PARADOXICAL EMBOLISM, MIGRAINE, AND CARDIAC SHUNT CLOSURE

J.G.L.M. Luermans

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Lay-out: Gildeprint Drukkerijen - Enschede, The Netherlands
Cover: Eefke Schramade, EEFKE Design - Den Haag, The Netherlands
Printed: Gildeprint Drukkerijen - Enschede, The Netherlands
ISBN: 978-94-90122-99-7

Publication of this thesis was financially supported by:
Nederlandse Hoofdpijn Vereniging, Remmert Adriaan Laan Fonds, St. Antonius Ziekenhuis, St. Jude Medical, Merck Sharp & Dohme, Menarini Farma and AstraZeneca.

PARADOXICAL EMBOLISM, MIGRAINE, AND CARDIAC SHUNT CLOSURE

Paradoxale embolisatie, migraine
en cardiale shunt sluiting
(met een samenvatting in het Nederlands)

Proefschrift ter verkrijging van de graad van doctor
aan de Universiteit Utrecht
op gezag van de rector magnificus, prof. dr. J.C. Stoof,
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen
op dinsdag 2 februari 2010 des middags te 2.30 uur

door

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geboren op 22 maart 1979 te Maastricht

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Financial support by the Netherlands Heart Foundation for the publication of this thesis is gratefully acknowledged

Aan Christel
en mijn ouders

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Part one

General introduction

Chapter 1

General introduction and outline of the thesis

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Defects in the inter-atrial septum may result in the presence of a cardiac shunt. Depending on the direction and/or size, cardiac shunting is associated with specific disease manifestations. A cardiac right-to-left shunt can result in paradoxical embolism and seems to be associated with cryptogenic stroke and migraine.

Atrial septal abnormalities

Patent foramen ovale

Anatomy and definition

The foramen ovale is a pivotal feature during intrauterine life and is located in the inter-atrial septum, where the septum primum on the left side and the septum secundum on the right side maintain a central communication. Before birth, the lungs are not yet functioning, and so blood bypasses the lungs via the foramen ovale. Immediately after birth the pulmonary vascular resistance drops, causing a decrease in right atrial pressure, which results in a functional closure of the foramen ovale. The latter may lead to fusion of the septa (anatomical closure). If a fusion of both inter-atrial septa does not take place, the foramen ovale remains in a state called "(probe)-patent", as it can open as a (one-way) valve. Under "normal" circumstances left atrial pressure exceeds right atrial pressure and the patent foramen ovale (PFO) will be functionally closed. During the Valsalva maneuver, the backflow to the heart is markedly reduced, and the right and left atrial pressure and volume will decrease. After releasing the Valsalva, the venous return will increase immediately and the right atrial pressure exceeds the left atrial pressure, allowing a right-to-left shunt (RLS) through the PFO during approximately five heartbeats. Hence, in the presence of a PFO, RLS can occur whenever right atrial pressure is greater than left atrial pressure, for example during sneezing or lifting a weight.

Prevalence

A PFO has been found during autopsies in about 27% of the general population with no variance between male and female subjects.[1] The prevalence decreases with each

decade of life from 34% in the first three decades to 20% in the 9th and 10th decades.[1] However, the size of an existing PFO tends to increase with age, from a mean of 3.4 mm in the first decade to 5.8 mm in the 10th decade of life.[1] Two echocardiographic studies have reported the prevalence of PFO in the general population. First, Di Tullio et al. detected a PFO by using transthoracic 2-dimensional echocardiography (TTE) with contrast injection in 14.9% of 1.100 stroke-free subjects older than 39 years of age.[2] Second, Meissner et al. found a prevalence of PFO of 24.3% in 585 subjects older than 45 years by using transesophageal echocardiography (TEE).[3]

Diagnosis

A variety of imaging modalities can be used to diagnose a PFO, such as TTE, transcranial Doppler (TCD) and TEE. The last is considered as the gold standard. The RLS through the PFO can be detected by injection of contrast (agitated saline). An advantage of TEE compared to the other modalities is that the site of the shunt and other anatomic abnormalities can be visualized. A disadvantage is the semi-invasive character. The efficacy of the different imaging modalities has been evaluated in a number of comparative studies. Compared to TEE as the gold standard, a sensitivity of 68-100% and a specificity of 65-100% has been observed for TCD[4-9] and a sensitivity of 22-100% and a specificity of 83-100% for TTE.[4, 6, 9, 10] In addition, an excellent negative predictive value of TCD has been reported.[11] Other diagnostic modalities to detect a PFO include cardiac magnetic resonance imaging (CMRI) and computed tomography (CT). However, these techniques are still under development. Nusser et al. found the present CMRI technique to be inferior to TEE in detection of contrast-enhanced RLS.[12] Nongated multidetector CT has been reported to diagnose high-grade shunts through a PFO with a sensitivity of 91% and a specificity of 98%.[13]

Pathophysiology

In most cases, the presence of a PFO is asymptomatic. However, the PFO has been associated with several clinical features such as cryptogenic stroke[14-16], decompression illness[17], refractory hypoxemia in patients with pulmonary arterial hypertension[18], obstructive sleep-apnea syndrome[19] and migraine.[20] Paradoxical embolism through a PFO implies to be the most likely mechanism in patients with cryptogenic stroke.[21, 22]

PFO closure

The first case series reporting the successful percutaneous transcatheter closure of a PFO by means of an umbrella device was published in 1992.[23] Subsequently, the results of transcatheter PFO closure are associated with improved outcomes. However, the percutaneous PFO closure is still a debated issue. Currently, the American Heart Association/American Stroke Association (AHA/ASA) guidelines[24] for secondary stroke prevention state that "insufficient data exist to make a recommendation about PFO closure in patients with a first stroke and a PFO" and that "PFO closure may be considered for patients with recurrent cryptogenic stroke despite optimal medical therapy" (class IIB, level of evidence C).[24]

Atrial septal aneurysm

Anatomy and definition

An atrial septal aneurysm (ASA) is characterized by redundant tissue in the region of the fossa ovalis that results in excessive mobility of the septal wall. ASA formation can be secondary to inter-atrial pressure differences but may also be a primary malformation involving the region of the fossa ovalis or the entire septum.[25-28] ASA's have been classified according to their intrusion into the left or right atrium or their motion during the respiratory cycle. However, the exact definition has not been well established. Some have defined an ASA as a protrusion of the aneurysm > 10 mm beyond the plane of the atrial septum into either the right or left atrium.[28] Others considered the atrial septum to be aneurysmal when either a dilated portion protruded at least 15 mm beyond the plane of the atrial septum or when the atrial septum showed phasic excursions during the cardio-respiratory cycle of ≥ 15 mm with the base of the aneurysm being ≥ 15 mm.[25]

Prevalence

In large autopsy series, ASA has been found in 1% of the general population, whereas a proportion of 1.9% to 2.5% has been observed in population-based studies using TTE or TEE.[2, 3, 28, 29] An ASA may be an isolated abnormality but is also often associated with other structural cardiac abnormalities, for instance mitral valve prolapse[30, 31] or

other atrial septal abnormalities.[32] Lamy et al. described a prevalence of ASA of 19.1% in cryptogenic stroke patients with a PFO as compared to 3.2% in those without a PFO.[15] In addition, a PFO is more common in patients with ASA. Inter-atrial shunting has been found in up to 78% of patients with ASA.[27-29, 32-35]

Diagnosis

As reported by Mugge et al., TEE is superior to TTE in the diagnosis of ASA.[27, 34] A TEE image of an ASA associated with a PFO is shown in Figure 1.

Pathophysiology

ASA has been associated with ischemic cerebral and/or peripheral embolic events.[25, 27, 32, 35-38] Potential mechanisms of cardio-embolism associated with ASA include RLS through an associated PFO permitting paradoxical embolism, thrombus formation in the ASA, associated mitral valve prolapse, and supraventricular arrhythmias.[27, 37, 39]

ASA treatment

Given the rarity of an isolated ASA, the best treatment for cerebral embolism is unclear.[27] Treating such patients with aspirin makes physiological sense, since the emboli probably originate from fibrin/platelet material dislodged from the left atrial surface of the aneurysm due to abrupt oscillations of the mobile aneurysm.[27] ASA's associated with PFO can be treated either medically or percutaneously.[14, 40, 41]

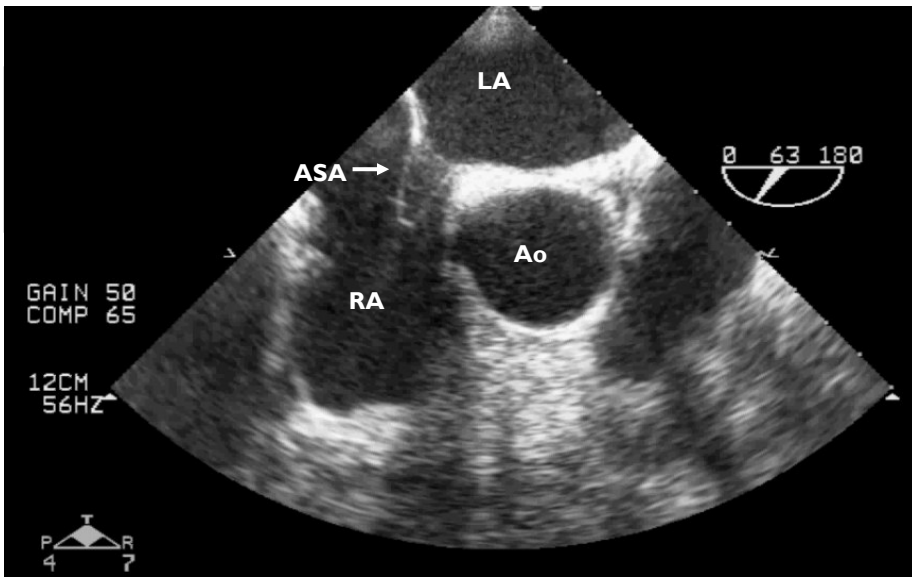

Figure 1. TEE image of ASA and PFO
ASA, atrial septal aneurysm; LA, left atrium; RA, right atrium; Ao, aorta

Atrial septal defect

Anatomy and definition

An atrial septal defect (ASD) occurs when a part of the inter-atrial septum is missing. Anatomically, it may take the form of either an ostium secundum type ASD located in the region of the fossa ovalis, an ostium primum defect in the lower part of the atrial septum, or a sinus venosus defect in the upper atrial septum. Although most ASD's result from spontaneous genetic mutations, some are inherited.[42-45] An ASD is characterized by bidirectional shunting with a predominant left-to-right shunt (LRS) and right ventricular volume overload.[46] However, a small RLS may occur during a Valsalva maneuver or exercise.[47]

Prevalence

An ASD is the most common congenital heart disease at adult age, accounting for about one-third of all congenital heart diseases detected in adults.[48] It occurs in women two to three times more often than in men.[48, 49] Secundum type ASD's make up 75% of all ASD's, ostium primum defects make up 15% and sinus venosus defects make up 10%.[46]

Diagnosis

A definite diagnosis of an ostium secundum type ASD is usually made by TTE. The M-mode echocardiogram shows right ventricular enlargement in patients with a sizable ASD, whereas discontinuity of the septum can be seen on two-dimensional TTE. Color flow, pulsed, and continuous wave Doppler are able to detect the inter-atrial shunt. A contrast injection can either visualize RLS or result in negative contrast in the right atrium in the presence of LRS.[50, 51] TEE is extremely accurate for the diagnosis of all three types of ASD[50, 52] and may aid in the sizing of defects and the assessment of associated anomalies. Additionally, CMRI can be used to determine defect size, estimate shunt flow and detect other anomalies.[53-56] During cardiac catheterization a step-up in oxygen saturation, which is indicative of a shunt, can be measured and the shunt fraction calculated. A TEE image of a secundum type ASD is shown in Figure 2.

Pathophysiology

A small ASD with minimal shunting usually causes no symptoms or haemodynamic abnormalities. Most patients with a moderate to large defect remain asymptomatic during the first two decades of life.[46] Eventually, though, most develop symptoms and disease manifestations, such as cardiac failure, pulmonary hypertension, atrial arrhythmias and paradoxical embolism, the last due to RLS.[47, 48] Some patients develop Eisenmenger syndrome with irreversible pulmonary hypertension and reversal of shunt flow to a predominantly right-to-left direction.[57]

ASD closure

The two main indications for closure of an ASD are the development of symptoms and a high rate of shunt flow. Surgical ASD closure used to be the only viable option when shunting compromised life expectancy.[58,59] The clinical feasibility of transcatheter ASD closure was first described by King and Mills in 1976.[60, 61] Although surgical closure has been the traditional recommendation, transcatheter closure has gained more acceptance, with similar success rate of closure, lower complication rates, and shorter length of hospital stay.[62] Nowadays, transcatheter closure is widely practiced and has to a large extent replaced the surgical closure of secundum type ASD's in many centres.[63]

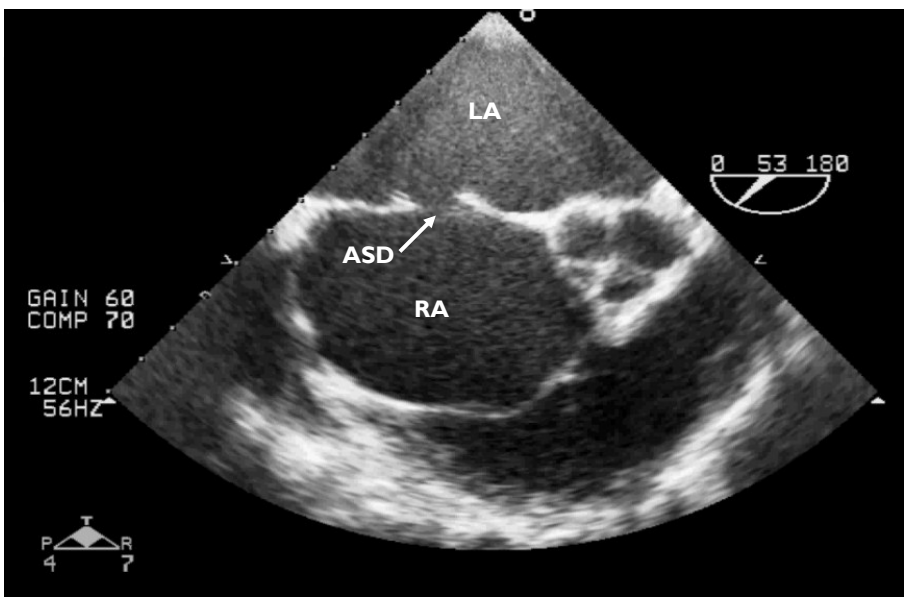

Figure 2. TEE image of secundum type ASD

ASD, atrial septal defect; LA, left atrium; RA, right atrium

Cryptogenic stroke

Definition

Stroke is the third leading cause of death among adults and a major contributor to long-term functional impairment and disability.[64] While a specific etiology can be found in 60 to 70% of patients suffering ischemic stroke[65, 66], no etiology can be found in the remaining patients. The latter are appropriately termed "cryptogenic".[67]

The definition of cryptogenic stroke was established in the "Trial of Org 10172 in Acute Stroke Treatment (TOAST)" study. In that study, the term "cryptogenic stroke" or "stroke of undetermined origin" was applied if a brain infarction could not, despite an extensive evaluation including imaging and cardiac and serologic studies, be attributed to a specific category of either cardio-embolism, large artery atherosclerosis or small artery disease.[68]

Prevalence

In 2007 in the Netherlands, 37.129 patients were admitted and 9.518 patients died because of stroke.[69] Eighty-seven percent of all strokes have an ischemic origin.[70] Cryptogenic stroke accounts for about 30 to 40% of ischemic stroke.[66, 71-74] In patients less than 55 years of age, higher proportions of cryptogenic stroke of about 64% have been observed.[75] However, in the "Northern Manhattan Stroke Study (NOMASS)" 55% of strokes in patients younger than 45 years were cryptogenic compared to 42% in the age group older than 45 years.[76] Other stroke registries found lower rates of 23-34%, similar to those in older age groups.[77-79]

Association with PFO

As early as 1877 the suspicion of a PFO mediated stroke was published by the German pathologist Cohnheim.[80] Since 1988, several case control and prospective studies reported a high prevalence of PFO in patients with cryptogenic stroke.[14-16, 81-86] These studies are summarized in Table 1. A prevalence of PFO between 28-54% has been observed in patients with cryptogenic stroke.[14-16, 81-86] This association has mainly been described in patients younger than 55 years.[16, 84, 86] However, Di Tullio et al. described an association in all age groups[81], which was later confirmed in the

prospective study by Handke et al.[83] Nedeltchev et al. reported a higher prevalence of PFO in men (38%) compared to women (28%) with cryptogenic stroke.[87] However, Gupta et al. could not confirm a corollary to gender.[82]

Different PFO characteristics have been identified as risk factors for cryptogenic stroke. Homma et al. found larger PFO's with a more extensive RLS in patients with cryptogenic stroke as compared to patients with stroke of known cause.[88] Additionally, Stone et al. found that patients with a large degree of shunting across a PFO were at significantly higher risk for subsequent adverse neurologic events compared to patients with a small degree of shunting.[89] Moreover, de Castro et al. observed that patients with PFO and acute stroke or TIA more frequently presented with RLS at rest and a higher membrane mobility than PFO patients without cerebral ischemic events.[90] In several studies, the presence of an ASA or a large RLS has been reported to increase the risk of stroke in patients with PFO.[24] Indeed, besides the PFO, the presence of ASA has also been associated with cryptogenic stroke.[27, 29, 33, 34, 75] In a meta-analysis of all case control studies describing the relation of cryptogenic stroke, PFO, and ASA, a significant association was found between PFO, ASA, and cryptogenic strokes in patients younger than 55 years of age but not above that age.[91] However, Handke et al. found a higher prevalence of PFO and ASA among both younger and older patients with cryptogenic stroke as compared to patients with stroke of known cause.[83] The presence of PFO was independently associated with cryptogenic stroke in both age groups.[83]

However, prevalence rates of PFO in patients with cryptogenic stroke do not equate with the longitudinal risk of stroke among asymptomatic subjects with a PFO. In the "Northern Manhattan Study (NOMAS)", a multi-ethnic cohort study of 1.100 stroke-free subjects with a mean age of 69 years, the presence of a PFO, with or without ASA, was not associated with an increased risk of stroke during a follow-up period of 80 months.[2] Similarly, in the prospective "Stroke Prevention: Assessment of Risk in a Community (SPARC)" study, in a random sample of 585 subjects > 45 years of age, the PFO was not an independent predictor of stroke during a median follow-up of 5.1 years.[3] However, the risk of a cerebrovascular event among subjects with ASA was nearly four times higher than that among subjects without ASA.[3] Significantly, in the NOMAS, only 15% of all patients were diagnosed a PFO.[2] This low prevalence of

documented PFO's, probably due to the low sensitivity of TTE, might have generated flawed data. It can be assumed that almost half of the PFO carriers were erroneously followed up in the group considered to have no PFO, perhaps explaining the lack of difference in stroke risk between PFO carriers and non-carriers. However during the SPARC study, a PFO was detected by TEE in 24.3% of patients, which is comparable with reported trends during autopsy studies.[1] The SPARC study also indicated that the presence of a PFO was not a predictor of stroke. However, in this study only few cerebrovascular events occurred during follow-up, a factor potentially limiting the ability for this study to detect a statistically significant hazard.[3]

To summarize, the presence of a PFO (and ASA) has been associated with cryptogenic stroke. However, a large community-based study with appropriate imaging techniques to detect a PFO and with a long follow-up duration is required to assess the longitudinal risk of stroke among asymptomatic subjects with a PFO (and/or ASA).

Pathophysiology of PFO in patients with cryptogenic stroke

Paradoxical embolism of thrombus through a PFO implies to be the most likely pathophysiologic mechanism in relatively young patients with cryptogenic stroke.[21, 22] In most case series, however, deep venous thrombosis and/or thrombus in transit have been identified in a minority of patients with PFO and cryptogenic stroke.[92, 93] Other potential mechanisms of cryptogenic stroke among patients with PFO include in situ thrombus formation secondary to stasis of blood in the PFO or paroxysmal atrial fibrillation.[94]

Table I. Prevalence of PFO in patients with (cryptogenic) stroke

Author	Year	Diagnostic test	Age (y)	Patients	N	Prevalence of PFO (%)
Lechat[16]	1988	TTE	<55	Cryptogenic stroke	26	54
				Control	100	10
Webster[86]	1988	TTE	<40	Ischemic stroke	40	50
				Control	40	15
Hausmann[84]	1992	TEE	<40	Cryptogenic stroke	18	50
Di Tullio[81]	1992	TTE	<55	Cryptogenic stroke	21	48
				Stroke of known cause	24	4
			≥55	Cryptogenic stroke	24	38
				Stroke of known cause	77	8
Steiner[85]	1998	TEE	64	Cryptogenic stroke	42	45
				Stroke of known cause	53	23
Homma[14]	2002	TEE	59	Cryptogenic stroke	265	39
				Stroke of known cause	365	30
Lamy[15]	2002	TEE	<55	Cryptogenic Stroke	581	46
Handke[83]	2007	TEE	<55	Cryptogenic stroke	82	44
				Stroke of known cause	49	14
			≥55	Cryptogenic stroke	145	28
				Stroke of known cause	227	12
Gupta[82]	2008	TEE	62	Ischemic stroke	974	30
			<30	Ischemic stroke	unknown	39

y, years; N, number; PFO, patent foramen ovale; TTE, transthoracic echocardiography; TEE, transesophageal echocardiography.

