting in those patients.

PFO closure (particularly device closure) carries the most controversial issue in this subject. With only –so far- one randomized large clinical trial and several prospective cohorts and case control studies, there is conflicting data about the benefit of PFO closure in relieving or treating the Migraine headache.

This chapter will talk first about the anatomy and physiology of Patent Foramen Ovale in normal population, anatomical variants of the PFO, the current diagnostic methods used by different institutions then seeks to summarize the current literature on the association of PFO and migraine headache and studies that have investigated PFO closure in this population.

1.1 Definitions

The topic of Migraine headache in association with Patent Foramen Ovale (PFO) has been one of the controversial topics in the literature. Since 1998 when the first scientific observation that patients with migraine headaches have higher prevelance of PFO(1), the dogma between causation, association and prevention has continued.

In order to make reading through this chapter easier, some definitions will be instated:

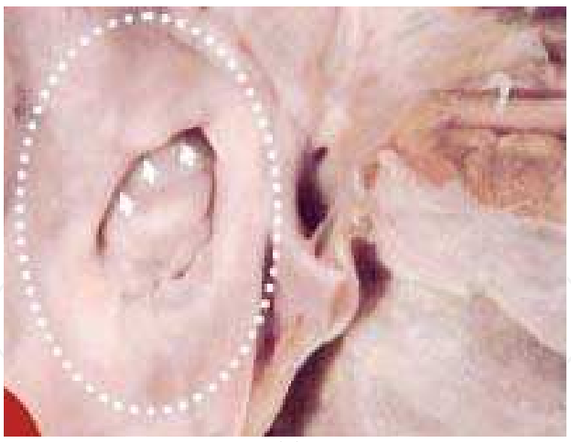
2. Patent foramen ovale in normal population

Several studies reported high prevalence of PFO in normal subjects. The highest prevalence reported was in autopsy studies. With a probe inserted in the region of the foremen ovale, if the probe can be passed through it then he/she will be labeled to have PFO. Such studies reported incidence of 25% (2). While looking for the incidence of PFO in Normal population by Trans Esophageal Echocardiogram reported to be less than autopsy studies about 15% (3-4).

The foramen ovale is composed of the septum primum and the septum secundum joined in parallel, forming a tunnel-like structure allowing the oxygenated blood from the placenta to pass towards the systemic circulation. Postnatally, it closes with a valve-like mechanism. Patent foramen ovale results from lack of post neonatal closure. Under certain hemodynamic conditions, when there is a transient pressure gradient from the right to left atria, a PFO can open and enable blood or any blood borne substances to pass from the venous to the arterial circulation. This process is the mechanism of paradoxical embolism, which has been frequently reported in the literature (5-8). There are multiple anatomical variants of PFO morphology (figure 1). Occasionally the PFO has an association with atrial septal aneurysm (figure 2). These variants and atrial aneurysm has been believed to play a major role of the amount and the direction of shunt across the PFO.

3. Migraine headache

Migraine is a common, disabling, largely inherited neurological disorder with a prevalence of 8% to 13% in the population of the Western hemisphere (9, 10), with a 3:1 female preponderance.



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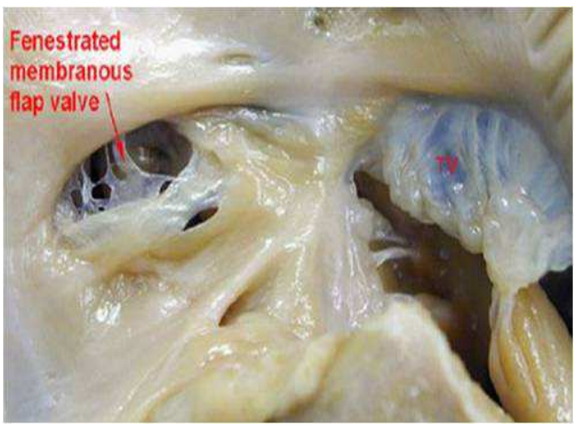