Management of patients with PFO and cryptogenic stroke

Cryptogenic stroke patients with PFO are at risk for stroke recurrence.[24] Although long-term treatment with antiplatelets or oral anticoagulants has traditionally been proposed in this patient population, there is still a high rate of recurring stroke or TIA despite medical treatment.[14, 40] Percutaneous PFO closure is suggested as an alternative or an additive to medical therapy for secondary prevention of (cryptogenic) stroke.[95-98] However, the most appropriate therapy to prevent recurrent events in cryptogenic stroke patients with PFO is unknown and remains controversial.

Currently, both the AHA/ASA[24] and American College of Chest Physicians (ACCP) guidelines[99] recommend antiplatelet therapy for patients with ischemic stroke or TIA in the presence of a PFO (AHA/ASA, class IIA, level of evidence B; ACCP, grade 1A), unless indications exist for oral anticoagulants (AHA/ASA, class IIA, level of evidence C; ACCP, grade 1C). The AHA/ASA guidelines state that "insufficient data exist to make a recommendation about PFO closure in patients with a first stroke and a PFO. PFO closure may be considered for patients with recurrent cryptogenic stroke despite optimal medical therapy (class IIB, level of evidence C)."[24]

Migraine

Definition

Migraine is a common neurological disorder with a large impact on the quality of life and social activities.[100] It is associated with substantial functional impairment,[101] which may include both physical and emotional ramifications. Migraine is an episodic neurovascular disorder that is diagnosed according to the criteria of the International Classification of Headache Disorders (ICHD-II) from the International Headache Society.[102]

Migraine attacks are characterized by severe, often unilateral, pulsatile headache that can be accompanied by nausea, vomiting, or hypersensitivity to sound and light. The headache increases with daily activities and attacks typically last several hours to days. Migraine with aura is defined as migraine accompanied by transient neurological aura symptoms. Aura symptoms almost always include visual symptoms, but sensory- or speech-related symptoms can also be involved.[103] One-third of migraine patients experience aura symptoms[104] and these usually occur before the headache phase, lasting from 20-60 minutes.

Prevalence

Migraine is a prevalent disorder that occurs in 10 to 12% of the general population, with 6% in men and 15 to 18% in women.[105-107] The prevalence of migraine increases with age until a peak prevalence of about 27% in women is reached in the fourth decade of life.[107]

Pathophysiology

Migraine seems to be a complex disorder in which both genetic and environmental factors play an important role.[108] Current molecular genetic insight into the pathophysiology of migraine comes predominantly from studies of a rare monogenic subtype of migraine with aura called familial hemiplegic migraine (FHM). Three FHM genes have been identified,[109-111] all of which encode ion transporters, suggesting that disturbances in ion and neurotransmitter balances in the brain are responsible for this migraine type, and possibly the common forms of migraine. Genetic investigations in patients with common forms of migraine has had limited success so far.[112] There has been a great deal of research into the mechanisms of migraine. The mechanisms for the aura and headache are relatively well understood, though little is known about why and how a migraine attack is initiated. The current view is that migraine has a neurovascular origin.[113] The headache is caused by the activation of the trigeminovascular system, which consists of blood vessels that are innervated by the trigeminal nerve. The trigeminovascular system projects to the trigeminal nucleus caudalis in the brainstem, which in turn projects into higher-order pain centers giving rise to the headache.

The aura is thought to be produced by "cortical spreading depression" (CSD).[114] CSD is characterized by a short-duration depolarization wave that progresses slowly over the cortex, followed by an inhibition of neuronal activity.[115] Elevated extracellular levels of potassium and glutamate are integral to the initiation and propagation of CSD. The electrophysiological changes caused by CSD are associated with a brief reduction, followed by a profound increase, in cerebral blood flow over the course of several minutes. Afterwards blood flow is reduced again for up to an hour. There is considerable clinical evidence suggesting that CSD is the likely basis of the migraine aura.[116-119] How this cascade is triggered, however, is to a large extent unclear. Evidence from animal experiments suggests that CSD might activate the trigeminovascular system, linking the mechanisms for aura and headache.[120] However, the connection between CSD and headache in patients remains an open question.[121, 122]

Association with PFO

A relationship between migraine and the presence of RLS, as seen in patients with PFO, has been supposed. In several studies, a high prevalence of RLS has been observed in patients with migraine with aura (MA+), but not migraine without aura (MA-). Initial reports found RLS by TCD in 41-62% of patients with MA+.[123-125] These findings were reproduced by Dowson et al., who observed RLS, as diagnosed by a contrast TTE, in 60% of 432 MA+ patients.[126] Schwerzmann et al. showed, by using a contrast TEE, that mainly larger PFO's were present in patients with MA+. This compared with controls, 38% vs. 8%.[127] Moreover, Anzola et al. analyzed shunt size with TCD in 420 patients and found a RLS twice as large in migraineurs than in non-migraineurs.[128] The largest shunts were seen in patients with a history of migraine and stroke.[128] The prevalence of RLS in patients with MA+ in comparison with patients with MA-, cluster headache, cryptogenic stroke or controls is summarized in Table II.

Conversely, in patients with a symptomatic RLS occurring by means of a paradoxical embolic event or decompression illness, a higher prevalence of migraine has been observed. Wilmshurst and Nightingale studied 200 patients with decompression illness and found a prevalence of MA+ of 48% in patients with RLS compared to 14% without.[20] Sztajzel et al. studied 74 patients with a cryptogenic stroke and found a prevalence of MA+ of 36% in patients with a PFO in comparison to 13% in patients without.[129] Lamy et al. reported in 581 cryptogenic stroke patients a prevalence of migraine of 27% in patients with PFO as compared to 14% in those without.[15] These studies are summarized in Table III.

These reports suggest an association between migraine, particularly MA+, and the presence of RLS. Moreover, this association seems to exist independent of shunt anatomy. In patients with ASD, who occasionally also exhibit RLS, a high prevalence of migraine of 30% and MA+ of 11-17% has been observed as well.[130-132] Moreover, the relationship has not only been described for cardiac RLS but also for pulmonary RLS. Post et al. studied 538 patients with hereditary haemorrhagic telangiectasia. These patients are characterized by a high prevalence of a pulmonary RLS through a pulmonary arteriovenous malformation (PAVM). They reported a significantly higher prevalence of migraine of 21% in patients with PAVM compared to 13% in those without.[133]

Table II. Prevalence of a right-to-left shunt in patients with migraine with aura compared with patients with migraine without aura, cluster headache, cryptogenic stroke or controls

Author	Year	Diagnostic test	Patients	N	Prevalence of RLS (%)
Del Sette[125]	1998	TCD	MA+	44	41
			Cryptogenic stroke	73	35
			Control	25	20
Anzola[123]	1999	TCD	MA+	113	48
			MA-	53	23
			Control	25	20
Dalla Volta[124]	2005	TCD	MA+	260	62
			MA-	74	16
			Cluster headache	38	37
Schwerzmann[127]	2005	TEE	MA+	93	47
			Control	93	17
Dowson[126]	2008	TTE	MA+	432	60

N, number; RLS, right-to-left shunt; TCD, transcranial Doppler; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography; MA+, migraine with aura; MA-, migraine without aura.

However, all these observational reports do not equate with a population-based, multi-ethnic cohort study by Rundek et al. In this substudy of the NOMAS[2], 1.100 stroke-free subjects were assessed for self-reported history of migraine.[134] The presence of a PFO was assessed by TTE. They found a prevalence of PFO of 15% in both patients with and without migraine. No correlation between PFO and migraine was found.[134] However, as already described, a 15% prevalence of a PFO is remarkably low. This might have influenced the results. Moreover, the mean age of the study subjects was 69 years, which also could have influenced the results.

Table III. Prevalence of migraine with aura in patients with and without right-to-left shunting

Author	Year	Diagnostic test	Patients	Shunt	N	Prevalence of MA+ (%)
Wilmshurst[20]	2001	TTE	Decompression	Large shunt	80	48
				No shunt	80	14
Sztajzel[129]	2002	TCD/TEE	Cryptogenic stroke	PFO	44	36
				No PFO	30	13
Lamy[15]	2002	TEE	Cryptogenic stroke	PFO	267	27[a]
				No PFO	314	14[a]

N, number; MA+; migraine with aura; TTE, transthoracic echocardiography; TCD, transcranial Doppler; TEE, transesophageal echocardiography; PFO, patent foramen ovale. [a]migraine prevalence

Pathophysiology and management of PFO in patients with migraine

Several pathophysiological hypotheses have been proposed to explain the association between migraine and PFO. A common explanation is that a PFO provides an anatomic substrate for RLS of migraine trigger substances to the brain. These triggers are otherwise trapped in the pulmonary capillaries. This hypothesis shows a lot of resemblance with that of the association between a PFO and cryptogenic stroke. Indeed, it is suggested that migraine and cryptogenic stroke share a common cause: the RLS (through a PFO). The relationship between migraine, stroke, and a PFO has been the subject of considerable research efforts. In fact, a lot of interest has focused on the potential benefits of percutaneous PFO closure.

Aims and outline of the thesis

This thesis concerns the transcatheter closure of inter-atrial shunts, in particular its efficacy in the management of patients with paradoxical embolic events and its effect on the occurrence of migraine.

In chapters 2 and 3 the efficacy and safety of percutaneous PFO closure in patients with paradoxical embolic events is examined, using the fourth generation Intrasept™ closure device and the biodegradable Biostar® device respectively. Chapter 4 deals with the same subject and describes a single centre experience using different device types for PFO closure. In chapter 5 the feasibility and success rate of percutaneous PFO closure in older patients with cryptogenic stroke is examined. Chapter 6 concerns the efficacy and safety of transcatheter ASD closure. In chapter 7 the haemodynamic effects of percutaneous PFO and ASD closure are examined, using non-invasive measurements. In chapter 8 a case of thrombosis on an ASD closure device is described. Finally, in chapters 9 and 10, the effects of respectively transcatheter PFO and ASD closure on the prevalence of migraine is studied.

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Part two

Percutaneous atrial shunt closure

Chapter 2.1

Outcome after percutaneous closure of a patent foramen ovale using the INTRASEPT™ device: A multi-centre study

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Catheterization and Cardiovascular Interventions 2008; 71: 822-828

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Abstract

Objectives: This multi-centre study reports safety and efficacy of percutaneous patent foramen ovale (PFO) closure, using the fourth generation Intrasept™ device.

Background: PFO has been associated with paradoxical embolism and cryptogenic stroke. Percutaneous PFO closure seems to reduce the risk for recurrent paradoxical thrombo-embolism. Currently, different devices are used for PFO closure.

Methods: Patients, who underwent a PFO closure with the Intrasept™ device (Cardia, Eagan, MN) between July 2002 and September 2006, were included in the study. The primary endpoint was defined as reoccurrence of stroke, transient ischemic attack (TIA), or peripheral thrombo-embolism. Peri-procedural and mid-term complications were reported.

Results: Four-hundred thirty patients (mean age 50.7±13.0 years, 231 men) underwent closure. The indications were cryptogenic stroke (69.8%), TIA (23.5%), peripheral embolism (3.3%), and other (3.5%). The median follow-up time was 0.8 years, range 3.9 years. The primary endpoint occurred in 0.5% for stroke, in 2.5% for TIA, and in none for peripheral embolism. Peri-procedural complications were reported in 11.5% of cases, from which 0.2% was defined as major. No severe complications occurred during mid-term follow-up.
A residual shunt was present in 12.5% of patients who did not suffer from a recurrent event, compared to 36.4% of patients who reached the primary endpoint (P=0.04).

Conclusion: This multi-centre study suggests that percutaneous closure of a symptomatic PFO with the fourth generation Intrasept™ device is safe and might be effective to prevent the recurrence of paradoxical thrombo-embolic events.

Introduction

The presence of a patent foramen ovale (PFO) has been associated with cryptogenic stroke.[1] This association is mainly found in patients younger than 55 years.[2-4] Indeed, paradoxical embolism through a PFO implies to be the most likely mechanism in relatively young patients with cryptogenic stroke.[5, 6] Moreover, the presence of an associated atrial septal aneurysm (ASA) seems to be related to a higher risk for stroke recurrence.[7-9] Although long-term treatment with antiplatelets or oral anticoagulants has traditionally been proposed, high recurrence rates of cerebrovascular events are reported.[9, 10]

Percutaneous PFO closure is suggested to be an alternative or an additive to medical therapy for secondary stroke prevention. Device closure has been shown to be feasible[11-14], but differences in efficacy, safety, and outcome between devices are reported.[11-16]

This multi-centre study describes the safety and efficacy of the fourth generation Intrasept™ device (Cardia, Eagan, MN).

Methods

Study population

Seven centres all over Europe participated in the study. Four-hundred thirty patients with a minimum age of 16 years (231 men, mean age 50.7±13.0 years), who underwent percutaneous PFO closure between July 2002 and September 2006, and in whom the Intrasept™ device was used, were included in the study. Four-hundred one patients (93.3%) had a history of cryptogenic stroke, including four patients with a retinal infarction. Fourteen patients (3.3%) suffered from a peripheral embolism. The presence of a right-to-left shunt (RLS) through a PFO was diagnosed by contrast (agitated saline) transesophageal echocardiography (TEE) with or without Valsalva-maneuver. An ASA was defined as a bulging of the atrial septum of at least 10 mm.

The study was approved by the local ethics committee of all centres.
Patients, PFO characteristics, and the indication for PFO closure are summarized in Table 1.

Characteristics of the Intrasept™ device

The Intrasept™ device (Cardia, Eagan, MN) is a double umbrella device with twofold six stranded wire arms. Each arm consists of 19 woven strands of Nitinol, formed with a shape memory and having atraumatic tips. The seals are made of polyvenyl alcohol (Ivalon™). An additional foam plug is present between the two umbrellas. The device has an articulating centre post for optimal adaptation on the septum and the Intrasept™ device is available in four sizes: 20-25-30-35 mm (Figure 1A). The 20 mm device requires a 10 French sheath for delivery, the 25 mm an 11 French sheath and the 30 and 35 mm device a 12 French sheath. Delivery is done with a forceps (Figure 1B) and the sizes used for this study are summarized in Table 1.

PFO closure

PFO closure was performed under general anaesthesia (propofol) in 77% of the cases. The remaining 23% underwent closure with local anaesthesia (midazolam). Continuous TEE monitoring was done in all patients. After accessing the right femoral vein, a bolus of 2500 to 5000 U of heparin was administered intravenously. Sheaths up to 12 French were used. The devices were implanted under fluoroscopic and echocardiographic guidance according to the standard technique as previously reported.[14] All patients received an intravenous prophylactic dose of antibiotics one hour before and six hours after closure (in most cases 1-2 grams of cefazolin).
Within 24 hours after closure, a chest X-ray and a transthoracic echocardiogram (TTE) were performed. All patients were discharged on antiplatelet therapy (clopidogrel 75 mg for at least four weeks and a minimum dose of aspirin 100 mg for at least six months). Prophylaxis against bacterial endocarditis was advised for a minimum of six months after discharge from the hospital.

Table I. Patients, PFO (closure) and device characteristics, and indications for PFO closure

	Number or value	Percentage (%)
Total	430	
Mean age ± SD (y)	50.7 ± 13.0	
Men	231	53.7
Women	199	46.3
Mean BMI ± SD[a] (kg/m²)	26.0 ± 4.4	
PFO characteristics		
RLS spontaneous[b]	66	18.3
RLS Valsalva	430	100
Aneurysm IAS[c]	193	45.4
Indication for closure		
Stroke	300	69.8
Single	223	51.9
Multiple	77	17.9
Stroke + additional TIA or peripheral thrombo-embolism	33	7.7
TIA	101	23.5
Single	73	17.0
Multiple	28	6.5
Peripheral embolism	14	3.3
Other	15	3.5
Diameter Intrasept™ device[d]		
20 mm	16	3.7
25 mm	304	70.9
30 mm	108	25.1
35 mm	1	0.2
Median fluoroscopic time; range[e] (min.)	6.0; 0.9 – 94	
Mean duration of hospitalization ± SD[f] (days)	2.2 ± 0.7	

SD, standard deviation; y, years; BMI, body mass index; kg/m², kilograms per square meter; PFO, patent foramen ovale; RLS, right-to-left shunt; IAS, inter-atrial septum; TIA, transient ischemic attack; mm, millimetres; min., minutes.

[a]Data available in 417 patients; [b]data available in 360 patients; [c]data available in 425 patients; [d]data available in 429 patients; [e]data available in 196 patients; [f]data available in 405 patients.

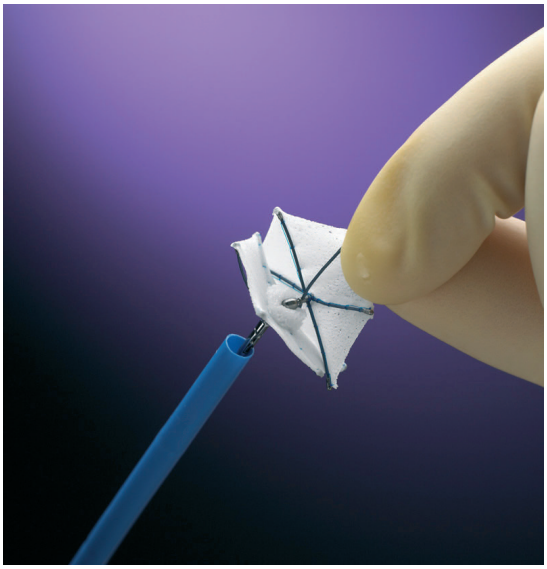

Figure 1A. Intrasept™ device (Cardia, Eagan, MN).

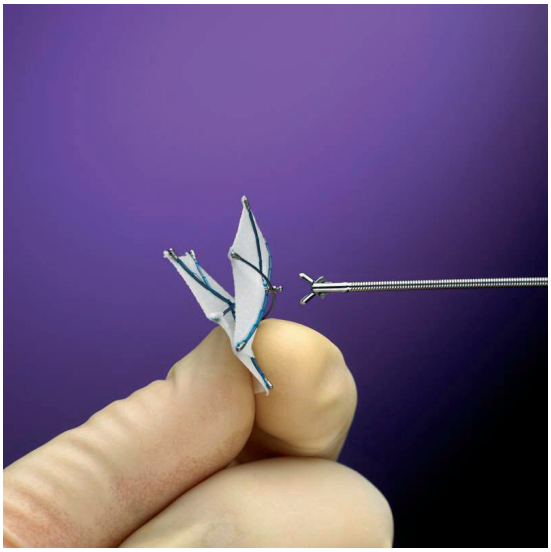

Figure 1B. Delivery of the device through a 10 - 12 French sheath using the forceps technique.

Follow-up evaluation (outcome, complications, and efficacy)

Follow-up information was obtained by periodical out-patient visits. The most recent medical records were reviewed.

The primary endpoint was defined as reoccurrence of stroke, transient ischemic attack (TIA), or any other thrombo-embolic event. When more than one event occurred, only the first event was counted for statistical analysis. All neurological embolic events needed to be established by a neurologist and, in case of stroke, confirmed by appropriate cerebral imaging.

Complications immediately related to the closing procedure and complications occurring within one month after PFO closure were noticed. Mid-term complications, defined as complications occurring at least one month after the closing procedure, were retrieved from the patients' records. Complications were categorized into major and minor, according to the classification used by Khairy et al.[17] Major complications included haemorrhage requiring blood transfusion, occurrence of cardiac tamponade, need for procedure related surgical intervention, massive fatal pulmonary emboli and death, related to the closing procedure. Minor complications were defined as device malpositioning with successful repositioning, bleeding not requiring blood transfusion, occurrence of new atrial arrhythmias (atrial flutter or fibrillation), transient atrioventricular node block, device arm fractures, device embolization with successful catheter retrieval, asymptomatic device thrombosis, need for recatheterization, transient air embolism, transient ST-segment elevation, femoral arteriovenous fistula formation, femoral haematoma, and other minor complications related to the closing procedure.

Efficacy of PFO closure was defined as the absence of residual shunting, based on a contrast TEE, TTE, or a transcranial Doppler (TCD) study.

Statistical analysis

Descriptive statistics were used to report patients' characteristics. Continuous variables were tested on normality and, if present, reported by mean ± standard deviation (SD). If normality was not present, data were reported by median and range (minimum and maximum). Percentages were used to report categorical variables; the Fisher exact test was performed where applicable. Kaplan-Meier survival analysis was

done on the primary endpoint. All tests were two sided and P<0.05 was considered to be statistically significant. All statistical analyses were performed using SPSS software (SPSS, version 11.5 for Windows).

Results

Results of follow-up evaluation

Outcome

The primary endpoint was reached in 12 patients within a median follow-up time of 0.8 years, range 0.02 - 3.9 years. The primary endpoint occurred in 0.5% for stroke and 2.5% for TIA. None of the patients developed a recurrent peripheral embolism. Kaplan-Meier event free survival curves are plotted in Figure 2A and B, respectively.

Two patients developed a stroke. A 77-year-old man had a stroke 0.3 years and a TIA 0.9 years after closure. A 70-year-old man suffered from stroke 0.5 years after closure. In the latter, residual RLS was present. TIA occurred in three patients within the first month after the procedure. Residual RLS was present in one of these. After one month, seven patients had TIA during the follow-up period. Residual RLS was present in one of these seven patients.

Two patients died during the entire follow-up period: a 49-year-old man because of severe systemic atherosclerosis and a 69-year-old woman after an acute coronary syndrome. Both deaths were considered not to be related to PFO closure. The outcome data are summarized in Table II.

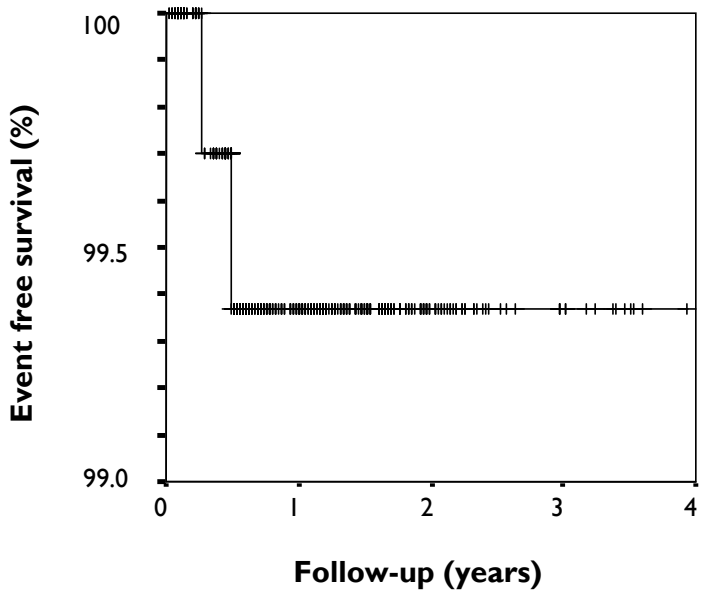

Figure 2A. Kaplan-Meier event free survival curve for stroke.

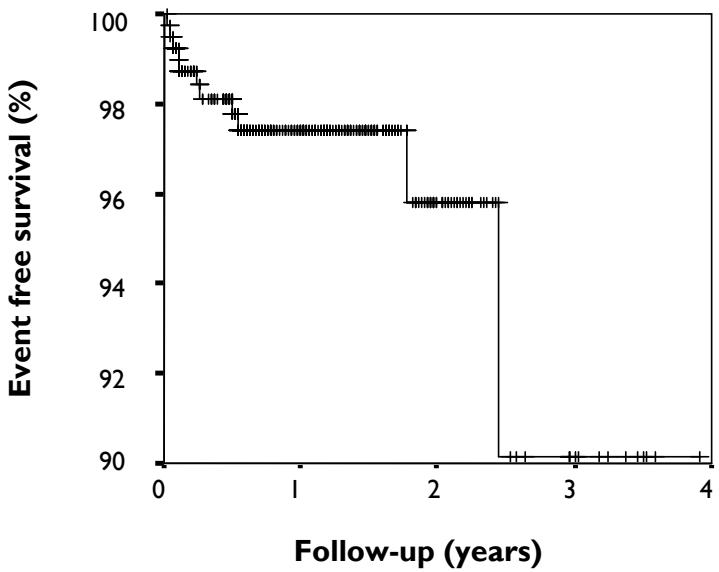

Figure 2B. Kaplan-Meier event free survival curve for stroke or TIA.

Table II. Outcome, complications, and efficacy

	Peri-procedural and < 1 month after PFO closure	> 1 month after PFO closure
Primary endpoint, n (%)		
Stroke	0 (0)	2 (0.5)[a]
TIA	3 (0.7)	7 (1.8)[a]
Other thrombo-embolic event	0 (0)	0 (0)[a]
Death, n (%)	0 (0)	2 (0.5)[a]
Complications, n (%)		
Major complications		
Hemorrhage requiring transfusion	0 (0)	0 (0)[a]
Cardiac tamponade	1 (0.2)	0 (0)[a]
Need for surgical intervention	0 (0)	0 (0)[a]
Massive fatal pulmonary emboli	0 (0)	0 (0)[a]
Death related to PFO closure	0 (0)	0 (0)[a]
Minor complications		
Device malposition	4 (1.3)[b]	0 (0)[c]
Bleeding not requiring transfusion	0 (0)	0 (0)[a]
New atrial arrhythmia	22 (5.1)	4 (1.1)[a]
Transient atrioventricular node block	0 (0)	0 (0)[a]
Device arm fracture	0 (0)	0 (0)[a]
Device embolization	0 (0)	0 (0)[a]
Asymptomatic device thrombosis	1 (0.2)	1 (0.4)[c]
Need for re-catheterization	0 (0)	0 (0)[a]
Symptomatic air embolism	0 (0)	0 (0)[a]
Transient ST-segment elevation	1 (0.2)	0 (0)[a]
Arteriovenous fistula formation	0 (0)	0 (0)[a]
Femoral haematoma	8 (1.9)	0 (0)[a]
Other	11 (2.6)	4 (1.1)[a]
Efficacy, n (%)		
Residual shunting	42 (10.3)[d]	46 (13.2)[e]
Reintervention	0 (0)	4 (1.1)[a]

n, number; TIA, transient ischemic attack; PFO, patent foramen ovale.

[a]Data available in 379 patients; [b]data available in 298 patients; [c]data available in 256 patients; [d]data available in 409 patients; [e]data available in 348 patients.

Peri-procedural and within one month complications

The overall peri-procedural complication rate was 11.5%. Major complications occurred only in 0.2% of the cases. One patient developed a cardiac tamponade, which could be successfully treated by pericardiocentesis. This complication was procedure, and not device related. Malpositioning occurred in four patients. However, repositioning or replacing was easy to do. Twenty-two patients developed (mostly transient) atrial arrhythmia. One patient was diagnosed to have a right ventricular thrombus during the procedure, which was not identified during echocardiography preclosure. In this patient, the closing procedure was abandoned and oral anticoagulants were started. One patient had ST-segment elevation immediately after closure, but it resolved spontaneously. Eight patients developed femoral haematoma; none of them needed surgical intervention or transfusion. Other complications included the following: three patients experienced palpitations because of premature ventricular complexes; three patients experienced mild cutaneous allergic reactions, one due to the use of cefazolin and two probably due to the use of clopidogrel; migraine with aura occurred in one patient; an other patient experienced nausea and vomiting after anaesthesia; two patients had fever of unknown origin, which lasted a few hours and resolved spontaneously; one patient suffered from pericarditis, successfully treated with medication.

Mid-term complications

The mid-term complication rate was 2.6% for a median follow-up time of 0.8 years, range 0.02 - 3.9 years. No major complications occurred during this period. Four patients developed atrial arrhythmia. One of them underwent a successful pulmonary vein ablation for atrial fibrillation. Transseptal puncture was done through the native inter-atrial septum. In one patient, a small thrombus on the left side of the closure device was detected by echocardiography at 9.2 months. Oral anticoagulants were started and no clinical events occurred. Other complications included the following: one patient had a mild cutaneous allergic reaction, probably because of clopidogrel; two patients complained of migraine with aura; one patient experienced recurrent epistaxis, even after stopping clopidogrel. These data are summarized in Table II.

Efficacy of the Intrasept™ device

TEE data immediately after device implantation were available in 409 of 430 patients. In 42 patients (10.3%) residual RLS was documented.

During follow-up, 348 patients underwent an ultrasound examination (TEE in 255, TTE in 69, and TCD in 24 patients). In 46 of 348 patients (13.2%), residual RLS was found. In most (90%), residual RLS was seen between both umbrellas of the device.

Residual RLS was present in 36.4% of the patients that reached the primary endpoint versus 12.5% of the patients without recurrent events during follow-up (P=0.04). No association between the diameter of the device and the presence of a residual shunt could be found.

During follow-up, four patients underwent reintervention with implantation of a second device because of RLS: three patients received another Intrasept™ device and one patient an Amplatzer PFO Occluder (AGA Medical Corporation, Golden Valley, MN). Efficacy data are summarized in Table II.

Discussion

The main finding of our study was that percutaneous PFO closure with the fourth generation Intrasept™ device after a history of paradoxical embolism seems to be safe and effective. The reoccurrence of stroke and TIA was low.

Recurrent thrombo-embolic events

In several observational studies, percutaneous PFO closure has been shown to be effective in the prevention of recurrent thrombo-embolic events.[11, 12, 14, 15, 18, 19] In a systematic review by Khairy et al., the one-year reoccurrence of neurological thrombo-embolism was between 0 and 4.9% after transcatheter intervention and between 3.8% and 12.0% after medical treatment.[17] Windecker et al. showed that percutaneous closure was at least as effective as medical treatment for the prevention of recurrent cerebrovascular events, and even more effective in patients without residual RLS after closure and a history of more than one cerebrovascular event.[20]

The recurrence rate of thrombo-embolism seemed to be the highest in the first

year after PFO closure. Device-related problems are hypothesized to explain this.[14] Therefore, the clinical outcome of different devices has been redundantly reported in literature. However, recurrence rates were dependent on follow-up time, definition of the clinical endpoints, and again the device type used.[11, 12, 14, 15, 18, 19, 21] The buttoned device (Sideris), Amplatzer PFO Occluder (AGA Medical Corporation, Golden Valley, MN), Angel-wings Occluder, Cardioseal Septal Occluder (NMT Medical), and the older generation PFO Star devices (Cardia, Eagan, MN) were, and some of them, are currently widely used in the treatment of cryptogenic stroke.

With the fourth generation Intrasept™ device from Cardia, Eagan, MN, we found a recurrence rate of thrombo-embolic events of 3.0% for a median follow-up time of almost one year. These results are equivalent with other devices. However, a recurrent neurological event might not only be related to the failure of the device (residual RLS, thrombus formation on the device) alone. Indeed, we found stroke recurrence in two patients, but both were older than 70 years, and, probably, at higher risk for systemic atherosclerosis. The latter suggests that outcome is also related to the correct indication for PFO closure. Indeed, at the age of 55 years or older, the relationship between the presence of a PFO and cryptogenic stroke is less well defined.[2, 22, 23] In addition, the prevalence of ASA in our study population was higher (45.4%) compared to most previous studies.[11, 14, 15, 19] The French study, carried out by Mas et al., indicated that cryptogenic stroke patients with both PFO and ASA carry an increased risk of stroke recurrence when treated medically.[9] However, no such association has been reported after PFO closure. Nevertheless, our study population constituted probably patients at high risk for stroke recurrence. The recurrence rate we found suggests that this high-risk population might derive a particularly high benefit from percutaneous PFO closure with the Intrasept™ device.

Complications related to the Intrasept™ device

A systematic review by Khairy et al., in which peri-procedural complications of ten transcatheter PFO closure studies were divided into minor and major, showed a complication rate of 7.9% and 1.5%, respectively.[17] Braun et al. reported a peri-interventional complication rate of 3% and a complication rate of 1.6% for a median follow-up time of 24 months. Their study consisted of 307 consecutive patients,

undergoing PFO closure, using three different types of devices.[11] Post et al. found a peri-procedural complication rate of 7.1% and a mid-term complication rate of 1.8% after percutaneous PFO closure in 112 patients without differences between several types of devices. The overall major complication rate in the latter was also low, 1.8%.[12] The results of our study are concordant with those previously reported. A peri-procedural complication rate of 11.5% was found. Mainly minor complications occurred, as stated in Table II. The mid-term complication rate was 2.6% and consisted only of minor complications. These results indicate that percutaneous PFO closure with the fourth generation Intrasept™ device might be considered as safe. Indeed, the delivery through a 12 French sheath is easy and achieved with a short learning curve. The device is fully retrievable, also after release. In addition, after retrieval, prior or after release, the device is still re-usable because of the memory shaped Nitinol and because the articulating centre post does not get damaged by the retrieval process. Replacement or repositioning was easy to do. Because of the articulating design of the device, the risk for perforation or erosion of the aortic root was low. No arm fractures could be found, which was a problem with the older generation devices. The latter might be explained by the Nitinol arms, which consist of 19 woven strands. The complication rate decreased substantially by the use of the Intrasept™ device when compared to older generation devices (PFO STAR device) from the same company.[16] The latter is probably due to the technical improvement of the device, as discussed earlier.

Efficacy of the Intrasept™ device

Residual RLS is widely discussed in literature. However, it is difficult to compare devices, because of different methodological descriptions of residual shunt.[11, 12, 14, 15, 18, 19, 24] Windecker et al. found residual RLS in 27% of their patients. Interesting was that RLS was a predictor for recurrent thrombo-embolism (RR=4.2).[14] In the series of Martin et al. complete closure was found in 51% of 110 patients at six months and in 66% at 12 months. Two device types were used: the buttoned device and Cardioseal Occluder device.[15] In contrast to this high number of residual shunt, some authors reported complete closure in up to 96% after two years of follow-up. No significant differences in closing rate were seen between the three types of implanted devices: the

PFO STAR-III generation, Amplatzer PFO Occluder, or Cardioseal device.[11] However, Schwerzmann et al. could detect a significant difference in residual RLS between the Amplatzer PFO occluder and the first generation Cardia PFO occluder. Complete closure was found in 94% and 66%, respectively.[16] Others found residual shunting in 10.8% of 403 patients six months after PFO closure using the three generations of PFO STAR devices from Cardia.[21] The decrease in residual RLS suggests technical improvement of the device.

With the fourth generation Intrasept™ device, residual RLS was present in 10.3% of the patients immediately after closure. This number remained stable within six months of follow-up (13.2%). The slight increase could be due to the use of different imaging techniques to detect RLS in which both over- and underestimation of residual shunting were possible.

Interestingly, residual RLS was present in 12.5% of the patients who had no recurrent event, as compared to 36.4% of the patients that reached the primary endpoint. This finding again supports an association between the presence of residual RLS and the recurrence of thrombo-embolic events.

Limitations

The first limitation of this study is the relatively short follow-up time. However, the latter is explained by logistic restrictions. This fourth generation device is only a few years on the market. Second, residual RLS at six months follow-up was not obtained in all patients and different imaging techniques were used to detect RLS. Both over- and underestimation of a residual shunt were possible.[25] Third, outcome (recurrence of a neurological event) is dependent on the correct indication for closure. Overtreatment will undoubtedly be related to a worse outcome. However, there are currently no prospective randomized trials to delineate the correct indication for percutaneous PFO closure. The results of the Closure 1, Respect, and PC trials will probably solve this problem in the near future.

Conclusions

This multi-centre study suggests that percutaneous closure of a symptomatic PFO with the fourth generation Intrasept™ device is safe and might be effective to prevent the recurrence of paradoxical thrombo-embolic events.

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Chapter 2.2

Editorial comment

Another addition to the tool box

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Catheterization and Cardiovascular Interventions 2008; 71:829–830
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Each year 780,000 people have a stroke in the United States. More than a fourth of these are recurrent events.[1] About one of every 16 deaths is due to stroke.[2] Of all strokes about 85% are ischemic. Direct and indirect cost of stroke for 2008 is estimated by the American Heart Association to be 65.5 billion dollars. It is obvious that a multidisciplinary collaborative effort is needed in order to reduce the impact of this disastrous problem. In about 40% of ischemic stroke patients, no identifiable cause is found, hence, the cryptogenic stroke. Patent foramen ovale and atrial septal aneurysm appear to be more frequent in patients with cryptogenic stroke. Given this relationship even though not proven to be an association of cause and effect, percutaneous closure of PFO is frequently proposed as the treatment of choice. Currently in the United States, there are no closure devices that are approved for indication of PFO closure. Randomized trials are underway, testing the safety and efficiency of the investigational devices. Intrasept™, which is a low profile device, has the advantage of being retrievable and repositionable and available in four sizes.

In this issue of the journal, Luermans et al. report the European experience with the Intrasept™ PFO closure device.[3] Over a four-year period, 430 patients, most of whom had a stroke or TIA, underwent closure procedures in seven centres. Most important finding of the study was that the Intrasept™ device could be placed safely in almost all patients. There was no peri-procedural death, stroke, or any other consequential serious complication. In this multi-centre study, investigators undoubtedly paid meticulous attention to every step of the procedure to avoid complications. Air or thrombo-embolism, cardiac perforation, and device embolization are some of the possible serious complications. Luermans et al. only report one major complication: procedure related cardiac tamponade, which was managed successfully. Most frequent minor complications were transient atrial arrhythmias and access site hematoma, which did not require transfusion or surgery.

Efficacy of the device is the next important component for optimal percutaneous closure. Immediately after the procedure 10.3% of the patients had residual right-to-left shunt. Lack of Valsalva maneuver in patients under general anesthesia might have led to underestimation of incidence of the shunt. There is neither systematic nor complete follow-up for residual shunts. It appears that months after closure more than 10% of patients had persistent shunts. Interestingly, the frequency of stroke or

TIA after closure was three times more frequent in the group with residual shunts. Small numbers and short duration of follow-up should make us cautious in the interpretation of these data. Moreover, the impact of residual right-to-left shunt on the post closure stroke and TIA rates is not clear in the literature.[4] The discrepancies in various reports may be due to the variability in the magnitude of the shunts and the differences between the sensitivity of diagnostic tools such as transthoracic, transesophageal echo, and transcranial Doppler.

In contrast to establishing the safety of the Intrasept™ device, this study does not say much about the effectiveness of the closure in prevention of recurrent strokes. The duration of follow-up is less than a year. Of the 430 patients not all could be considered typical cryptogenic stroke patients. Two patients who developed stroke during follow-up were 70 and 77 years old, two patients who died had extensive atherosclerosis. It is quite possible that neither index events nor recurrent strokes of such patients were related to PFO. In older patients, particularly in those with clinically evident atherosclerosis, there may be other etiologic factors that are present but not readily identifiable. Few baseline patient characteristics were included in the manuscript, which limits the interpretation of the study. Patient selection is arguably the most important aspect of PFO closure.

Intrasept™ device, which has the advantage of being retrievable and repositionable, can be deployed very safely. Complete closure can be achieved 90% of the time. The long-term outcome of the Intrasept™ device placement is not clear. We need the results of the randomized trials in order to answer the important question: Is PFO closure the best treatment to prevent recurrent events in patients with cryptogenic stroke.

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Chapter 3

The Biostar device versus the Cardioseal device in patent foramen ovale closure: Comparison of mid-term efficacy and safety

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Submitted

Abstract

Aims: To compare the mid-term efficacy and safety of the bioabsorbable Biostar® device with the non-bioabsorbable Cardioseal® device for percutaneous patent foramen ovale (PFO) closure.

Methods and results: All 81 consecutive patients who underwent PFO closure with the Cardioseal® or Biostar® device between June 2003 and July 2008 were included. The presence of a residual shunt (minimal, moderate or large) was measured in both groups at six months follow-up, using contrast transthoracic echocardiography. Forty-four patients (48.4±11.4 years) received the Cardioseal® device and 37 patients the Biostar® device (47.9±10.7 years). There were no significant differences in short-term complications. Two patients who received the Biostar® device developed a recurrent transient cerebral ischaemic event. Overall, atrial arrhythmias occurred in 19%, with no difference between both groups. At six months, a residual shunt was present in 29% (27% minimal, 2% moderate) using the Cardioseal® device compared to 28% (17% minimal, 11% moderate) using the Biostar® device (P=0.18). A predictor for residual shunt could not be found.

Conclusion: There is no difference in safety and efficacy at six months between the Cardioseal® and Biostar® device used for PFO closure. However, using the Biostar® device tends to be associated with a higher percentage of moderate shunting.

Introduction

A patent foramen ovale (PFO) has been associated with paradoxical embolic events such as cryptogenic stroke, peripheral embolism and decompression illness in divers, especially in young adults.[1-3] These patients are at increased risk of recurrent thrombo-embolic events, despite the use of anticoagulation or antiplatelet therapy.[4-6] Moreover, patients with an atrial septal aneurysm (ASA) have a higher risk of stroke recurrence.[7-9] Since the initial report in 1992[10], percutaneous PFO closure has been used with increasing frequency and has shown promising results regarding safety and efficacy. Various occlusion systems have been used, with different complication and success rates.[11-14] A new bioabsorbable device (Biostar®, NMT Medical, Boston, USA) has been developed to avoid potential problems such as thrombo-embolism, erosion and inflammation which have been attributed to permanent synthetic implants. The Biostar® device consists of a totally biodegradable matrix made of a porcine intestinal collagen layer, mounted on a nitinol framework. Initially, promising results were shown in the first in human trial.[15] However, a high rate of residual shunting was noticed at short-term follow up.[16] Another self-expanding, double umbrella device mounted on the same framework is the Cardioseal® device (NMT Medical, Boston, USA). This non-bioabsorbable, permanent device is widely used and associated with a low incidence of complications and recurrent thrombo-embolic events.[17, 18] Both devices are shown in Figure 1. The aim of our study is to compare these two devices in patients with presumed paradoxical embolism undergoing percutaneous PFO closure with respect to peri-procedural and mid-term complications, the recurrence of paradoxical embolism and the efficacy of PFO closure.