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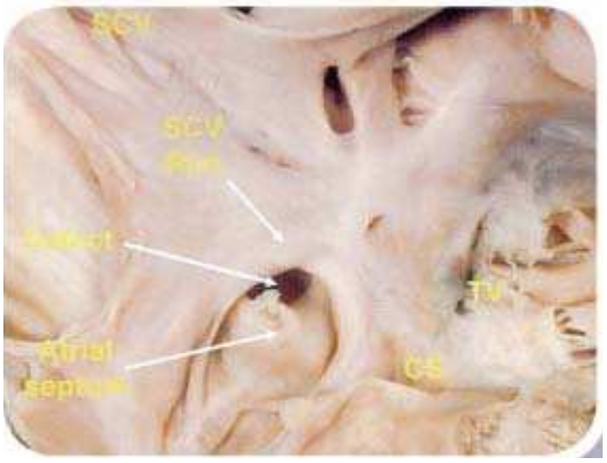

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Fig. 1. Several Morphologies of Patent Foramen Ovale. a: the common type of PFO with a tunnel (white arrows) that can stretch with Valsava. b: Multi fenestration defects in the PFO region. c: a deficient part of the secundum septum covering the PFO from the left side of the atrial septum.

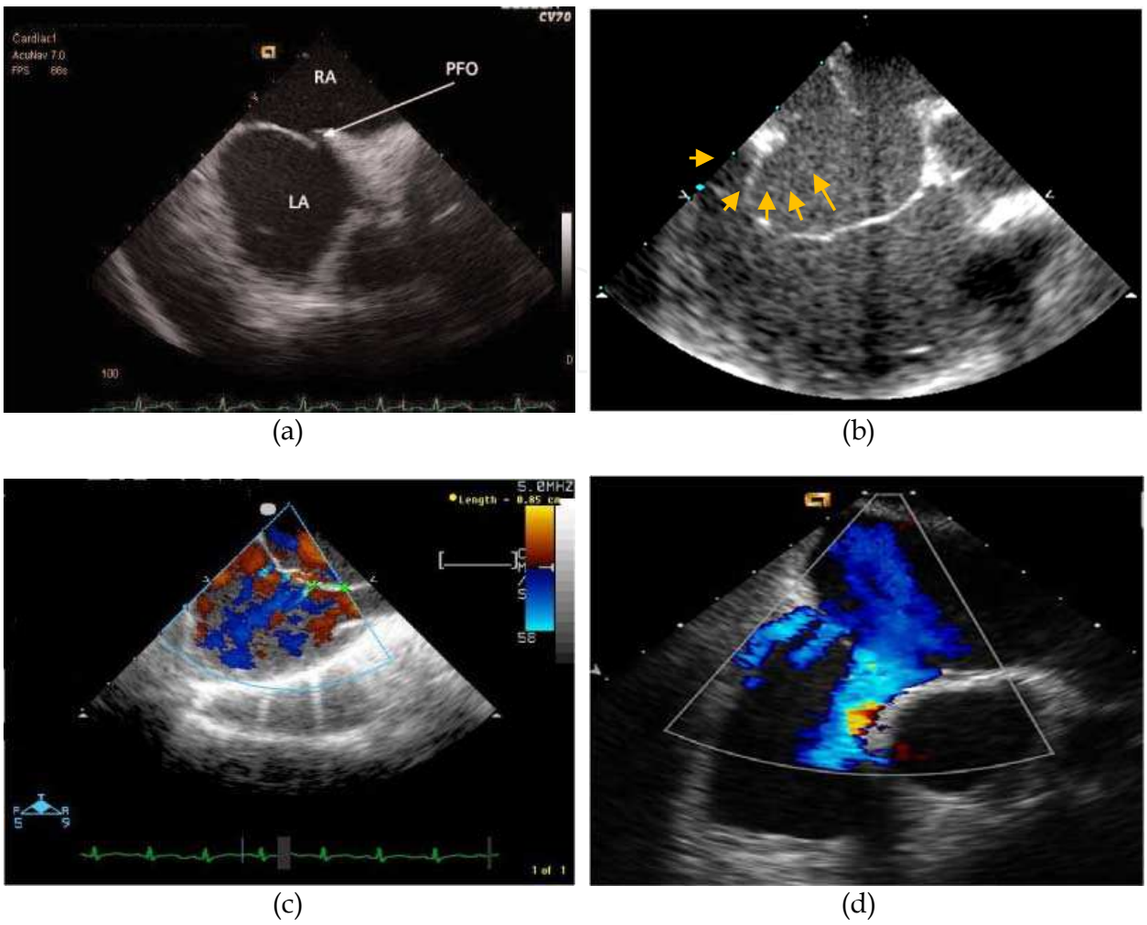

Fig. 2. Echocardiographic appearance of different PFO morphologies, a: Intra Cardiac Echo (ICE) of a tunnel shape PFO. b: Large atrial aneurysm (orange arrow heads) by trans thoracic echo(TTE). c: small multi fenestration by TTE color Doppler. d: larger fenestrations by TEE color Doppler.

Migraine is a common, chronic, disabling neurovascular disorder characterized by attacks of severe headache, autonomic nervous system dysfunction, and, in some patients, an aura and neurological symptoms (11). The suffering associated with migraine headaches accounts for a significant loss in productivity and a substantial increase in healthcare-related costs. About 60% of the patients with Migraine reported that they can't go to work while having the headache. In approximately one third of sufferers, an aura—consisting of reversible neurological symptoms such as visual illusions, unilateral paresthesias, and expressive/receptive language dysfunction—will precede or occur during some attacks. A typical migraneurs has one to two attacks per month, with a median duration of 24 hours. In addition, approximately 2% of the population experiences a more disabling form of migraine, known as chronic migraine, which is characterized by headache on more than 15 days/month.

The diagnosis of migraine is purely clinical, and its physiopathology is complex and not fully understood, with both genetic and environmental factors appearing to play an important role. Genetic effects, including autosomal dominant inheritance with incomplete penetrance (12, 15) and coinheritance, (13) have also been reported.