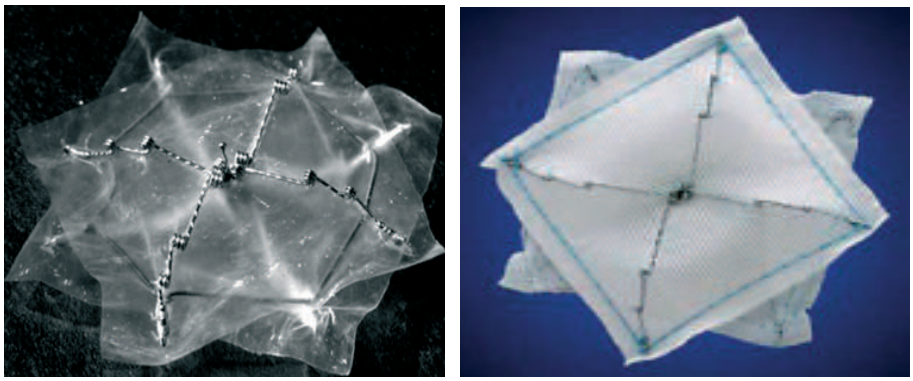

Figure 1. The Biostar® device (left) and the Cardioseal® device (right).

Methods

Study population

All 81 patients who underwent a PFO closure in our centre using the Cardioseal® or Biostar® device between June 2003 and July 2008 were included. During that study period 87 PFO closing procedures were performed. In six patients an Amplatzer® PFO occluder (AGA Medical, Golden Valley, USA) was used and these patients were excluded. Between June 2003 and October 2007 the Cardioseal® device was used in 44 patients. From November 2007 until July 2008 the Biostar® device was used for PFO closure in 37 consecutive patients. A PFO was identified by standardized contrast transthoracic echocardiography (cTTE) using second harmonic imaging or contrast transesophageal echocardiography (cTEE) with spontaneous or provokable right-to-left shunt after injection of 10 mL of agitated saline in an antecubital vein. An atrial septal aneurysm was defined as an excursion of the inter-atrial septum of at least 10 mm. The study was approved by the local ethics committee.

Closing procedure

As described previously, closure of the PFO was performed under general anaesthesia and TEE monitoring in all patients who received the Cardioseal® device and in the first six patients who received the Biostar® device.[16, 19] Thereafter, the Biostar® device

was implanted under local anaesthesia using intra-cardiac echocardiographic (ICE) guidance. Concomitant biplane fluoroscopic guidance was used in all patients. All patients were treated with antiplatelet therapy prior to the closing procedure. A bolus of 5000 U of heparin was administered after accessing the right femoral vein and each patient received an intravenous prophylactic dose of antibiotics at the time of the procedure. The left femoral vein was used in case of ICE-guiding. The PFO was passed using a standard multipurpose catheter and exchange wire. After thoroughly flushing to prevent air embolism, the loaded implantation system was advanced across the atrial septum and the device expanded and released under fluoroscopic and echocardiographic guidance. Within 24 hours after closure, an electrocardiogram, chest X-ray and cTTE were performed. All patients were discharged on aspirin 100 mg once a day for a period of six months and clopidogrel 75 mg once a day during one month. Patients on oral anticoagulant therapy before the procedure were discharged on a combination of oral anticoagulant therapy and clopidogrel for one month. Endocarditis prophylaxis precautions were recommended for six months.
Successful device implantation was defined as completion of the procedure without the occurrence of major events (death, device embolization, device malpositioning with replacement or need for surgical intervention).

Complications and outcome

All procedural complications, immediately related to the procedure within six months, were reported. Complications were divided into major and minor complications according to the classification scheme of Khairy et al.[20] According to this review article, major complications include haemorrhage requiring blood transfusion, occurrence of cardiac tamponade, need for procedure related surgical intervention, massive fatal pulmonary emboli and death, related to the closing procedure. Minor complications were defined as device malpositioning with successful catheter repositioning, bleeding not requiring blood transfusion, occurrence of new onset atrial arrhythmias (atrial flutter or fibrillation), transient atrioventricular block, device arm fractures, device embolization with successful catheter retrieval, asymptomatic device thrombosis, need for re-catheterization, transient air embolism, transient ST-segment elevation, femoral arteriovenous fistula formation, femoral haematoma, and other minor complications related to the closing procedure.

Clinical information was obtained by an out-patient visit to a cardiologist at six months.

New-onset supraventricular tachyarrhythmias (SVT) were diagnosed by a 12-lead electrocardiogram or Holter monitoring in patients without a history of SVT at baseline. The recurrence of stroke or TIA was confirmed by a neurologist using the appropriate imaging techniques.

Efficacy

The routine follow-up program for the Cardioseal® device group included TTE without contrast at 24 hours and cTTE at six months after device implantation. The group who received the Biostar® device had a cTTE at 24 hours and at six months and an additional cTTE one month after implantation. All echocardiographic examinations, six months after device implantation, were reviewed by two independent physicians. The efficacy of PFO closure was based on the residual shunt. Microbubbles were counted in the left atrium within three cardiac cycles after right heart opacification. Residual shunting was categorized as follows: small shunt (< 30 bubbles in the left atrium), moderate shunt (30-100 bubbles in the left atrium) and severe shunt (> 100 bubbles in the left atrium). Recently, an excellent inter-observer variability has been demonstrated using cTTE for right-to-left shunt detection.[21] All cTTE examinations were performed using second harmonic imaging.[22]

Statistical analysis

Descriptive statistics were used to describe patients' characteristics. Continuous variables with normal distribution are presented as mean ± standard deviation. Univariate statistical analysis was used to identify risk factors for residual shunting after PFO closure. All statistical analyses were performed by using SPSS software (version 14.0 for Windows).

Results

Patient population

Baseline and PFO characteristics of the patient population are listed in Table I. In 44 patients PFO closure was performed with the Cardioseal® device. Thirty-six percent were female with a mean age of 48.4±11.4 years. In the Biostar® device group, 60% were women with a mean age of 47.9±10.7 years. An ASA was detected in 46% and 49% in the Cardioseal® device group and in the Biostar® device group respectively. All patients in the Cardioseal® device group underwent PFO closure because of cryptogenic stroke or TIA. In the other group, one patient was treated because of decompression illness. Twenty-one patients (26%) had a history of more than one thrombo-embolic event.

Table I. Baseline characteristics

	Cardioseal®	Biostar®	P
Total	44	37	
Age ± SD (y)	48.4±11.4	47.9±10.7	0.85
Female, n (%)	16 (36)	22 (60)	0.05
Weigth ± SD (kg)	82±14	78±15	0.28
Risk factors (%)			
Hypertension	29	22	0.61
Hypercholesterolemia	34	32	1.00
Diabetes	5	8	0.66
Family history	26	30	0.80
Smoking	26	24	1.00
PFO characteristics (%)			
Spontaneous RLS	69	42	0.03
ASA	46	49	0.83
Indication for closure, n[a]			
Single TIA	13	11	
Multiple TIA	8	9	
Single CVA	26	18	
Multiple CVA	2	2	
Decompression illness	0	1	

SD, standard deviation; y, years; n, number; kg, kilogram; PFO, patent foramen ovale; RLS, right-to-left shunt; ASA, atrial septal aneurysm; TIA, transient ischemic attack; CVA, cerebrovascular accident.

[a]21 patients had a history of more than one event.

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Peri-procedural complications

The implantation of the Cardioseal® device was successful in 98% of the patients. In one patient a 28 mm device was malpositioned and successfully replaced by a 33 mm device. A 28 mm device was delivered in 86% of the patients in this group. One patient developed a minimal groin haematoma immediately after the procedure not requiring a blood transfusion nor surgical intervention. There were no other in-hospital complications.

In the Biostar® device group, 36 patients (97%) had a successful device delivery and deployment. In one patient the device was pulled through the PFO before it was released, but could not be recovered into the sheat. Therefore, surgical exploration of the femoral vein was necessary to retrieve the device. This patient successfully received an Amplatzer® Septal Occluder device one month later. A 28 mm device was implanted in 92% of the patients in this group. Four patients (11%) developed a minimal inguinal haematoma. The closure characteristics are summarized in Table II. The in-hospital complications are shown in Table III.

Table II. Procedural characteristics

	Cardioseal®	**Biostar®**
Total, n	44	37
Diameter device, n (%)		
23 mm	5 (11)	0
28 mm	38 (86)	34 (92)
33 mm	1 (2)	3 (8)
Echocardiography, n (%)		
TEE	44 (100)	6 (16)
ICE	0	31 (84)
Anaesthesia, n (%)	44 (100)	6 (16)
Procedural complications, n (%)		
Minimal surgical intervention	0	1 (3)
Device malposition	1 (2)	0
Hospital stay (days)	2	2

n, number; mm, millimeters; TEE, transesophageal echocardiography; ICE, intra-cardiac echocardiography

Table III. Complications and re-occurrence of cerebral ischemia

	In Hospital		6 month	
	Cardioseal®	**Biostar®**	**Cardioseal®**	**Biostar®**
Total, n	44	37	44	36
Major complications, n (%)				
Surgical intervention	0	1 (3)	0	0
Minor complications, n (%)				
Inguinal haematoma	1 (2)	4 (11)	0	0
New SVT	0	0	9 (21)	6 (17)
Re-occurrence ischemia, n (%)				
TIA	0	0	0	2 (6)

n, number; SVT, supraventricular tachycardia; TIA, transient ischemic attack.

No significant differences between both groups.

Mid-term complications and outcome

Within six months after closure, no major complications occurred in either of the two groups. In the Cardioseal® device group, nine patients (21%) developed a SVT. Seven patients were treated successfully with anti-arrhythmic drugs, two patients needed electrical cardioversion. No other complications occurred in this group. No re-occurrence of stroke or TIA was reported.

In the Biostar® device group, six patients (17%) experienced a new paroxysmal SVT, one patient needed electrical cardioversion, three patients were treated medically, the other two patients had a transient atrial tachycardia which resolved spontaneously. No predictor for the development of SVT after PFO closure could be identified by univariate analysis. A 51-year-old male patient developed a TIA within one month after closure with the Biostar® device. This patient had a residual shunt at that time and an atrial septal aneurysm on baseline echocardiography. A 50-year-old female patient suffered from a recurrent TIA six months after closure in the absence of a residual shunt on cTTE (Table IV).

Table IV. Residual shunt at six months follow-up

	Cardioseal®	Biostar®	P
Total, n	44	36	
Shunt, n (%)			0.18
No shunt	31 (71)	26 (72)	
Grade 1	12 (27)	6 (17)	
Grade 2	1 (2)	4 (11)	
Grade 3	0	0	
Shunt, n (%)			0.17
No or minimal	33 (98)	32 (89)	
Moderate or large	1 (2)	4 (11)	

n, number

Efficacy

At six months follow-up, complete closure was present in 71% of the patients who received the Cardioseal® device and in 72% of the patients who received the Biostar® device (P=0.18). In the Cardioseal® device group, 27% had a trivial shunt and 2% had a moderate shunt, compared with 17% and 11% respectively in the Biostar® device group. No large shunts were detected. The efficacy data are shown in Table IV and Figure 2. Combining moderate and large shunts results in a non-significant higher percentage of residual shunt in the Biostar® device group (11% versus 2 %, P=0.17). No predictor for the presence of a residual shunt at six months follow-up could be identified by univariate analysis.

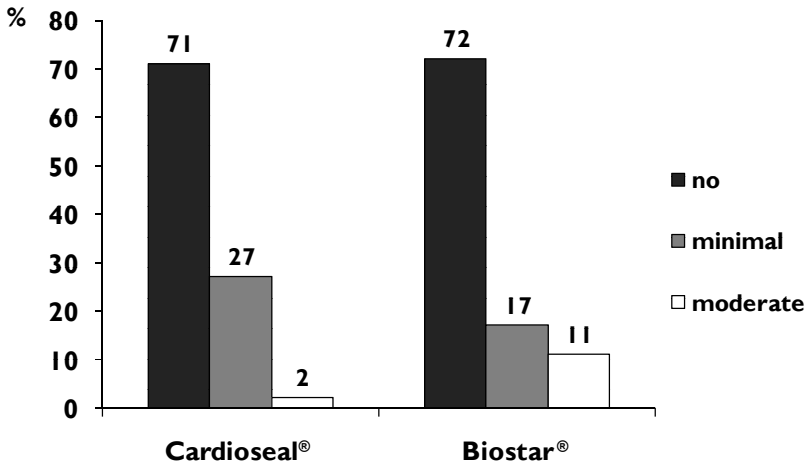

Figure 2. Percentage of residual shunting diagnosed by cTTE at six months follow-up.

Discussion

In the past, several occluder systems have been used for transcatheter PFO closure.[13,14,23] They all have different designs and consist of a synthetic matrix, which is encapsulated by fibrous tissue over time. Inherent risks include device embolization and device fracture, infection, erosion, thrombus formation and arrhythmias.[24-26] Therefore, a bioabsorbable closure device has been introduced recently. It is associated with the ability to induce a host connective tissue response and should lead to a more rapid and complete neo-endothelialization. The collagen matrix is gradually resorbed over a period of about two years, leaving only the frame behind.[27,28] The non-absorbable Cardioseal® device, used in our study, is constructed from a knitted Dacron® fabric, mounted on the same low profile nitinol framework as the bioabsorbable device. We accomplished the first "head-to-head" comparison of these two devices in a single centre setting.

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Complications

The rate of complications of PFO closure with the Cardioseal® device is described in several studies. The peri-procedural major complication rate varies between 1.6% and 4.6%.[29, 30] We found a peri-procedural complication rate of 2% in the Cardioseal® device group. Recently, Taaffe et al. described a randomized comparison of the Cardioseal® device with the Amplatzer® and Helex® device.[23] They examined 660 patients, with 220 patients per group and found more thrombus formation (3.6%) and atrial fibrillation (4.5%) one month after the procedure, in the group who received the Cardioseal® device. Anzai et al. showed that the Cardioseal® device is more likely (22%) to have thrombus formation than the Amplatzer® device, using cTEE.[31] We found a short-term complication rate of 21% in the Cardioseal® group, all related to supraventricular arrhythmias. We did not detect any thrombus in the Cardioseal® group, realizing that thrombus assessment with TTE only might be not revealing.

In the BEST trial, 58 patients (54 PFO, 4 ASD) were treated with the Biostar® device.[15] In two patients (3%), the device was malpositioned. In one of them a larger device was introduced and in the other patient the defect was closed with an alternative device. Furthermore, they described no major adverse events during follow-up. Five patients (8.6%) were treated for supraventricular arrhythmia, one patient developed urticaria and in one patient a mobile echogenic mass was seen on the right atrial side of the device, which resolved after anticoagulation therapy. As previously reported, we had a procedural complication in one patient (3%).[16] In our series, 17% developed a new transient SVT, no other complications did occur during mid-term follow-up. Comparing the Biostar® device and the Cardioseal® device, no significant differences could be observed regarding peri-procedural, short- and mid-term complications. However, quite a high percentage of new SVT is seen in both groups. On the other hand, there seems to be a trend towards a higher percentage of inguinal haematoma (11% versus 2%) in the Biostar® device group, probably due to the extra access site using ICE. In two reports which compared PFO closure guiding with ICE and TEE, no differences could be found regarding safety.[32, 33]

Re-occurrence of thrombo-embolic events

A recent report showed an annual re-event rate of 0.9% for stroke and a combined annual event rate for stroke and TIA of 3.4% in 216 patients treated with the Cardioseal® device.[34] Interestingly, they found that 30% of the patients with a recurrent event had clear evidence of pathology unrelated to a cardio-embolic source. In our Cardioseal® group, no recurrence of stroke or TIA did occur within six months after PFO closure.

In the BEST trial, no thrombo-embolic events were noticed after six months follow-up.[15] We report two patients (5.6%) with symptoms of recurrent TIA in the Biostar® device group. Previous studies support the hypothesis of the increased risk of re-events in the presence of a residual shunt and/or ASA.[7, 8] One patient indeed had a residual shunt and an ASA. In the other patient PFO closure was achieved and confirmed by cTTE and no thrombus was seen on the device. It may be presumed that the cause of recurrent TIA might be other than paradoxical embolism.

Residual shunt

The presence of a residual right-to-left shunt after PFO closure is widely described in literature. Recently, Wahl and Meier addressed that complete PFO closure is achieved in 51-100% of patients, using a variety of devices.[35] According to this review paper, complete PFO closure at six months using the Cardioseal® device varies between 51% and 89%.[8, 17, 18, 30, 36] Braun et al reported a residual shunt, using cTEE, in 28% of the patients after one month and in 20% of the patients after six months, using the Cardioseal® device.[28] At six months after the procedure, we found an overall residual shunt rate (including small shunts) of 29% for the Cardioseal® device. Only 2% of the patients had a moderate shunt and no large shunts were detected.

The BEST trial showed a residual shunt rate of 8% at one month and of 4% at six months, using cTTE. Successful defect closure was defined as procedural success with no shunt or trivial (< 10 bubbles) shunt, so only moderate and large shunts were reported.[15] In our series, a residual shunt rate of 28% was noticed at six months follow-up in the Biostar® group. We earlier reported a residual shunt rate of 45% (minimal 30%, moderate 12%, severe 3%) in 33 patients, one month after the implantation of the Biostar® device.[16] Comparison of our results with the results of

the BEST trial is difficult regarding the difference in shunt grading. When we only count moderate and large shunts, a residual shunt rate of 15% at one month and of 11% at six months is achieved.

Overall, a comparable closure rate is seen between the Cardioseal® and the Biostar® device. However, more moderate shunts were detected (11% versus 2%) using the Biostar® device. A hypothesis for the difference in residual shunting is that in some patients, a mechanical occlusion of the defect with a synthetic device might result more rapidly in defect closure compared to the more natural healing process using the Biostar® device. This is in contrast to the findings of Jux et al., who showed a significantly more thorough coverage of the device by tissue in a sheep model.[27] Maybe there is an inter-individual difference regarding the formation of neo-endothelium and granulation tissue in response to the Biostar® device.

Limitations

Limitations of the study are the non-randomized, retrospective design, the single-centre characteristics and the small number of patients. Regarding complications, we must stress that we only performed TTE during follow-up, which is less sensitive for thrombus detection on the devices.

Conclusion

In conclusion, our study shows that percutaneous PFO closure can be achieved safely with the Cardioseal® device and with the Biostar® device. No significant differences could be revealed regarding implantation success, peri-procedural, short-term and mid-term complications. The efficacy of closure is comparable, however the use of the Biostar® device is associated with a higher percentage of moderate shunting. Larger, randomized trials are necessary to determine the optimal closure device in this patient population.

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Chapter 4

Complications and mid-term outcome after percutaneous patent foramen ovale closure in patients with cryptogenic stroke

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Netherlands Heart Journal 2008; 16: 322-326

Abstract

Background: Percutaneous patent foramen ovale (PFO) closure seems to reduce the risk of recurrent thrombo-embolism. We report the safety and efficacy of percutaneous PFO closure in our centre.

Methods: All patients, >16 years of age, who underwent a percutaneous PFO closure in our centre were included. Re-occurrence of stroke, transient ischemic attack (TIA) and peripheral thrombo-embolism were assessed. Peri-procedural and mid-term complications are reported.

Results: Eighty-three consecutive patients (mean age 49±13 years) were included. Indications for PFO closure were cryptogenic stroke (59.0%), TIA (33.7%), peripheral embolism (2.4%) and other (4.8%). For PFO closure, a Cardioseal/Starflex® device was used in 63 patients and an Amplatzer® PFO Occluder device in 20 patients. Stroke recurred in 1.2%, TIA in 3.6%, peripheral embolism in 0% during a mean follow-up of 1.9 ± 1.2 years. Major peri-procedural complications occurred in 1.2%. The mid-term complication rate was 2.4% and only consisted of minor complications. During follow-up, a residual right-to-left shunt was present in 5.7% of the patients. No significant difference in outcome, complications or residual shunting could be documented between the two device types.

Conclusion: In our centre, the percutaneous closure of a PFO seems to be a safe and effective procedure to prevent recurrence of paradoxical thrombo-embolic events.

Introduction

The presence of a patent foramen ovale (PFO) with or without atrial septal aneurysm (ASA) has been associated with cryptogenic stroke or stroke of undefined cause, especially in young adults.[1-3] Paradoxical embolism through a PFO is thought to be the most likely stroke mechanism.[4,5] Patients with cryptogenic stroke related to PFO, particularly those with an associated ASA, seem to be at risk for stroke recurrence.[6-9] High recurrence rates of stroke or transient ischemic attack (TIA) are reported after medical treatment.[9,10]

Percutaneous PFO closure is suggested to be an alternative or an additive to medical therapy for secondary prevention of (cryptogenic) stroke. This technique has been shown to be feasible in patients with presumed paradoxical embolism.[11-14] Differences in efficacy, safety, and outcome after this procedure, using different types of devices, have been reported.[11-16] Most of these studies are limited by a short follow-up period. In this single-centre study, we report safety and efficacy of percutaneous PFO closure during mid-term follow-up, using two types of closure devices.

Methods

Study population

All patients (>16 years of age) who underwent a percutaneous PFO closure in our centre between May 1998 and November 2006 were included. In all these patients, the PFO was considered to be related to one of the following clinical manifestations: a documented presumed paradoxical thrombo-embolic event, such as stroke, TIA, or a peripheral embolism or in a few cases decompression illness, pulmonary arterial hypertension with refractory hypoxemia or the presence of a therapeutically resistant migraine with aura. In case of presumed paradoxical embolism, other sources of systemic emboli were ruled out. The presence of a PFO was confirmed by contrast transesophageal echocardiography (TEE) with a spontaneous or provocable (Valsalva-maneuver) right-to-left shunt (RLS). An atrial septal aneurysm (ASA) was defined as a bulging of the septum of at least 10 mm.

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PFO closure

Closure of the PFO was performed under general anaesthesia (propofol) and continuous TEE monitoring. After accessing the right femoral vein, a bolus of 5000 U of heparin was administered. Sheaths up to 12 French were used. The devices were implanted under fluoroscopic and echocardiographic guidance according to the standard technique as previously reported.[14] The choice of the device type was made in accordance to the clinical preference of the interventional cardiologist. All patients received an intravenous prophylactic dose of antibiotics one hour before and six hours after PFO closure (in most cases cefuroxim).

Within 24 hours of closure, a chest X-ray and a transthoracic echocardiogram (TTE) were performed. All patients were discharged on antiplatelet therapy (clopidogrel for at least four weeks and low-dose aspirin for at least six months). Prophylaxis against bacterial endocarditis was advised for a minimum of six months after the closing procedure.

Follow-up evaluation: Outcome, complications and efficacy

Follow-up information was obtained by periodical outpatient visits and phone calls. The most recently available medical records were reviewed.

Re-occurrence of stroke, TIA, or any other thrombo-embolic event was recorded. All neurological embolic events needed to be established by a neurological evaluation and, in case of stroke, confirmed by the appropriate cerebral imaging studies.

All procedural complications immediately related to the closing procedure and occurring within two months were recorded. Mid-term complications occurring at least two months after the closing procedure were retrieved from the most recently available medical records. Complications were divided into major and minor complications according to the classification scheme of Khairy et al.[17] According to this review article, major complications include haemorrhage requiring blood transfusion, occurrence of cardiac tamponade, need for procedure-related surgical intervention, massive fatal pulmonary emboli and death, related to the closing procedure. Minor complications were defined as device malpositioning with successful catheter repositioning, bleeding not requiring blood transfusion, occurrence of new onset

atrial arrhythmias (atrial flutter or fibrillation), transient atrioventricular block, device arm fractures, device embolization with successful catheter retrieval, asymptomatic device thrombosis, need for re-catheterization, transient air embolism, transient ST-segment elevation, femoral arteriovenous fistula formation, femoral haematoma, and other minor complications related to the closing procedure.

Efficacy of PFO closure was defined as the absence of residual shunting, based on a contrast TTE or TEE study, performed six months after PFO closure.

Statistical analysis

Descriptive statistics were used to report patients' characteristics. Continuous variables were tested on normality and, if present, reported by mean ± standard deviation (SD). Percentages were used to report categorical variables. Patients' data were compared among groups with Chi-square or Fisher's exact test for nominal variables and independent Student's *t* test for continuous variables. Kaplan-Meier survival analysis was done on the re-occurrence of stroke, TIA or peripheral embolism. Curves were compared using the log-rank test. All tests were two sided and $P<0.05$ was considered to be statistically significant. All statistical analyses were performed using SPSS software (SPSS Inc., version 11.5 for Windows).

Results

Patient and closure characteristics

Between May 1998 and November 2006, percutaneous PFO closure was performed in 83 consecutive patients: 52 men and 31 women, with a mean age of 49.3±12.9 years. Seventy-seven patients (93%) had a history of a cerebral paradoxical embolic event prior to PFO closure. Twenty-two (26.5%) of them had suffered multiple cerebrovascular events. Patient and PFO characteristics and the indications for PFO closure are summarized in Table I.

The devices used for PFO closure were the Cardioseal/Starflex® device in 64 (77.1%) and the Amplatzer® PFO Occluder device in 19 (22.9%) patients.

Table I. Patients' and PFO characteristics and indications for PFO closure

	Number or value	Percentage (%)
Total	83	-
Mean age ± SD (y)	49.3 ± 12.9	-
Men	52	62.7
PFO characteristics		
RLS spontaneous	37	44.6
RLS Valsalva	83	100
Aneurysm IAS	29	34.9
Indication for closure		
Stroke	49	59.0
TIA	28	33.7
Peripheral embolism	2	2.4
Decompression illness	1	1.2
PAT with refractory hypoxemia	2	2.4
Migraine	1	1.2
Closure devices		
Cardioseal/Starflex®	64	77.1
23 mm	9	10.8
28 mm	52	62.7
33 mm	3	3.6
Amplatzer® PFO Occluder	19	22.9
9 mm	1	1.2
18 mm	2	2.4
25 mm	9	10.8
35 mm	7	8.4

SD, standard deviation; y, years; PFO, patent foramen ovale; RLS, right-to-left shunt; IAS, inter-atrial septum; TIA, transient ischemic attack; PAT, pulmonary arterial hypertension; mm, millimeters.

Follow-up evaluation

Outcome

One patient (1.2%) suffered a stroke, three patients (3.6%) a TIA and none a peripheral embolism, during a mean follow-up of 1.9±1.2 years.

A 58-year-old man developed a stroke 0.4 years after PFO closure with an Amplatzer® device. In this patient residual shunting was present. A 61-year-old man and a 57-year-old woman suffered a TIA nine days and 1.1 years after PFO closure with a Cardioseal/Starflex® device, respectively. Echocardiography revealed no residual shunting in these patients. Finally, a 61-year-old man developed a TIA 1.0 year after PFO closure with an Amplatzer® device, despite no residual shunting at echocardiography.

Kaplan-Meier event free survival curves for the recurrence of stroke, TIA or peripheral embolism for both devices are plotted in Figure 1.

During the follow-up period, a 42-year-old man died 0.2 years after PFO closure due to suicide. Follow-up data are summarized in Table II.

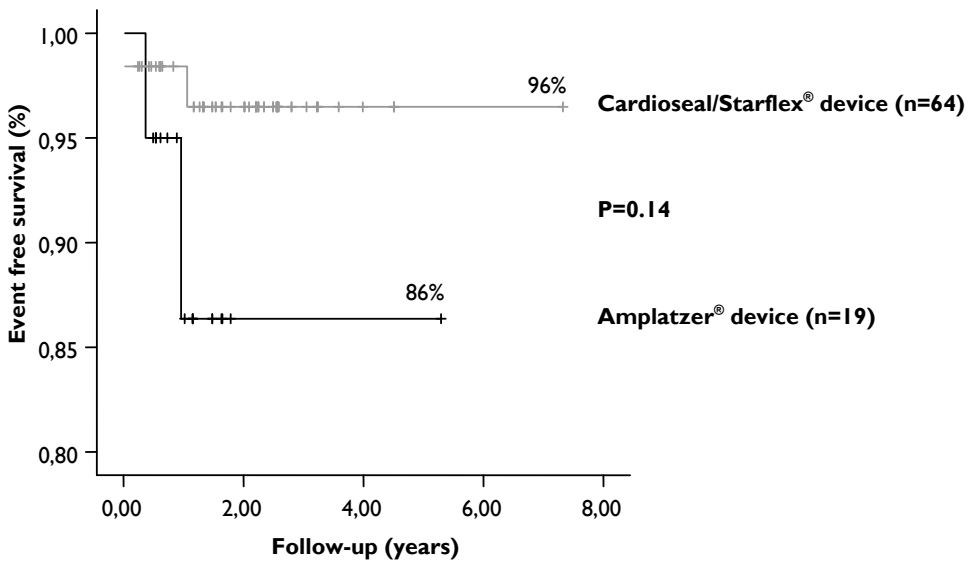

Figure 1. Kaplan-Meier event free survival for the two types of devices used for PFO closure

Complications

The major complication rate was 1.2%. The total peri-procedural complication rate, both major and minor complications, was 12.0%, according to the classification scheme mentioned previously.[17] The only major peri-procedural complication occurred in a patient when the Cardioseal/Starflex® device did not unfold. While trying to remove this device, it was lost in the subcutis, making a minimal invasive surgical procedure necessary. One month later, this patient succesfully received an Amplatzer® device. However, he developed a TIA during follow-up. Minor peri-procedural complications included the following: one patient developed atrioventricular block shortly after implantation of an Amplatzer® device. He was treated with a temporary pacemaker and recovered quickly without atrioventricular conductance abnormalities. One patient suffered an inguinal haematoma, which recovered spontaneously without the need for surgery or blood transfusion. Seven patients suffered atrial arrhythmias, mostly atrial fibrillation, within two months of PFO closure with a Cardioseal/Starflex® device. They were all treated medically, resulting in sinus rhythm.

The mid-term complication rate was 2.4% and consisted of only minor complications. These included two patients who developed atrial fibrillation after PFO closure using a Cardioseal/Starflex® device. They both required medical treatment and are doing well.

None of the patients with atrial arrhythmias developed a recurrent thrombo-embolic event. All these data are summarized in Table II.

Efficacy

TTE for diagnosing residual shunting could be obtained in 70 patients (84%). Six of them underwent additional TEE, because of an inconclusive TTE. Within a mean follow-up time of 0.6 years, residual shunting was present in four patients (5.7%). Stroke recurred in one of these four patients. There was no statistical difference in the occurrence of a residual shunt between the devices (P=0.15). These data are summarized in Table II.

Table II. Outcome, complications and efficacy related to the type of device used for PFO closure

	Cardioseal/ Starflex®	Amplatzer®	P
Number, n (%)	64 (77)	19 (23)	
Re-occurrence, n (%)	2 (3)	2 (10)	0.24
Stroke	0 (0)	1 (5)	0.24
TIA	2 (3)	1 (5)	0.57
Other thrombo-embolic event	0 (0)	0 (0)	-
Death not related to PFO closure, n (%)	1 (2)	0 (0)	1.0
Early complications, n (%)			
Mal-unfolding of device	1 (2)	0 (0)	1.0
AV-block	0 (0)	1 (5)	0.24
Inguinal haematoma	1 (2)	0 (0)	1.0
New atrial arrhythmia	7 (11)	0 (0)	0.19
Mid-term complications, n (%)			
New atrial arrhythmia	2 (3)	0 (0)	1.0
Atrial arrhythmia total	9 (14)	0 (0)	0.11
Efficacy, n (%)			
Residual shunting[a]	2 (4)	2 (15)	0.15

PFO, patent foramen ovale; n, number; TIA, transient ischemic attack; AV, atrioventricular.

[a]Data available in 70 patients

Discussion

The main finding of this study is that percutaneous PFO closure in patients with a history of paradoxical embolic events appears to be safe and effective with a low recurrence rate of cerebral ischaemia, independent of the type of device used for closure.

Recurrence of thrombo-embolic events

Patients with cryptogenic strokes related to a PFO are at risk for stroke recurrence.[6-9] Percutaneous PFO closure has been shown to be effective in the prevention of

recurrent thrombo-embolic events.[11, 12, 14, 15, 18, 19] Although randomized trials that compare medical treatment and transcatheter closure are lacking, the case-control study by Windecker et al. showed that percutaneous closure related to the presence of a PFO, in cryptogenic stroke patients, was at least as effective as medical treatment for prevention of recurrent cerebrovascular events and even more effective in patients with complete PFO closure and a history of more than one cerebrovascular event.[20] Additionally, Khairy et al. reported a one-year rate of recurrent neurological thrombo-embolism of 0-4.9% with transcatheter intervention as compared with 3.8-12.0% with medical treatment.[17]

We found a yearly recurrence rate of thrombo-embolic events of 2.5%. These results are comparable with previous reports. All events occurred in the first year following PFO closure. Indeed, Windecker et al. reported that the recurrence rate of thrombo-embolism seemed to be highest in the first year after PFO closure, as hypothesized to be due to device-related problems.[14] However, a recurrent neurological event might not be related to failure of the PFO device (residual RLS, thrombus formation on the device) alone. We only found residual shunting in one patient with a recurrence of stroke. The events that occurred in the other patients might be due to atherosclerosis instead of device failure. Indeed, all patients who had recurrence of stroke or TIA were older than 55 years and at this age the relationship between the presence of a PFO and cryptogenic stroke is less well defined.[1, 21, 22]

Moreover, the prevalence of ASA of 34.9% that we found in our study population appeared to be higher than most previous studies.[11, 14, 15, 19] Mas et al. indicated that cryptogenic stroke patients with both PFO and ASA carry an increased risk of stroke recurrence when treated medically.[9] No such association has been reported after PFO closure. Nevertheless, our study population might constitute patients at high risk for stroke recurrence.

Complications

A systematic review by Khairy et al., in which peri-procedural complications of ten transcatheter PFO closure studies were divided into minor and major, showed a complication rate of 7.9 and 1.5%, respectively.[17] Braun et al. reported a peri-interventional complication rate of 3% and a complication rate of 1.6% for a

median follow-up time of 24 months. Their study included 307 consecutive patients undergoing PFO closure, using three different types of devices.[11] Post et al. found a peri-procedural complication rate of 7.1% and a mid-term complication rate of 1.8% after percutaneous PFO closure in 112 patients without differences between several types of devices. However, the overall major complication rate was low, 1.8%.[12]

The results of our study are concordant with those previously reported in the literature. A peri-procedural complication rate of 12% was found, of which only 1.2% was defined as major. Transient atrial fibrillation was responsible for most of these complications (8.4%). The mid-term complication rate was 2.4% and consisted of atrial arrhythmias only. We found no statistical differences in the complication rate between the two devices used for PFO closure. These results indicate that percutaneous PFO closure in our centre can be considered to be safe.

Efficacy

Reports about residual shunting after PFO closure are conflicting and range from 4-49%, probably dependent on the use of different types of devices, the follow-up time and the method used for diagnosing residual shunting.[11, 12, 14, 15, 18, 19, 23] Windecker et al. found residual shunting in 27% of 80 patients using TEE with contrast six months after PFO closure. The presence of a residual shunt was a predictor of recurrent thrombo-embolic events with a relative risk of 4.2.[14] However, Martin et al. showed a progressive increase in the number of patients without a residual shunt during the first year of follow-up using TTE with contrast. Full occlusion was present in 51% of the 110 patients at six months follow-up and in 66% at 12 months follow-up using two types of devices: the buttoned device or Cardioseal Occluder device.[15] However, Schwerzmann et al. reported a significant difference in the prevalence of a residual shunt diagnosed by TEE with contrast between the Amplatzer PFO Occluder and the older PFO STAR device. Six months after PFO closure complete closure was found in 94% of 50 patients in whom the PFO was closed with the Amplatzer PFO Occluder and 66% complete closure was found in a similar number of patients in whom an older (first) generation PFO STAR device was used.[16] However, others found residual shunting in 10.8% of 403 patients six months after PFO closure using the three generations of PFO STAR devices.[24]

We found a prevalence of residual shunting of 5.7% six months after PFO closure, with no significant difference between the two device types. These results appear to be better than previously reported data. An explanation for this could be that we generally used a contrast-TTE examination to diagnose residual shunting as compared to contrast-TEE in most previous studies, which is the gold standard. A TTE could give an overestimation or underestimation of residual shunting.[25]

Limitations

The first limitation is the relatively small patient population, which limits comparison of the re-occurrence of paradoxical embolism between the two devices used. However, this is due to the single-centre character of the study. Second, we generally used a contrast-TTE as the imaging technique to detect residual shunting. Both overestimation and underestimation of a right-to-left shunt compared with TEE are possible with this technique.[25]

Conclusion

In our centre, we found that percutaneous closure of a PFO, which is suggested to be related to a paradoxical embolism, is a safe and effective procedure to prevent the recurrence of paradoxical thrombo-embolic events, independent of the device used for closure.

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Chapter 5

Worse outcome in elderly after patent foramen ovale closure: Reduced efficacy versus higher risk population?

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Abstract

Background and objectives: The efficacy of percutaneous patent foramen ovale (PFO) closure in elderly remains uncertain. We compared the efficacy of PFO closure between patients younger and older than 55 years.

Methods: All 335 consecutive adult patients (mean age 50.2±12.6 years; 205 men) with a cryptogenic thrombo-embolic event who underwent a PFO closure in our centres between May 1998 and January 2008 were included. Comparative statistics were performed between patients younger than 55 years (n=215) and patients older than 55 years (n=120).

Results: The mean follow-up period was 4.2±1.9 years in the elderly and 3.8±2.4 years in the younger patients (P=0.15). The prevalence of hypertension, diabetes, hyperlipidemia and coronary and peripheral artery disease was higher in the elderly (P<0.05 for all). Re-occurrence of stroke or TIA was higher in the elderly compared to the younger (annual event rate 2.4% versus 0.6%; log rank, P=0.005). Re-occurrence of stroke alone was higher in the elderly (annual event rate 1.2% versus 0.1%; log rank, P=0.01). Multivariate analysis showed that an age of >55 years was an independent predictor of recurrent stroke or TIA (OR 3.8, P=0.04).

Conclusions: Percutaneous PFO closure appears to be effective for secondary prevention of cryptogenic stroke in younger patients but seems to be related with less beneficial outcome in elderly. Randomized controlled trials are needed to confirm our findings.

Introduction

The presence of a patent foramen ovale (PFO) has been associated with cryptogenic stroke.[1] This association has predominantly been found in patients younger than 55 years of age.[2-4] In several studies percutaneous PFO closure has been shown effective for secondary prevention of cryptogenic thrombo-embolic events.[5-10] However, most of these studies concerned younger patients. Little is known about the recurrence rate of stroke and TIA in older patients with cryptogenic stroke with presumed thrombo-embolism undergoing PFO closure. Recently, Handke et al. reported an association between the presence of a PFO and cryptogenic stroke in older patients.[11] These results seem to be in agreement with previous studies.

Therefore, we conducted a retrospective analysis to determine the outcome of percutaneous PFO closure in older patients.

Methods

Study population

We included all consecutive 335 patients who were referred for percutaneous PFO closure because of a cryptogenic thrombo-embolic event between May 1998 and January 2008 in the St. Antonius Hospital, Nieuwegein, the Netherlands or the University Hospital Gasthuisberg, Leuven, Belgium. Of these patients, 120 (36%) were older than 55 years of age and 215 (64%) were younger. All patients were required to have suffered at least one cryptogenic thrombo-embolic event. The diagnosis of a cryptogenic thrombo-embolic event was made by the treating physician in the referring hospital. Other sources of systemic emboli had been ruled out, according to the local criteria. All neurological embolic events needed to be established by a neurological evaluation and, in case of stroke, confirmed by the appropriate cerebral imaging studies. The presence of a right-to-left shunt (RLS) through a PFO was diagnosed by a contrast (agitated saline) transesophageal echocardiography (TEE) with Valsalva-maneuver. An atrial septal aneurysm (ASA) was defined as a bulging of the atrial septum of at least 10 mm. The presence of risk factors for cardiovascular

disease and co-morbidities was retrieved from medical records. Informed consent was obtained from all patients and the study was approved by the local ethics committee.

PFO closure

As previously reported, the PFO closure was performed according to standard techniques, under general anaesthesia and continuous TEE monitoring.[8, 10]

Follow-up evaluation (outcome, complications, and efficacy)

We compared all follow-up data after PFO closure between patients older and younger than 55 years at closure. Follow-up information was obtained by review of the medical records and a phone call to the patients.

The primary endpoint was defined as re-occurrence of stroke, transient ischemic attack (TIA), or any other thrombo-embolic event. The diagnosis of a recurrent event was made by the treating physicians. Neurological embolic events needed to be established by a neurological evaluation and, in case of stroke, confirmed by the appropriate cerebral imaging studies

Peri-procedural and long-term complications related to PFO closure were noticed and retrieved from the patients' records. Complications were categorized into major and minor, according to the classification used by Khairy et al.[12]

Efficacy of PFO closure was defined as the absence of residual shunting, based on a contrast TEE or TTE study performed six months after closure.

Statistical analysis

Patients were grouped according to their age (younger or older than 55 years). Descriptive statistics were used to report patients' characteristics. Continuous variables were tested on normality and, if present, reported by mean ± standard deviation (SD). Percentages were used to report categorical variables. Nominal data were compared using the Chi-square test. Continuous data were compared using the unpaired, two-sided Student's *t* test. Kaplan-Meier survival analysis was done on the primary endpoint. Log-rank test was used to compare the occurrence of the primary endpoint between the groups. Univariate and multivariate logistic-regression analyses were used to estimate the unadjusted and adjusted odds ratios (OR) and

the corresponding 95% confidence intervals (CI). The characteristics that affected the univariate analysis were included in the multivariable models. For these analyses, the presence of risk factors for cardiovascular disease were grouped as having no, one, or two or more risk factors. All tests were two sided and $P<0.05$ was considered to be statistically significant. Analyses were performed using SPSS Inc., version 12.0 for Windows.

Results

Patient characteristics

Between May 1998 and January 2008 335 patients (mean age 50.2±12.6 years; 205 (61%) men) underwent percutaneous PFO closure in our centres. Of these, 120 (35%) patients were older than 55 years of age (mean age 63.0±5.9 years) and 215 (64%) patients were younger (mean age 43.0±9.1 years). Baseline and PFO characteristics, cardiovascular risk factors, and indication for closure are summarized in Table 1. In seven patients (2%) a non-neurological paradoxical embolic event was the indication for PFO closure: one patient with a myocardial infarction, three patients with renal infarctions and three with peripheral limb embolization. Different devices had been used without difference between both age groups. An Amplatzer® device (AGA Medical Corporation, Golden Valley, MN, USA) was used in 62 patients (19%), a Cardioseal/Starflex® device (NMT Medical, Inc., USA) in 85 patients (25%), a PFO Star® generations 1-3 device (Cardia, Eagan, MN, USA) in 159 patients (48%), an Intrasept® device (Cardia, Eagan, MN, USA) in 13 patients (4%), a Premere® device (St. Jude Medical, Inc., USA) in 13 patients (4%), and a Helex® device (W.L.Gore and Associates, Flagstaff, Ariz, USA) in 3 patients (1%).