The prevailing hypothesis regarding the pathogenesis of migraine is an inherited excitability of certain brain networks that, when triggered by particular endogenous or exogenous factors, leads to a cascade of events that result in head pain, in addition to a multitude of other symptoms, including a heightened sensitivity to movement and ambient light, noise, and odor; nausea; emesis; cognitive impairment; vertigo; depression; and lethargy (14). Commonly used preventive medications such as Propranolol, Amitryptiline or anticonvulsants reduce headache frequency in the range of 30-50%, as compared to placebo (16-17).

Migraine occurs in about 15% of the pediatric population, with approximately

One-third of cases associated with an aura (18).

3.1 The association of migraine headache and patent foramen ovale

The initial observation of this association came from the studies of vascular embolic strokes and PFO. The initial observation of increased prevalence of PFO in migraneurs came out in 1998 (1). Then subsequently several studies looked specifically for the prevalence of PFO in Migraneurs. Anzola and colleagues performed a case control study including 113 consecutive patients with migraine with aura, 53 patients with migraine without aura and 25 ages matched no migraine subjects. The presence of PFO was assessed indirectly by using transcranial Doppler sonography with IV. Injection of agitated saline. The prevalence of PFO was 48% in patients with migraine with aura, 23% in patients with migraine without aura and 20% in controls. The difference between migraine with aura and migraine without aura was significant (odds ratio=3.13) as well as between migraine with aura and control group (odds ratio=3.66) (19).

Schwedt et al. (2008) performed a systematic review of 18 out of 134 identified articles to examine the prevalence of migraine in patients with PFO. The results demonstrated that people with migraine with aura are more likely to have a PFO than people with migraine without aura or healthy controls (20). Migraine with aura not related with diving occurred significantly more frequently in patients with large right to left shunt which was present at rest (38 of 80, 47.5%), compared with patients who had a smaller shunt (four of 40, 10%) or with patients with no shunt at all (11 of 80, 13.8%). The prevalence of migraine without aura was similar in all groups. Authors concluded that migraine with aura was associated with presence or absence of PFO but also with the shunt size (21).