Table 1. Patient characteristics, risk factors and co-morbidities, indications for PFO closure, and PFO characteristics for the younger (< 55 years) and older (>55 years) patient group

	Total	< 55 years	> 55 years	P
Patient characteristics				
Patients, n (%)	335 (100)	215 (64)	120 (36)	
Men, n (%)	205 (61)	124 (58)	81 (68)	0.08[a]
Women, n (%)	130 (39)	91 (42)	39 (32)	
Mean age ± SD (y)	50.2±12.6	43.0±9.1	63.0±5.9	<0.001
Heigth ± SD (cm)	172±9.6	173±10.3	171±8.2	0.19
Weight ± SD (kg)	77±15	76±16	77±13	0.62
SBP ± SD (mmHg)	133±19	131±20	136±17	0.04
DBP ± SD (mmHg)	81±12	80±14	81±10	0.56
Risk factors and co-morbidities				
Hypertension, n (%)[b]	82 (25)	38 (18)	44 (37)	<0.001[a]
Diabetes, n (%)[b]	13 (4)	4 (2)	9 (8)	0.01[a]
Hyperlipidemia, n (%)[b]	105 (32)	54 (26)	51 (43)	0.002[a]
Smoking, n (%)[c]	80 (25)	54 (27)	26 (22)	0.34[a]
CAD, n (%)[c]	13 (4)	2 (1)	11 (9)	<0.001[a]
PAD, n (%)[b]	10 (3)	2 (1)	8 (7)	0.004[a]
Family history CVD, n (%)[d]	80 (25)	43 (21)	37 (31)	0.05[a]
History of SVT, n (%)[e]	12 (4)	5 (3)	7 (6)	0.11[a]
Indication for PFO closure				
Stroke and/or TIA, n (%)	328 (98)	211 (98)	117 (98)	0.7[a]
Stroke, n (%)	227 (68)	143 (67)	84 (70)	0.5[a]
Single, n (%)	182 (80)	120 (84)	62 (74)	0.07[a]
Multiple, n (%)	45 (20)	23 (16)	22 (26)	
TIA, n (%)	135 (40)	83 (39)	52 (43)	0.4[a]
Single, n (%)	92 (68)	56 (68)	36 (69)	0.8[a]
Multiple, n (%)	43 (32)	27 (33)	16 (31)	
Stroke and TIA, n (%)	34 (10)	15 (7)	19 (16)	0.01[a]
Other paradoxical embolic event, n (%)	7 (2)	4 (2)	3 (3)	0.7[a]
PFO characteristics				
RLS spontaneously, n (%)[f]	174 (55)	102 (50)	72 (64)	0.02[a]
ASA, n (%)	147 (44)	75 (35)	72 (60)	<0.001[a]

n, number; SD, standard deviation; y, years; cm, centimeters; kg, kilograms; SBP, systolic blood pressure; DBP, diastolic blood pressure; CAD, coronary artery disease; PAD, peripheral artery disease; CVD, cardiovascular disease; SVT, supraventricular tachycardia; TIA, transient ischemic attack; PFO, patent foramen ovale; RLS, right-to-left-shunt; ASA, atrial septal aneurysm. All tests performed were Student's *t* test except for [a]Chi-square test.

[b]Data available in 328 patients; [c]data available in 324 patients; [d]data available in 325 patients; [e]data available in 317 patients; [f]data available in 316 patients.

Follow-up evaluation

Outcome

The mean follow-up time of all patients was 4.0±2.2 years. Mean follow-up time for patients older than 55 years was 4.2±1.9 years, as compared to 3.8±2.4 years for the younger age group (P=0.15). The primary endpoint (recurrence of stroke, TIA or any other thrombo-embolic event) occurred in 17 patients (5.1%; annual event rate 1.3%). In the older age group 12 patients (10%) reached the primary endpoint, resulting in an annual event rate of 2.4%: six patients (5%) suffered from recurrent stroke (annual event rate 1.2%) and another six (5%) developed a TIA (annual event rate 1.2%). In the younger age group 5 patients (2.3%) reached the primary endpoint, resulting in an annual event rate of 0.6%: one patient (0.5%) suffered a recurrent stroke (annual event rate 0.1%) and four patients (1.9%) a TIA (annual event rate 0.5%). The event free survival for the primary endpoint was significantly better in the younger age group when compared to the older age group (log rank test, P=0.005). The event free survival for stroke was also better in the younger age group when compared to the older age group (log rank test, P=0.01). The recurrence of TIA did not differ significantly between the two groups (log rank test, P=0.14). Kaplan-Meier curves are plotted in Figures 1A, 1B and 1C.

In univariable analysis, age >55 years, a history of supraventricular tachycardia (SVT) prior to PFO closure, the presence of two or more cardiovascular risk factors, the presence of multiple paradoxical embolic events prior to PFO closure and the presence of residual shunting after PFO closure were found to be predictors of the primary endpoint (Table II). In multivariable analysis, age >55 years, a history of SVT, the presence of multiple paradoxical embolic events prior to PFO closure and the presence of residual shunting after PFO closure remained predictors of the primary endpoint (Table III).

During follow-up four patients (3.3%) in the older age group and six patients (2.8%) in the younger age group died (log rank test, P=0.92). One death could have been device-related. This concerned a 53-year-old woman, who died because of recurrent stroke. Echocardiography during follow-up revealed left atrial thrombus and device-thrombus for which coumadin had been started. These thrombi might have been the embolic source and cause of death.

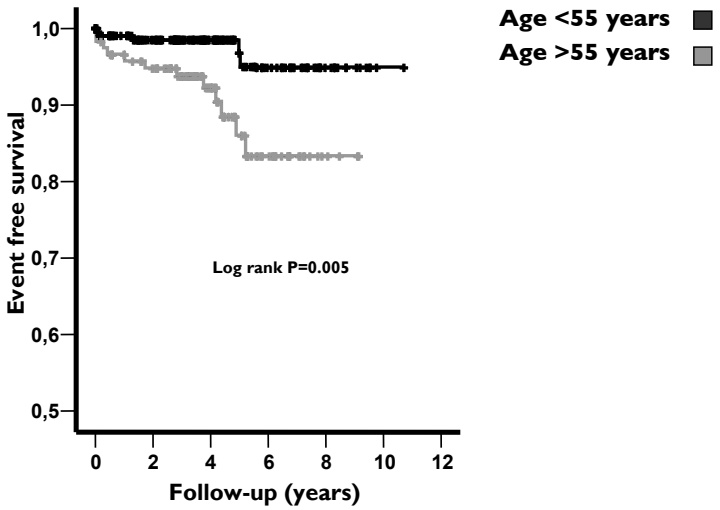

Figure 1A. Kaplan-Meier event free survival curves for patients older and younger than 55 years of age

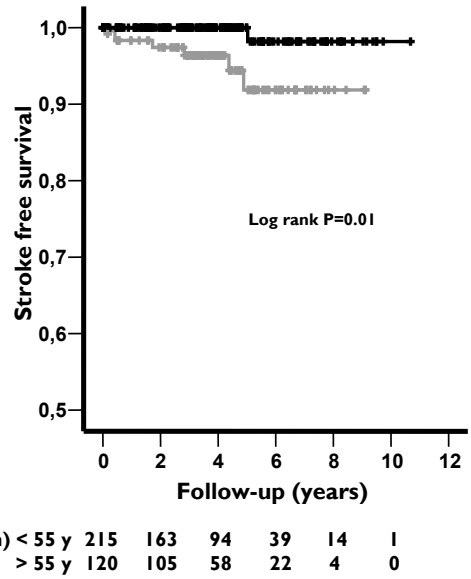

Figure 1B. Kaplan-Meier stroke free survival curves for patients older and younger than 55 years of age

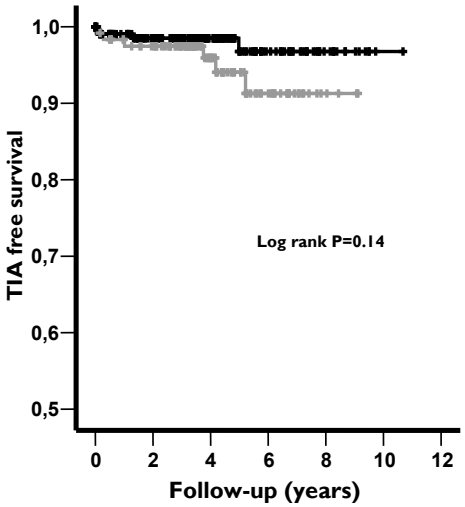

Figure 1C. Kaplan-Meier TIA free survival curves for patients older and younger than 55 years of age

Table II. Predictors of the primary endpoint (recurrence of stroke, TIA or any other embolic event), univariate analysis

Variable	Odds ratio	95%-confidence interval	P
Age > 55 years	4.7	1.6-13.6	0.005
Male gender	0.9	0.3-2.4	0.84
Risk factors and co-morbidities			
History of SVT	6.9	1.7-28.4	0.007
0 risk factors	0.3	0.06-1.1	0.07
1 risk factor	0.9	0.3-2.5	0.78
≥2 risk factors	3.2	1.2-8.5	0.02
Indication for PFO closure			
Multiple (vs single) embolic events	7.7	2.5-24.4	<0.001
PFO characteristics			
Spontaneous RLS	0.8	0.3-2.4	0.70
ASA	1.1	0.4-3.0	0.79
Residual shunting after PFO closure	6.5	2.0-21.2	0.002

SVT, supraventricular tachycardia; PFO, patent foramen ovale; RLS, right-to-left-shunt; ASA, atrial septal aneurysm.

Table III. Predictors of the primary endpoint (recurrence of stroke, TIA or any other embolic event), multivariate analysis

Variable	Odds ratio	95%-confidence interval	P
Age > 55 years	3.8	1.0-14.3	0.04
Risk factors and co-morbidities			
History of SVT	8.6	1.4-53.2	0.02
≥2 risk factors	1.4	0.4-4.9	0.61
Indication for PFO closure			
Multiple (vs single) embolic events	4.9	1.4-17.5	0.02
Residual shunting after PFO closure	4.2	1.1-16.5	0.04

SVT, supraventricular tachycardia; PFO, patent foramen ovale

Complications

Predefined overall complications of PFO closure occurred in 52 patients (15.5%) with no significant difference between the elderly (18.3%) and the young (14.0%) (P=0.29). Complications included peri-procedural (13.1%) and long-term (3.6%) complications and mainly consisted of minor complications, mostly transient atrial fibrillation (8.7%). Only three (0.9%) were major complications and included the following cases: in a 60-year-old man the closure device did not unfold properly. While trying to retrieve it, it was lost in the inguinal subcutis making minimal invasive surgery necessary. In a 54-year-old woman the closure device embolized to the pulmonary artery. She was successfully treated by percutaneous retraction of the device and implantation of a second device. The third patient, a 53-year-old man, suffered a cardiac tamponade after PFO closure, probably due to perforation of the device. He was treated surgically and the device was extracted.

Efficacy

At six months follow-up 281 patients (83.9%) underwent a TTE or TEE to diagnose residual shunting after PFO closure. The presence of residual shunting was 9.3% in the entire study population with no significant difference between the older (12.1%) and the younger age group (7.7%) (P=0.22).

Discussion

Our findings confirm that percutaneous PFO closure in patients with a history of paradoxical embolism appears to be effective for prevention of recurrent stroke and TIA in patients younger than 55 years. Recurrence was significantly higher in the older patients' group, suggesting that either percutaneous PFO closure may be less beneficial in elderly or that they constitute a high risk population.

PFO closure and recurrent thrombo-embolism

Patients with cryptogenic strokes related to a PFO are at risk for stroke recurrence.[13-16] Percutaneous PFO closure has been shown effective in the prevention of recurrent thrombo-embolism.[5-10, 17] In a review article, Khairy et al. reported a one-year rate of recurrent neurologic thrombo-embolism of 0% to 4.9% with transcatheter intervention as compared to 3.8% to 12.0% with medical treatment.[12] However, randomized trials that compare medical treatment and transcatheter closure are still lacking.

We found a yearly recurrence rate of stroke, TIA or any other thrombo-embolic event of 1.3% in 335 patients during a mean follow-up time of 4.0±2.2 years which is low and comparable with previous reports.

PFO closure and recurrent thrombo-embolism in the elderly

To date, there have been only a few reports that address the outcome of older patients with cryptogenic thrombo-embolism who have undergone transcatheter PFO closure. Kiblawi et al. found no significant differences in the rate of recurrent stroke or TIA in 184 patients older than 55 years (mean age 66.9±8.3 years) as compared to 272 younger patients (mean age 41.1±7.7 years) after PFO closure with a Cardioseal Septal Occluder®.[18] Annual recurrence rates were 1.1% and 1.0% respectively during a mean follow-up of 17.8±11.1 months. Spies et al. compared the outcome of PFO closure in 423 elderly (median age 63 years, range 56-88) and 632 younger patients (median age 42 years, range 14-55).[19] They found a similar annual incidence of recurrent thrombo-embolism in both groups during a median follow-up time of 18 months, 1.8% in elderly compared to 1.3% in younger patients. Finally,

Wahl et al. evaluated 525 patients with a median age of 52 years (range 16-79) who underwent PFO closure and found a low annual recurrence rate of thrombo-embolic events of less than 2%.[20] In this study older age (>55 years) did not adversely affect outcome.

In contrast to these earlier reports, our study is the first to describe a significant difference in the outcome of percutaneous PFO closure in older patients as compared to younger patients. We found an annual recurrent rate of 2.4% for stroke or TIA and 1.2% for stroke alone in patients older than 55 years, as compared to an annual recurrent rate of 0.6% for stroke or TIA and 0.1% for stroke alone in patients younger than 55 years. (log rank test, P=0.005 for recurrent stroke and TIA and P=0.01 for recurrent stroke). The mean follow-up time (4.0±2.2 years) in our study was longer than in the studies described above. As our Kaplan-Meier curves indicate, many events in the older patient group occurred during longer-term follow-up, which could be an explanation for our findings compared to earlier reports. Although an annual recurrence rate of 2.4% for stroke or TIA in the older patients is low compared to previous reports of PFO closure and medical treatment[12], it remains significantly higher than the recurrence rate we found in the younger patients. Additionally, age above 55 years was an independent predictor of recurrent stroke or TIA. (OR 4.7, P=0.005 in univariate analysis and OR 3.8, P=0.04 in multivariate analysis). This can be explained in a variety of ways. First, it could be due to residual shunting after PFO closure. We found that residual shunting, although not significantly, was slightly higher in the older age group. Residual shunting after PFO closure has been described as a predictor for recurrent thrombo-embolism.[10, 20] Also in our study residual shunting was an independent predictor of the primary endpoint. However, age above 55 years remained an independent predictor of the primary endpoint even after correction for residual shunting. It could be that venous thrombogenesis is higher among patients >55 years[21, 22], leading to a higher chance of thrombo-embolism in the presence of residual RLS. Second, a recurrent event after PFO closure might have another cause than paradoxical embolism. The higher event rate in the older age group might be due to systemic atherosclerosis. As indicated in Table 1, the prevalence of hypertension, diabetes, hyperlipidemia and coronary and peripheral artery disease was higher in the older age group. Having two or more risk factors for atherosclerosis was

associated with recurrence of stroke or TIA by univariate analysis. However, it was not an independent predictor for the primary endpoint. Interestingly, after correction for these risk factors, higher age remained an independent predictor of recurrent stroke and TIA. Third, the incidence of atrial fibrillation (AF) is higher at older age.[23] This is associated with stroke and TIA in this age group.[24] Kiblawi et al. found a higher incidence of new onset AF in elderly who underwent a percutaneous PFO closure, compared to younger patients.[18] In our study, new onset AF was only slightly higher in the older age group (9.2%) compared to the younger age group (8.4%). However, there could have been a higher incidence of asymptomatic and undetected AF in the elderly. Moreover, we found a history of supraventricular tachycardia (SVT) to be an independent predictor of recurrent stroke and TIA. Patients with a history of SVT are probably at higher risk for developing new onset AF after PFO closure, leading to recurrent neurological events. Moreover, there could be other (unmeasured) confounding factors that cause a recurrent stroke or TIA, especially in older patients. The annual recurrence rate of stroke or TIA after medical treatment in elderly with a cryptogenic stroke and a documented PFO is 10%.[25] We found an annual recurrence rate of stroke or TIA of 2.4% in elderly who underwent a PFO closure for a cryptogenic embolic event. Hence, the transcatheter PFO closure might have beneficial effects in both younger and older patients with cryptogenic thrombo-embolism, but the higher recurrence rate of stroke or TIA in older patients compared to younger patients might be attributable to other factors.

Complications

In a systematic review describing ten transcatheter PFO closure studies, the minor and major complication rates were 7.9% and 1.5% respectively.[12] We found a total complication rate of 15.5%. However, only 0.9% were major complications. An explanation for the high minor complication rate could be that we counted all new episodes of transient AF as a complication of PFO closure during the entire follow-up period. Transient AF accounted for 56% of all complications. It is not certain, whether the occurrence of AF at long-term follow-up is related to PFO closure.

We found no difference in the occurrence of complications between the two age groups (18.3% for the elderly and 14.0% for the young), which is comparable with

the results of the study conducted by Kiblawi et al. in which a minor complication rate of 3.8% for the older patients is described as compared to 4.4% for the younger. Moreover, during follow up 22% of the elderly suffered atrial arrhytmias compared to 17% of the younger. However, the incidence of new-onset AF was significantly higher in the older patients (7.6%) as compared to the young (0.7%) (P<0.025).[18]

Efficacy

Reports about residual RLS after PFO closure are conflicting and range from 4 to 49%. This might be due to differences in device types, follow-up time, and methods used for diagnosing residual shunting.[5, 7, 8, 10, 26, 27] Kiblawi et al. found no difference in the occurrence of residual shunting as diagnosed by TTE six months after PFO closure between patients older and younger than 55 years (2.3 vs. 2.8%).[18] Spies et al. also found no difference in residual shunting between the elderly (10%) and the young (8.4%) based on a TEE, TTE or transcranial Doppler study performed at least six months after PFO closure.[19]

In our study, residual RLS was non-significantly higher in the older age group (12.1%) as compared to the young (7.7%). By multivariable analysis, residual shunting was an independent predictor of the primary endpoint. (OR 4.2, P=0.04)

Limitations

The study has a retrospective design and there might be referral bias. The diagnosis of cryptogenic thrombo-embolic events was made by the referring physicians and there might be no uniform evaluation. The residual RLS detection was not obtained in all patients, and different imaging techniques (TTE and TEE) were used to detect RLS. Both over- and underestimation are possible.[28] However, this is inherent to the retrospective character of the study. Another limitation is the lack of a control group of patients treated medically. All patients were referred for PFO closure after the occurrence of a cryptogenic embolic event, and none of them wanted to leave the PFO unclosed. By multivariable analysis we tried to adjust for most factors, however there remain some unmeasured confounders. Hence, recurrent events in the elderly group might not be due to reduced effectiveness of PFO closure since the mechanism of recurrence could be not related to the PFO. As already described, our data do

not answer the important remaining question of how transcatheter PFO closure compares to medical treatment for prevention of recurrent thrombo-embolism. The results of ongoing randomized trials (CLOSURE-1, PC, RESPECT) will hopefully answer this question. Unfortunately, a common exclusion criterion for most ongoing trials is age above 60 years. Randomized trials that include older patients are needed to develop management strategies in this large patient group.

Conclusion

Percutaneous PFO closure appears to be effective for secondary prevention of cryptogenic stroke in younger patients but seems to be related with less beneficial outcome in elderly. Randomized controlled trials are needed to confirm our findings and to study whether PFO closure has a reduced efficacy in older patients.

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Chapter 6

Long-term outcome of percutaneous closure of secundum type atrial septal defects in adults

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EuroIntervention (Accepted for publication)

Abstract

Aims: Transcatheter closure of the secundum type atrial septal defect (ASD) is widely practised. We report complications and efficacy of percutaneous ASD closure in adults using the Amplatzer® ASD occluder and Cardioseal/Starflex® device during long-term follow-up.

Methods and Results: Between 1996 and 2008 percutaneous ASD closure was performed in 133 patients (mean age 46.8±16.9 years; 36 men) by using the Amplatzer® device in 104 and the Cardioseal/Starflex® device in 29 patients. During a mean follow-up of 3.4±2.8 years the occurrence of major complications was higher in patients with Cardioseal/Starflex® compared to patients with Amplatzer® devices (17.2 vs. 2.9%, log rank, P=0.005), due to a higher embolization rate (13.8 vs. 1.0%, log rank, P=0.002). In univariable analysis, the implantation of a Cardioseal/Starflex® device (OR 6.0 (CI 1.4-25.2); P=0.01) and a larger device diameter (OR 1.1 (CI 1.0-1.2); P=0.04) were found to be predictors of the occurrence of major complications. Minor complications occurred in 10.5%, recurrent thrombo-embolism in 2.3% and residual shunting at six months was 13.9% without differences between devices. NYHA class improved from 1.8±0.6 before to 1.2±0.4 after closure (P<0.001) without differences between devices.