McCandless et al (2011) conducted pediatric study involved a population consisted of 109 children with migraine; 38 (35%) with aura and 71 (65%) without aura. The overall PFO prevalence was 35%, similar to the general population (35% vs. 25%; P = .13). However, compared with the general population (25%), the PFO prevalence was significantly greater in subjects with aura (50%, P = .0004) but similar in those without aura (27%, P = .73). Atrial shunt size was not associated with the presence or absence of aura. Their conclusion was that Children with migraine with aura have a significantly higher prevalence of PFO compared with those without aura or the general population. These data suggest that PFO may contribute to the pathogenesis of migraine with aura in children and have implications for clinical decision making (22).

A meta analysis of 7 studies in adult population with migraine headache and aura showed association of PFO in this particular population ranging from 41- 62% (composite of 56% by meta-analysis) (23-29).

On the other hand; NOMAS study (30) involved screening of population from Northern Manhattan area showed no significant association of PFO with Migraine headache population. This study has several limitations though. It included only non-stroke patients who are older than 39 years, they used Trans thoracic Echocardiography for the screen of PFO with no Trans Cranial Doppler evaluation of the bubble study and they depended on self-reporting headache with obvious recall bias.

Table one summarized the major studies of PFO association with Migraine headache. It is clear from all previously mentioned studies that Migraine with Aura has higher association of PFO compared to migraine without aura. Both (with and without aura) has higher prevalence of PFO compared to general population please see Table 1.

Study	PFO Method	Migraine With Aura, n/N (%)	Migraine Without Aura, n/N (%)
Del Sette et al	TCD	18/44 (41)	NA
Anzola et al	TCD	54/113 (48)	12/53 (23)
Schwerzmann et al	TEE	44/93 (47)	NA
Dalla Volta et al	TCD	161/260 (62)	12/74 (16)
Carod-Artal et al	TCD	25/48 (52)	32/93 (34)
Domitrz et al	TCD	33/61 (54)	15/60 (25)
NOMAS	TTE	26/140 (19)	4/38 (11)

TCD indicates transcranial Doppler; TEE, transesophageal echocardiography.

Table 1. Prevalence of PFO Among Subjects With Migraine Selected From the Literature

The prevailing hypothesis regarding the pathogenesis of migraine is an inherited excitability of certain brain networks that, when triggered by particular endogenous or exogenous factors, leads to a cascade of events that result in head pain. The presence of PFO might trigger this process by allowing substances or metabolites to pass from the hepatic or portal circulation to the carotids circulation. Migraneurs have increased platelet activation and aggregation in response to serotonin. Normally serotonin is metabolized by lung mono amino oxidase (MAO), but if blood is shunted through a PFO and avoids the pulmonary circulation it has been postulated that this can trigger migraine onset and precipitate aura (31). Another mechanism could possibly be transient hypoxemia caused by the PFO, causing subclinical infarcts in the brain, leading to irritation and propensity for migraines. Naqvi et al. report different manifestations of PFO including resting and stress hypoxemia related to left to right shunting across a PFO in the absence of pulmonary hypertension (32).

4. Results of studies of PFO closure to relief migraine headaches

Initial observation from studies involves Stroke prevention by PFO device-closure, showed patients with Migraine headaches improve after the procedures (34-38).

Recently Wahl et al (2010) reported a large cohort of Migraneurs (150 patients 96 of them had aura) who underwent closure of PFO for stroke prevention. Of those 34% showed complete resolution of the headache and 48% showed significant improvement of their

headaches, making total of 82% of the migraneurs benefited from the closure. The presence of aura was associated with higher improvement in their study population. Still they showed improvement in non-aura migraneurs.

Daniela Trabattoni reviewed 305 patients who underwent closure of their PFO for stroke prevention, 77 of them have migraine headache (~55% are female). Follow up of these migraine patients at 3 months showed complete cessation of headache in 46% of the patients and 40% had improvement of their headache intensity score (total improvement of 86% of the patients). They found maintenance of these results up to 5 years of follow up (44).

After these initial observations of improved migraine headache in the patients who underwent prevention of stroke by device-closure of their PFO (table 2), then several studies were conducted primarily for Migraine headaches relief.

Author, year (Ref.)	N of pts	Patients with migraine	Pts with migraine and aura	Pts with migraine without aura	Age migraine-pts	Sex (F/M) MH- pts	Indications for defect closure	Defect type	Devices used
Anzola, 2006 [16]	77	77 (100%)	54 (70%)	23 (30%)	Between 36 ± 11 and 40 ± 12 (see text)	58/19	Stroke pts and no stroke pts with MH (see text)	PFO	NA
Morandi, 2003 [18]	17	17 (100%)	8 (47%)	9 (53%)	48 ± 11	12/5	Stroke	PFO	Amplatzer
Reisman, 2005 [19]	162	50 (31%)	38 (76%)	12 (24%)	47 ± 12	38/12	Stroke	PFO	Amplatzer = 11 pts CardioSeal: 151 pts
Post, 2004 [22]	66	26 (39%)	12 (46%)	14 (54%)	55 ± 10	9/17	Stroke and peripheral embolism	PFO	NA
Schwerzmann, 2004 [23]	215	48 (22%)	37 (77 %)	11 (23 %)	49 ± 11 MHA 49 ± 12 MHnoA	31/17	Stroke and decompression illness	PFO	NA
Giardini, 2006 [24]	131	35 (27%)	35 (100 %)	0 (0%)	45 ± 13	10/25	Stroke	PFO	Amplatzer = 71 pts CardioSeal = 52 pts Helex = 8 pts
Slavin, 2007 [25]	131	50 (42%)	40 (80%)	10 (20%)	45.7 ± 11.5	36/14	Stroke	PFO	Amplatzer 101 pts CardioSeal = 30 pts
Dubiel, 2008 [28]	191	46 (24%)	24 (52%)	22 (48%)	44 ± 13.5	35/11	Stroke	PFO	Amplatzer = 38 pts Cardio-SEAL/Starflex = 8 pts
MIST, 2008 [29]	147	74 (100%)	74 (100%)	0 (%)	44.6 ± 10.6	12/62	Migraine with aura	PFO	Starflex = 74 pts
Jesurum, 2008 [30]	77	77 (100%)	55 (71%)	22 (29%)	47 ± 12 MHA 46 ± 10 MhnoA	57/20	Stroke or paradoxical embolism	PFO	CardioSeal = 67 pts Amplatzer = 10 pts
Luermans, 2008 [31]	92	24 (28,6%)	10 (42%)	14 (58%)	51.6 ± 12.3	9/15	Stroke or paradoxical embolism	PFO	Amplatzer = 7 pts CardioSeal/Star-flex = 42 pts Cardiastar = 38 pts Helex = 2 pts
Total	1,306	524 (40%)	387 (74%)	137 (26%)					

Table 2. Meta Analysis of 11 studies reported by Gianfranco Butera et al (40)

Luciane Piazza et al. evaluated 42 patients with migraine headache (28 with aura and 14 without aura) after PFO closure for the migraine headache as a primary reason. After 6 months follow up they found complete resolution of the migraine in 26%, and significant improvement in 52% of the study group. Interestingly they found patients improvement (total 78%) regardless of the presence of aura history. Multiple logistic regression analysis showed that the improvement in migraine with aura and migraine without aura was independent of migraine type, sex, age, cerebrovascular risk factors and cerebrovascular events, type of cardiac defect, and thrombophilic conditions (41).

Another study by Andreas Wahl and his group was conducted on 17 patients with Migraine headache underwent closure of the PFO primarily for the headache reason (no stroke). They found total improvement in 71% of their patients with complete resolution of the headache in 26%. Their follow up was up to 30 months. They found slightly higher improvement in patients with aura (42).