Conclusion: During long-term follow-up percutaneous ASD closure in adults is safe and effective when using the Amplatzer® device. Larger Cardioseal/Starflex® devices are related to a higher embolization rate. Randomized trials are needed.

Introduction

An atrial septal defect (ASD) accounts for about one third of all congenital heart diseases detected in adults.[1] The secundum type ASD is located in the region of the fossa ovalis and makes up 75% of all ASD's.[2] An ASD is characterized by predominant left-to-right shunting and right ventricular volume overload.[2] Most patients with a sizable ASD remain asymptomatic during the first two decades of life.[2] However, eventually, most develop symptoms due to cardiac failure, pulmonary hypertension, atrial arrhythmias and paradoxical embolism, the latter due to right-to-left shunting.[1, 3] To avoid the increase in the incidence of severe disability and death, surgical ASD closure used to be the only option that increased survival when shunting compromised life expectancy.[4, 5] Nowadays, transcatheter ASD closure is widely practised and has replaced to a large extent surgical closure in many centres.[6]

We report our experience in percutaneous closure of a secundum type ASD in adults. We compared complications and efficacy of the Amplatzer® ASD occluder (AGA Medical Corporation, Golden Valley, MN, USA) and the Cardioseal/Starflex® device (NMT Medical, Inc., USA) during long-term follow-up.

Methods

Patient selection

We included all patients (> 16 years of age) who underwent percutaneous ASD closure by means of an Amplatzer® ASD occluder or a Cardioseal/Starflex® device in the St. Antonius Hospital, Nieuwegein, the Netherlands between November 1996 and January 2008.

All secundum type ASD's were identified by transthoracic and transesophageal echocardiography (TTE and TEE) using color Doppler techniques and/or contrast examination. Pre-, peri- and postprocedural data were collected, including demographic, echocardiographic, angiographic and procedural parameters. All patients gave informed consent.

ASD closure

As previously reported, ASD closure was performed according to standard techniques, under general anaesthesia and continuous TEE monitoring.[7] The choice of the device type was made in accordance to the clinical preference of the interventional cardiologist.

Complications and efficacy

Follow-up information was obtained by periodical outpatient visits and a telephone interview. The most recently available medical records were reviewed. We compared data for the two ASD closure devices used.

Complications

Complications of transcatheter ASD closure, including peri-procedural complications (occurring during hospitalization) and complications during follow-up, were noticed. They were classified as major or minor according to the following scheme.

The primary endpoint was defined as the total of major complications related to percutaneous ASD closure. Major complications included haemorrhage requiring blood transfusion, occurrence of cardiac tamponade, need for procedure-related surgical intervention, massive fatal pulmonary emboli, occurrence of new thrombo-embolic event and death, related to the closing procedure.

Minor complications were defined as device malpositioning or embolization with successful catheter repositioning, bleeding not requiring blood transfusion, occurrence of new-onset atrial arrhythmias (atrial flutter or fibrillation), transient atrioventricular block, device arm fractures, asymptomatic device thrombosis, need for re-catheterization, transient air embolism, transient ST-segment elevation, femoral arteriovenous fistula formation, femoral haematoma, and other minor complications related to the closing procedure.

Efficacy

Some patients underwent ASD closure because of a paradoxical thrombo-embolism (stroke, TIA, or other thrombo-embolic event). Therefore, the recurrence of thrombo-embolic events was evaluated during follow-up. All neurological embolic

events needed to be established by a neurological evaluation and, in case of stroke, confirmed by the appropriate cerebral imaging studies.
To evaluate symptoms related to the ASD, the New York Heart Association (NYHA) functional class was recorded before and after ASD closure by a telephone interview. The presence of residual shunting after ASD closure was evaluated based on a contrast TTE or TEE study performed at least six months after ASD closure.

Statistical analysis

Descriptive statistics were used to report patients' characteristics. Continuous variables were tested on normality and, if present, reported by mean ± standard deviation (SD). Median and range were used when normal distribution was absent. Percentages were used to report categorical variables. Patients' data were compared among groups with Chi-square or Fisher exact test for nominal variables and independent Student's *t* test for continuous variables. Paired samples *t* test was used for within group comparison of continuous variables. The log rank test was used where applicable. Kaplan-Meier survival analysis was done on the primary endpoint and the occurrence of minor complications. Predictors of the primary endpoint and the occurrence of minor complications were assessed using a Cox proportional hazards model. Univariate logistic-regression analyses were used to estimate the unadjusted odds ratios (OR) and the corresponding 95% confidence intervals (CI). All tests were two sided and $P<0.05$ was considered to be statistically significant. All statistical analyses were performed using SPSS software (SPSS Inc., version 12.0 for Windows).

Results

Patient characteristics

Between November 1996 and January 2008 percutaneous ASD closure was performed in 133 consecutive patients (mean age 46.8±16.9 years (range 16.1-81.0 years); 36 men). Patient characteristics, prevalence of risk factors for cardiovascular disease, co-morbidities and the reason of ASD detection are summarized in Table I.

Table I. Patients', ASD and haemodynamic characteristics and closure devices

	Number
Total, n	133
Mean age ± SD (range) (y)	46.8 ± 16.9 (16.1-81.0)
Men, n (%)	36 (27.1)
Women, n (%)	97 (72.9)
Mean weight ± SD (kg)	72.4 ± 14.6
Mean length ± SD (cm)	171.2 ± 10.7
Mean SBP ± SD (mmHg)	131.4 ± 19.3
Mean DBP ± SD (mmHg)	80.9 ± 10.7
Risk factors and co-morbidities, %	
Hypertension	23.5
Diabetes	3.0
Hyperlipidemia	6.1
Smoking	20.5
CAD	4.6
PAD	1.5
Family history of CVD	19.1
History of SVT	29.3
Reason of ASD detection, %	
Asymptomatic	17.3
Dyspnoea/fatigue	35.3
Palpitations/atrial fibrillation	21.8
Syncope	1.5
Stroke/TIA	24.1
ASD characteristics	
Diameter ± SD (range) (mm)[a]	17.7 ± 6.6 (4-34)
Aneurysm IAS (on echocardiography), %	27.1
Haemodynamic characteristics	
PAP systolic ± SD (mmHg)[b]	32.4 ± 10.5
PAP diastolic ± SD (mmHg)[b]	11.0 ± 5.8
PAP mean ± SD (mmHg)[b]	19.2 ± 7.2
PCWP ± SD (mmHg)[c]	10.5 ± 5.2
RAP mean ± SD (mmHg)[d]	5.8 ± 3.9
Qp:Qs ± SD[e]	2.1 ± 1.0

Table I. Continued	
Closure devices	
Cardioseal / Starflex®, n	29
Median device diameter (range) (mm)	33 (20-43)
Mean ASD diameter ± SD (range) (mm)	13.7 ± 5.0 (4-24)[f]
Amplatzer ASD occluder®, n	104
Median device diameter (range) (mm)	24 (12-38)
Mean ASD diameter ± SD (range) (mm)	18.9 ± 6.5 (5-34)

n, number; SD, standard deviation; y, years; kg, kilograms; cm, centimeters; SBP, systolic blood pressure; DBP, diastolic blood pressure; CAD, coronary artery disease; PAD, peripheral artery disease; CVD, cardiovascular disease; SVT, supraventricular tachycardia; ASD, atrial septal defect; TIA, transient ischemic attack; IAS, inter-atrial septum; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; Qp:Qs, pulmonary to systemic blood flow ratio; mm, millimeters.

[a]Data in 115; [b]data in 47; [c]data in 39; [d]data in 41; [e]data in 36 patients; [f]P<0.001 vs Amplatzer®

ASD and closure characteristics

On echocardiography before ASD closure, all shunts were bidirectional, but predominantly from left to right. An associated atrial septal aneurysm (ASA) was found in 27%. Fourty-seven patients (35%) underwent invasive determination of haemodynamic characteristics before closure. Mean Qp:Qs ratio was 2.1±1.0. Echocardiographic data and haemodynamic characteristics before ASD closure are summarized in Table I.

The mean ASD diameter on balloon sizing before ASD closure was 17.7±6.6 mm (range 4-34 mm). For ASD closure, we used the Amplatzer® ASD occluder in 78% and the Cardioseal/Starflex® device in 22%. In the beginning of the study period the Cardioseal/Starflex® device prevailed. Later on the Amplatzer® ASD Occluder was implanted in most cases. The mean ASD diameter was larger in patients that received an Amplatzer® device compared to patients that received a Cardioseal/Starflex® device: 18.9±6.5 vs. 13.7±5.0 mm (P<0.001). These data are summarized in Table I.

Complications

Primary endpoint

The mean follow-up time was 3.4±2.8 years (range 0-10.9 years) and differed between the two devices used for ASD closure (Table II).

The primary endpoint occurred in eight patients (6.0%). In five patients device embolization occurred (two periprocedurally and three during follow-up). In a 56-year-old man, an Amplatzer® 22 mm device embolized into the left ventricle during the procedure, requiring immediate surgery. The device was removed and the ASD was closed. Another embolization occurred in a 34-year-old woman during implantation of a Cardioseal/Starflex® 43 mm device. The device embolized into the pulmonary artery and was successfully removed surgically combined with surgical ASD closure. A 49-year-old woman suffered embolization into the pulmonary artery of a Cardioseal/Starflex® 40 mm device two weeks after the procedure. She required an operation to remove the device and close the ASD. In a 54-year-old man device embolization into the pulmonary artery was diagnosed three months after implantation of a Cardioseal/Starflex® 40 mm device. The device was removed surgically and the ASD was closed with sutures. However, he needed re-operation because of rupture of a suture. Eventually, he received a Goretex patch, after which the ASD was closed. Finally, in a 61-year-old woman, migration of a Cardioseal/Starflex® 40 mm device in the inter-atrial septum was diagnosed five months after implantation. The device was surgically removed and a Goretex patch was used to close the ASD. Other major complications occurred in the following three patients: a 25-year-old woman suffered a haemopericardium immediately after having received a Cardioseal/Starflex® 28 mm device. The haemopericardium was probably due to perforation of the device or catheter and required pericardial drainage, which was successful. An 81-year-old woman required surgery for an inguinal pseudo-aneurysm she developed one month after ASD closure with an Amplatzer® 24 mm device. The pseudo-aneurysm was caused by inadvertent puncture and laceration of the femoral artery. Finally, a 41-year-old woman with a history of atrial arrhythmias suffered an episode of atrial fibrillation one week after implantation of an Amplatzer® 20 mm device. After electrical cardioversion in the referring hospital she suffered a stroke, probably due to an atrial thrombus, for which coumadin was started.

The occurrence of the primary endpoint was significantly higher in patients that had received a Cardioseal/Starflex® device as compared to patients that had received an Amplatzer® device (17.2 vs 2.9%; log rank, P=0.005) (Table II). Kaplan-Meier event-free survival curves for the primary endpoint for patients with Amplatzer® and Cardioseal/Starflex® devices are plotted in Figure 1A. The higher occurrence of the primary endpoint in patients with Cardioseal/Starflex® devices is attributable to a higher embolization rate of these devices compared to the Amplatzer® devices (13.8 vs. 1.0%; log rank, P=0.002) (Table II). In patients who received Cardioseal/Starflex® devices, the initial ASD and device diameters were significantly higher in patients in whom the device embolized compared to the others, 18.8±3.8 vs. 12.9±4.7 mm for ASD diameter (P=0.03) and 40 (40-43) vs. 33 mm (20-40) for device diameter (P=0.004). In univariable analysis, the implantation of a Cardioseal/Starflex® device (OR 6.0 (CI 1.4-25.2); P=0.01) and a larger device diameter (OR 1.1 (CI 1.0-1.2); P=0.04) were found to be predictors of the primary endpoint.

Table II. Complications and efficacy related to the type of device used for ASD closure

	Total	Amplatzer®	Cardioseal®	P
Number, n (%)	133	104 (78)	29 (22)	
Mean FU ± SD (range) (y)	3.4 ± 2.8 (0-10.9)	2.7 ± 2.1 (0-7.5)	6.1 ± 3.2 (0.1-10.9)	<0.001[a]
Major complications, n (%)	8 (6.0)	3 (2.9)	5 (17.2)	0.005
Embolization	5 (3.8)	1 (1.0)	4 (13.8)	0.002
Tamponade	1 (0.8)	0 (0)	1 (3.4)	0.06
Pseudo-aneurysm	1 (0.8)	1 (1.0)	0 (0)	0.60
New stroke	1 (0.8)	1 (1.0)	0 (0)	0.59
Minor complications, n (%)	14 (10.5)	9 (8.7)	5 (17.2)	0.23
Inguinal haematoma	1 (0.8)	1 (1.0)	0 (0)	0.60
New-onset AF	13 (9.8)	8 (7.7)	5 (17.2)	0.16
Persistent AF, n (%)	19 (14.2)	13 (12.5)	6 (20.7)	0.37[b]
Recurrence TE, n (%)	3 (2.3)	2 (1.9)	1 (3.4)	0.77
Stroke	2 (1.5)	1 (1.0)	1 (3.4)	0.45
TIA	1 (0.8)	1 (1.0)	0 (0)	0.56
Residual shunting, n (%)[c]	16 (13.9)	10 (11.4)	6 (22.2)	0.20[b]

n, number; FU, follow-up; y, years; SD, standard deviation; AF, atrial fibrillation; TE, thrombo-embolism; TIA, transient ischemic attack. All tests are log rank tests, except for [a]Students' *t* test and [b]Chi-square test. [c]Data in 115 patients.

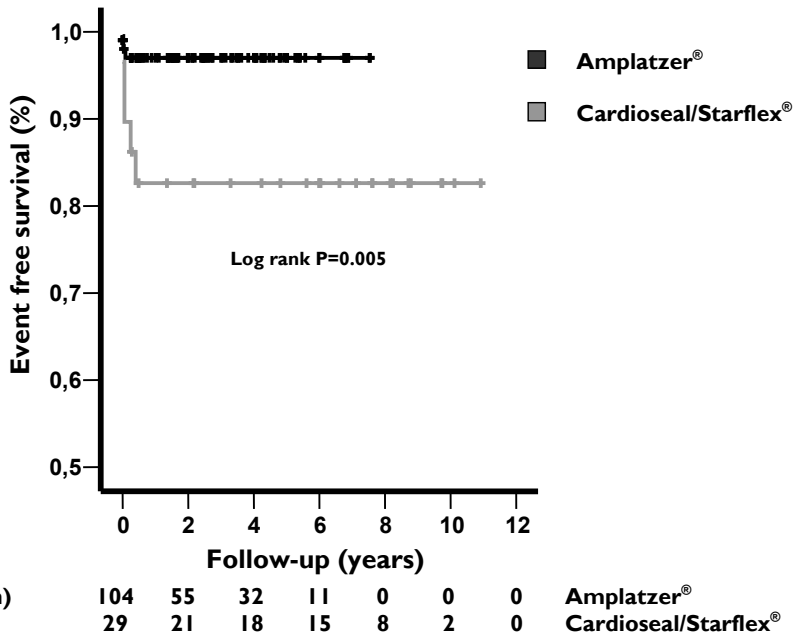

Figure 1A. Kaplan-Meier event free survival curves for the primary endpoint for the Amplatzer® and Cardioseal/Starflex® device.

Minor complications

Minor complications related to the percutaneous ASD closure occurred in 14 patients (10.5%). Minor peri-procedural complications (3.0%) consisted of three patients with new-onset atrial fibrillation (AF) successfully treated with medication or electrical cardioversion and one patient who suffered an inguinal haematoma, which was treated conservatively.

Minor complications during follow-up consisted of ten patients (7.5%) with new-onset AF. All were successfully treated with medication or electrical cardioversion. The occurrence of minor complications did not differ between the device types used (Table II). Kaplan-Meier event-free survival curves for the occurrence of minor complications for both closure devices are plotted in Figure 1B. In univariable analysis, a higher age (OR 1.03 (CI 1.0-1.07); P=0.04) was found to be a predictor of the occurrence of minor complications.

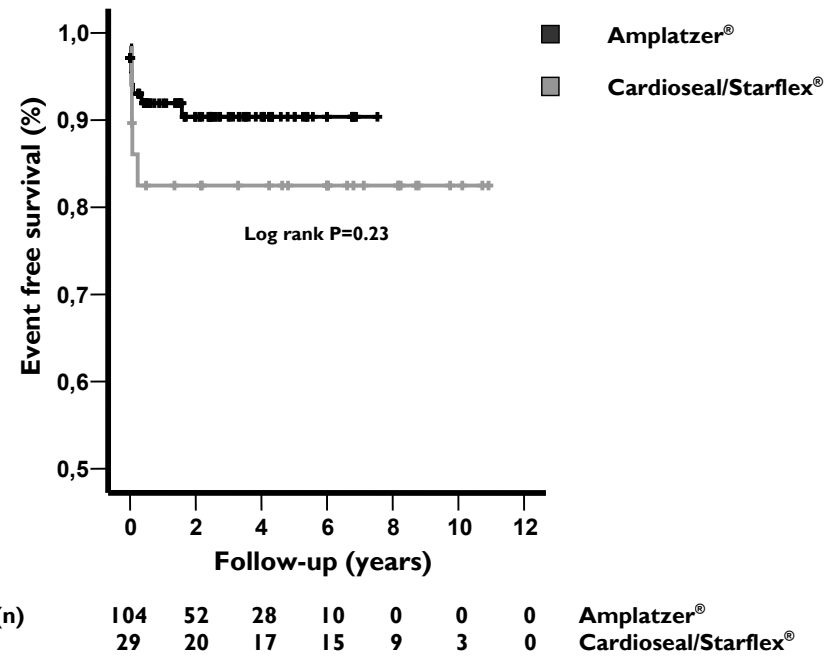

Figure 1B. Kaplan-Meier event free survival curves for the occurrence of minor complications for the Amplatzer® and Cardioseal/Starflex® device.

The occurrence of AF after ASD closure was high. However, 59% of these patients already had a history of AF. Thirteen patients (9.8%) suffered new-onset AF, whereas 19 patients (14.2%) with a history of AF suffered a new episode after ASD closure (Table II). Device type or size and age did not influence the occurrence of new-onset AF.

In three patients, closure devices were removed during follow-up for different reasons, other than complications. One patient underwent a MAZE procedure for AF, during which the device was removed and the ASD was closed surgically. Another patient suffered from multiple ASD's, as diagnosed during the closing procedure. Percutaneous closure of the largest ASD in this patient was successful and without complications. However, she had persistent symptoms due to the remaining ASD's and eventually underwent surgical closure. The third patient, who had a history of paradoxical embolism, was diagnosed moderate residual shunting after an uncomplicated ASD

closure. There was no dislocation. We advised coumadin, however, the patient had the closure device surgically removed, followed by surgical ASD closure in another hospital.

Efficacy

Recurrent thrombo-embolic events

Recurrent thrombo-embolic events after ASD closure occurred in three patients (2.3%). The annual recurrent thrombo-embolic event rate was 0.7%. A 58-year-old woman with a history of multiple strokes, in whom a Cardioseal/Starflex® 28 mm device was implanted, suffered a recurrent TIA and stroke. Echocardiography revealed no residual shunting, however, there was a suspicion of left atrial thrombus, for which coumadin was started. A 38-year-old woman with a history of stroke, in whom an Amplatzer® 35 mm device was implanted, suffered a recurrent stroke. Echocardiography revealed no residual shunting in this patient. Finally, a 36-year-old woman, with a history of TIA, in whom an Amplatzer®16 mm device was implanted, suffered a recurrent TIA. No residual shunting was found on echocardiography. The recurrence of thrombo-embolic events did not differ between the two device types used (Table II).

NYHA functional class

Analysis of NYHA functional class was obtained in 77 patients (58%). Mean NYHA class before ASD closure was 1.8±0.6 and decreased to 1.2±0.4 at latest follow-up after ASD closure ($P<0.001$). No differences between the two device types used were found.

Residual shunting

On peri-procedural TEE, residual shunting after ASD closure was found in 23 patients (17.7%). At latest follow-up, residual shunting, as diagnosed with a contrast TTE (or TEE in some cases), was reduced to 13.9% based on analysis of 115 patients. There was no difference in the prevalence of residual shunting between the device types used (Table II). Residual shunting was not a predictor of thrombo-embolism after ASD closure.

Discussion

Our results demonstrate that transcatheter closure of ASD's of the secundum type in an adult patient population is safe and effective during long-term follow-up using an Amplatzer® device. However, using the Cardioseal® device is related to a high rate of major complications.