Gianluca Rigatelli et al. conducted prospective study on 34 patients with Migraine headache (22 females and 12 male) and underwent closure of the atrial defect by one of two devices (Amplatz cribriform, AGA PFO device or Premere Occlusion System). They found about 55% of their study group have moderate to large atrial septal aneurysm. After a median of 9 months follow up period they have significant improvement in all the patients with 20 patients stopped completely their anti headache medications and the rest have improvement with less number of their medications (43).

The only randomized prospective study with patients blinded for PFO closure conducted for migraine headache is MIST trial. They included about 147 patients randomized for device closure or Sham procedure (patients will have general anesthesia with incision in the groin without device implantation). The study had an ambitious primary end point which was complete cessation of Migraine headache in 40% of the patients who receive PFO device closure. They chose STARFlex® and they have much higher rate of complications in their study (~12%) compared to other PFO device studies. They showed in 6 months no statistical difference between the two groups in complete cessation of Migraine headache. *Post-hoc* analysis revealed that, when two extreme outliers were removed, a significant reduction in the median total headache days was observed in patients assigned to PFO closure ($P = 0.027$). A number of methodological reasons could explain why the primary end point of the MisT trial was not achieved. First, this ambitious primary end point, presumably selected to justify the risks of an interventional procedure, was so strict as to be unrealistic, and was arguably less clinically relevant than a quantifiable reduction in headache days. Although the path physiology of migraine is not fully elucidated, the probable multifactorial nature of migraine triggers means that correction of one potential trigger is unlikely to result in headache cure. Second, the patients for whom migraine improvement was previously reported had PFO closure for either cryptogenic stroke or decompression illness. However, such patients were specifically excluded from the MIST trial. The amount of residual shunt in MIST trial was extremely high (~35%) in 6 months follow up probably due to inherent device limitations used in the study. Other potential confounding factors include the 'hangover effect' of antiplatelet therapy and the difficulty of distinguishing between cardiac-level and pulmonary-level shunt when using transthoracic echocardiography (TTE). nonetheless, as the first randomized, controlled trial of its kind, the MIST trial has pioneered a robust study design for PFO closure trials and raised questions to be addressed in future studies.

In Summery: The association of migraine headache with Patent Foramen Ovale is higher than normal population (more than double) by most of the studies. Trans Cranial Doppler has higher sensitivity than Echo (TTE, TEE or ICE) in detecting the right to left shunt across the atrial septum. Because of the anatomical orientation of the Inferior Vena Cava towards the Foramen Ovale, injection of bubble contrast in lower limbs veins might be higher sensitive than injection in upper limbs veins. Whether the PFO/Migraine association means also a causation relationship: a question still needs more definite answer. Most of the studies (from stroke studies and primary studies for Migraine relief) are pointing towards the causation relationship. Although the only randomized prospective study in the literature failed to show a definite answer, several confounding factors (as mentioned above in the text) can explain the negativity of this study. Most of the studies showed higher response and benefit to patients suffer from Migraine with aura compared to others.

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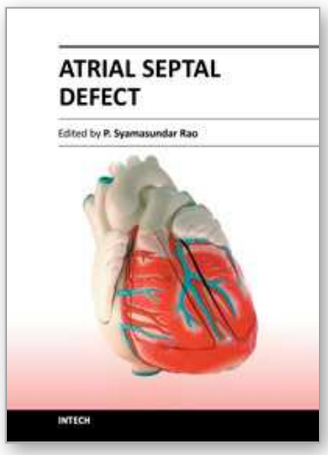

Atrial Septal Defect

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Atrial Septal Defects (ASDs) are relatively common both in children and adults. Recent reports of increase in the prevalence of ASD may be related use of color Doppler echocardiography. The etiology of the ASD is largely unknown. While the majority of the book addresses closure of ASDs, one chapter in particular focuses on creating atrial defects in the fetus with hypoplastic left heart syndrome. This book, I hope, will give the needed knowledge to the physician caring for infants, children, adults and elderly with ASD which may help them provide best possible care for their patients.

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