Surgical ASD closure

In the past, in patients with sizable ASD's, surgical closure was the only option that increased survival.[4, 5, 8] Historically, the operation in adults had an early mortality rate of 1.2-3.3% and moderate to severe complications were observed in 9-13% of patients.[5, 8, 9] Recent comparative data between surgical and percutaneous ASD closure in children and adults described 0% mortality rates for both treatment modalities.[10-12] However, a higher major complication rate of 10.5-25% was found in patients who underwent surgical closure as compared to 1-13.2% for percutaneous closure.[10-12] Surgery was strongly related to the occurrence of total and major complications.[10] The higher event rate was associated with age > 40 years.[12] However, as for transcatheter closure techniques, surgical techniques have been improved as well. Mishra et al. compared 470 patients who underwent transcatheter ASD closure with 170 patients taken for ASD closure through minimal invasive port access surgery and found both techniques to be equally safe and effective with a success rate of 97.1 and 99.4% and a major complication rate of 1.8 and 2.9%, respectively.[13]

Percutaneous ASD closure

The clinical feasibility of transcatheter ASD closure was first described by King and Mills in 1976.[14, 15] Since then the technique and devices have been continuously improved and have to a large extent replaced the surgical ASD closure. Percutaneous closure of a secundum type ASD is nowadays widely practiced. There have been numerous reports that describe the safety and efficacy of transcatheter ASD closure.[16-26]

Complications

Major complications

In several studies major complication rates of 0-11.1% of transcatheter ASD closure have been reported, which is comparable with the rate of 6.0% we found.[16-26] Importantly, we found a higher major complication rate in patients, who had received a Cardioseal/Starflex® device (17.2%) as compared to patients with an Amplatzer® device (2.9%). In univariable analysis, the presence of a Cardioseal/Starflex® device and a larger device diameter were predictors of the occurrence of major complications. These major complications were mainly attributable to device embolization. We reported a total embolization rate of 3.8%, which is comparable with embolization rates of 0-7.4% reported in several studies.[16-26] However, the occurrence of embolization was significantly higher in patients, who had received a Cardioseal/Starflex® device (13.8%) as compared to patients with Amplatzer® devices (1.0%). In contrast, Butera et al. found a non-significant difference in embolization rate between these two devices.[16] They reported embolization in three (2.5%) of 121 patients who received the Cardioseal/Starflex® device as compared to one (0.7%) of 153 patients who received an Amplatzer® device.[16] An explanation for the high embolization rate using the Cardioseal/Starflex® devices in our study could be the larger diameter of the ASD and closure device in these patients. These diameters seem to be larger in our study compared to others who used the Cardioseal/Starflex® device.[16, 23] This is supported by the fact that initial ASD and device diameters were significantly larger in patients in whom the device dislocated or embolized compared to the others. However, the four Cardioseal/Starflex® devices that embolized or migrated were part of the first 30% of all transcatheter ASD closing procedures performed in our centre. We have to take into account a learning curve and the fact that closing techniques and some closure devices are continuously technically improved. During the last 70% of all procedures, only one device (Amplatzer®) embolized. Nowadays, we preferably use the Amplatzer® device in patients with large ASD's and only consider Cardioseal/Starflex® devices in patients with small defects.

Minor complications

A minor complication rate of 0-37% has been reported for transcatheter ASD closure.[16-26] These varying numbers are probably the result of differences in follow-up time, the definition of complications and the device types used.

In our study, minor complications occurred in 10.5%. Taking into account the follow-up period of three and a half years in our study, which is longer compared to other studies, our results are even more beneficial. We found no differences in the occurrence of minor complications between the two devices used. In univariable analysis, higher age was found to be a predictor of the occurrence of minor complications.

In our study new-onset AF was the most frequent complication (9.8%) after ASD closure. Spies et al. found an annual incidence of new-onset AF of 4.1% in 240 patients after ASD closure during a median follow-up of 20 months[27] compared to an annual incidence of 2.9% in our study. In our study, device type or size and age did not influence the occurrence of new-onset AF.

Efficacy

Recurrent thrombo-embolic events

The occurrence of thrombo-embolic events after ASD closure varies between 0% and 2.3%.[16-26] In most studies, it remains unclear, whether these events are recurrent or not. We found recurrent thrombo-embolic events in 2.3% which is comparable with previous reports. However, the follow-up period of our study was longer compared to other reports. The chance of having a thrombo-embolic event increases with longer follow-up duration. Indeed, the annual recurrent event rate was only 0.7%. Additionally, recurrent thrombo-embolic events might not be related to ASD closure but to for instance systemic atherosclerosis. In support, in our study, the recurrent thrombo-embolic event in one patient could have been device related. This concerns the patient who was diagnosed possible left atrial or device thrombus. In the two other patients who suffered a recurrent thrombo-embolic event, no device thrombus or residual shunting could be found on echocardiography. These events were probably not device-related.

NYHA functional class

An improvement in symptoms and exercise tolerance has been reported in patients undergoing percutaneous ASD closure.[23, 28] We also found an improvement in NYHA functional class after ASD closure. This finding is compatible with the improvement in exercise capacity and cardiac function in adult patients after ASD closure reported by Giardini et al.[29]

Residual shunting

Residual shunting during follow-up after ASD closure has been reported in 0-50%.[16-26] These differences can be explained from the differences in follow-up time, the definition of residual shunting and the use of different imaging modalities to diagnose residual shunting. We found residual shunting, as diagnosed by a contrast TTE (and in a few cases TEE) and including very small shunts, in 13.9% of patients after ASD closure at latest follow-up. No differences were found between the two devices used.

Limitations

The first limitation of our study is the single centre character. The second limitation is that data on residual shunting and NYHA functional class were not available in all patients. The third limitation is that the comparison of the Amplatzer® and the Cardioseal/Starflex® device could be affected by the continuous technical improvement of the closing technique and the devices.

Conclusion

Percutaneous closure of a secundum type ASD in adults is safe and effective, especially when using the Amplatzer® device. The larger Cardioseal/Starflex® devices are possibly related to a higher rate of embolization. Prospective randomized trials that compare different types of devices are needed.

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Chapter 7

Haemodynamic effects of patent foramen ovale and atrial septal defect closure: A comparison during percutaneous shunt closure

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Clinical Physiology and Functional Imaging (Accepted for publication)

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Abstract

Objectives: We investigated the haemodynamic effect of percutaneous closure of an inter-atrial shunt, using non-invasive finger pressure measurements.

Background: Percutaneous closure of both patent foramen ovale (PFO) and atrial septal defect (ASD) is widely practised. Currently no data are available on short-term haemodynamic changes induced by closure.

Methods: Twenty-five consecutive patients (mean age 49±17 years, 10 men) who underwent a percutaneous closure of a PFO (n=15) or ASD (n=10) were included in this study. During the procedure blood pressure and heart rate (HR) were monitored continuously with a Finometer®. Changes in systolic, mean, and diastolic pressure, stroke volume (SV), cardiac output (CO), and total peripheral resistance (TPR) were computed from the pressure registrations using Modelflow® methodology.

Results: Baseline characteristics were similar for the PFO and ASD patients. After PFO closure none of the haemodynamic parameters changed significantly. After ASD closure the systolic, mean, and diastolic pressures increased 7.1±5.4 (P=0.003), 3.8±3.5 (P=0.007) and 2.0±3.0 mmHg (P=ns), respectively. HR decreased 5.1±5.3 beats per minute (P=0.01). SV, CO and TPR increased 8.5±6.4 ml (13.5%; P=0.002), 0.21±0.45 l/min (5.6%; P=ns) and 0.02±0.14 dynes (4.1%; P=ns), respectively. The changes in SV differ between the PFO and ASD patients (P=0.009).

Conclusions: Using non-invasive finger pressure measurements, we found that stroke volume, mean and systolic blood pressure increased immediately after percutaneous closure of an ASD in adults, whereas the percutaneous PFO closure had no effect on haemodynamic characteristics.

Introduction

Patent foramen ovale (PFO) and atrial septal defect (ASD) are both atrial septal abnormalities. Whereas a PFO does not affect cardiac function, an ASD has been associated with right ventricular volume overload, which in turn can cause an impaired left ventricular (LV) function.[1-3]

The percutaneous closure of both PFO and ASD is widely practised. No data are available on haemodynamic changes during PFO closure. Literature about haemodynamic changes following percutaneous ASD closure is scarce. An improvement of LV function is described after ASD closure.[3, 4] A limitation of these studies is that the measurement of LV function is based on echocardiography before and when the patients were fully recovered after percutaneous closure of the defect.[3, 4] No data are available on short-term haemodynamic changes induced by closure of both PFO and ASD.

We investigated the short-term haemodynamic effects of percutaneous closure of PFO and ASD, using non-invasive finger pressure measurements.

Methods

We included 25 consecutive patients (mean age 49±17 years, 10 men) who underwent a percutaneous closure of a PFO (n=15) or ASD (n=10) in the St. Antonius Hospital, Nieuwegein, the Netherlands and who provided written informed consent.

Definition of PFO and ASD

A PFO was defined as a valve-like opening in the atrial septal wall. A PFO is a tunnel between the septum primum and secundum. It is established when septum primum and secundum fail to fuse after birth. Acting as a one-way valve, a PFO can cause spontaneous or provocable (Valsalva) right-to-left shunting (RLS).

An ASD was defined as a congenital heart defect in which a part of the inter-atrial septum is missing. The resulting inter-atrial communication causes left-to-right-shunting (LRS), because left atrial pressure usually exceeds right atrial pressure.

However, in cases of increased right atrial pressure, for instance a Valsalva maneuver, RLS may manifest.
We diagnosed a PFO or an ASD using transesophageal echocardiography (TEE) with agitated saline.

Closure of PFO and ASD

The percutaneous closure of the atrial septal abnormalities was performed under general anaesthesia (propofol) and continuous TEE monitoring. After access through the right femoral vein, a bolus of 5000 U of heparin was administered. Sheaths up to 12 French were used. The closure devices were implanted under fluoroscopic and echocardiographic guidance.[5] The type of device was chosen by the interventional cardiologist depending on the anatomy and diameter of the defect. For ASD's a sizing balloon was used. All patients received an intravenous dose of antibiotics one hour before and six hours after closure (in most cases 750 mg of cefuroxim).
Within 24 hours after closure, a chest X-ray and a transthoracic echocardiogram (TTE) were performed. All patients were discharged on antiplatelet therapy: clopidogrel (75 mg) for four weeks and low-dose aspirin (80-100 mg) for at least six months. Prophylaxis against endocarditis was advised for a minimum of six months counting from the closing procedure.

Haemodynamic measurements

Non-invasive finger arterial pressure

Arterial pressure was measured in the left middle finger by a Finometer® device (FMS, Finapres Medical Systems, Amsterdam, the Netherlands). Finometer® measures blood pressure by the volume clamp method of Peñáz, and the "Physiocal" criteria developed by Wesseling.[6] The finger was kept at heart level. An arm cuff was wrapped around the same arm for individual upper arm cuff systolic calibration using return-to-flow calibration.[7]

Maneuvers

Finometer® measurements were performed during anaesthesia after stabilization of the finger pressure signal during a one minute period immediately before and after the closing procedure. At the time of closure, measurements were not possible due to distortion of the signal, probably due to arrhythmias caused by manipulation of the catheter and the closure device.

Data registration and analysis

Finger pressures and time markers were monitored and stored on line in a computer. Off line review of data was performed using BeatScope® software. Four second and one minute averages of systolic (SBP), mean (MAP) and diastolic blood pressure (DBP), heart rate (HR), stroke volume (SV), cardiac output (CO) and total peripheral resistance (TPR) were computed off line after an electronic calibration procedure. Using the Modelflow® method SV was calculated from the finger pressure wave.[8] CO was the product of SV and HR. TPR was MAP divided by CO. The SV, CO and TPR were not calibrated with invasive determinations. Differences between uncalibrated model values and invasive determinations in individual patients are small in most but can be substantial in some. The standard deviation of the difference may be 19%.[9] Absolute and relative changes from baseline are presented. Absolute values of SV, CO and TPR need to be interpreted with caution.

Statistical analysis

Descriptive statistics were used to describe patient characteristics. Continuous variables with normal distribution are presented as mean ± SD. Paired samples *t* tests were performed to describe within group changes of continuous variables. For between groups comparison of (changes of) continuous variables we used the independent Student's *t* test. The Fisher exact test was performed where applicable. $P<0.05$ was considered to be statistically significant. Analyses were performed using SPSS version 11.5 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Baseline

At baseline there were no significant differences between the PFO and ASD patients, as summarized in Table I. Haemodynamic measurements before percutaneous closure are summarized in Table II.

Table I. Baseline characteristics of PFO and ASD groups

	PFO	ASD	P
Total, n	15	10	
Men, n (%)	8 (53)	2 (20)	0.21
Mean age ± SD (y)	55.0 ± 14.7	41.1 ± 17.1	0.05
Mean weight ± SD (kg)	77.5 ± 17.6	72.7 ± 12.2	0.43
Mean lenght ± SD (cm)	175.8 ± 9.6	171.4 ± 10.2	0.29
Mean BMI ± SD (kg/m²)	24.9 ± 4.6	24.7 ± 3.4	0.89
Mean Oxygen saturation before closure ± SD (%)	98.3 ± 1.7	99.1 ± 0.7	0.10
Medication, n (%)			
Betablocker	4 (26.7)	1 (10)	0.62
Calcium channel blocker	2 (13.3)	1 (10)	1.0
ACE-inhibitor/AT2-antagonist	6 (40)	0 (0)	0.05
Nitrate	1 (6.7)	1 (10)	1.0
Diuretic	3 (20)	1 (10)	0.63
Digoxine	0 (0)	1 (10)	0.40
Closure devices, n			
Amplatzer®	0	10	
Cardioseal/Starflex®	12	0	
Premere®	3	0	

PFO, patent foramen ovale; ASD, atrial septal defect; n, number; SD, standard deviation; y, years; kg, kilograms; cm, centimeters; kg/m², kilograms per square meter; ACE, angiotensin converting enzyme; AT2, angiotensin 2 receptor.

Table II. Haemodynamic measurements of PFO and ASD groups before percutaneous closure

	PFO	ASD	P
SBP ± SD (mmHg)	89.7 ± 17.6	92.6 ± 10.0	0.64
DBP ± SD (mmHg)	59.6 ± 8.5	58.7 ± 9.8	0.80
MAP ± SD (mmHg)	70.5 ± 11.4	70.2 ± 9.2	0.95
HR ± SD (beats/min)	67.5 ± 15.4	65.7 ± 10.9	0.76
SV ± SD[a] (ml)	63.5 ± 24.7	69.1 ± 14.4	0.53
CO ± SD[a] (l/min)	4.2 ± 1.5	4.4 ± 0.8	0.65
TPR ± SD[a] (dynes)	1.2 ± 0.3	1.1 ± 0.3	0.44

PFO, patent foramen ovale; ASD, atrial septal defect; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; HR, heart rate; SV, stroke volume; CO, cardiac output; TPR, total peripheral resistance; SD, standard deviation; min, minutes; ml, milliliters; l/min, liters per minute.

[a]Differences between uncalibrated model values and invasive determinations in individual patients are small in most but can be substantial in some. The standard deviation of the difference may be 19 %.[9]

Closure of atrial septal abnormality

The percutaneous PFO and ASD closure was performed without complications.

In the PFO group no significant haemodynamic changes occurred after percutaneous closure. In the ASD group SBP and MAP increased immediately after closure: 7.1±5.4 mmHg (P=0.003) and 3.8±3.5 mmHg (P=0.007), respectively. HR decreased: -5.1±5.3 beats per minute (P=0.01), whereas SV increased: 8.5±6.4 ml (13.5%; P=0.002). The changes in SV differ between the PFO and ASD patients (P=0.009). Haemodynamic changes after percutaneous closure for both groups and comparison of changes are summarized in Table III. Haemodynamic measurements before and after the closing procedure for both groups are illustrated in Figure 1.

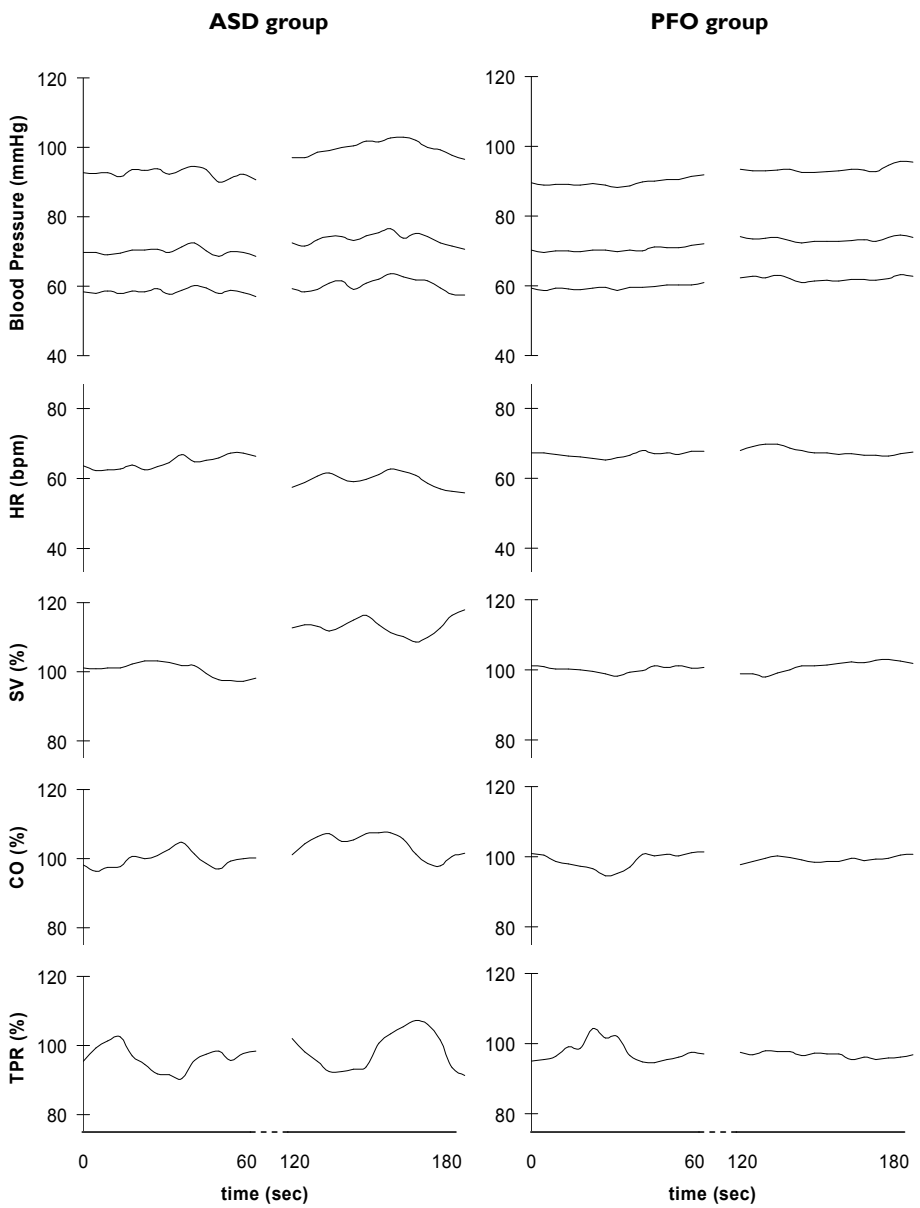

Figure 1. Average responses of systolic, mean and diastolic blood pressure and average responses of heart rate (HR), stroke volume (SV), cardiac output (CO) and total peripheral resistance (TPR) after closure of ASD (left panels) and PFO (right panels). Gaps in graphs represent closing procedure. Four second averages are presented. bpm, beats per minute; sec, seconds.

Table III. Haemodynamic changes after percutaneous closure for both groups

	PFO (n=15)			ASD (n=10)			PFO vs. ASD	
	delta absolute	delta percent	P	delta absolute	delta percent	P	P absolute	P percent
SBP (mmHg)	3.7	5.1	0.11	7.1	7.5	0.003	0.27	0.56
DBP (mmHg)	2.5	4.7	0.13	2.0	3.3	0.06	0.83	0.71
MAP (mmHg)	2.9	4.9	0.13	3.8	5.2	0.007	0.70	0.94
HR (beats/min)	0.4	0.49	0.84	-5.1	-7.3	0.01	0.05	0.05
SV (ml)	0.5	1.7	0.65	8.5	13.5	0.002	0.001	0.009
CO (l/min)	-0.02	-1.3	0.82	0.2	5.6	0.17	0.15	0.39
TPR (dynes)	0.007	1.4	0.80	0.02	4.1	0.61	0.76	0.56

PFO, patent foramen ovale; ASD, atrial septal defect; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; HR, heart rate; SV, stroke volume; CO, cardiac output; TPR, total peripheral resistance; n, number; min, minutes; ml, milliliters; l/min, liters per minute.

Discussion

This study shows that important haemodynamic changes occur immediately after the percutaneous closure of an ASD, whereas closure of a PFO does not result in significant haemodynamic changes.

Haemodynamic effects of PFO and ASD closure

A PFO does not affect cardiac function and there are no reports about haemodynamic changes following PFO closure.

An ASD, in contrast, has been associated with a depressed LV function. Dexter et al. first proposed that volume loading of the right ventricle in patients with uncomplicated ASD might result in impaired filling of the otherwise normal left ventricle by a "reverse Bernheim's syndrome."[1] The same phenomenon was reported by Louie et al. who described a depressed LV ejection fraction in patients with right ventricular volume overload due to end-diastolic leftward ventricular septal shift, resulting in reduction of systolic shortening in the septal-to-free wall dimension.[2] Walker et al. confirmed this adverse ventricular interdependence associated with

right ventricular volume overload and stated that the mechanical disadvantage of a non-circular short-axis configuration and changes in chamber and myocardial preload are the mechanisms underlying decreased LV performance associated with right ventricular volume overload.[3]

Reports on the effects of percutaneous ASD closure on LV function and other haemodynamic parameters are lacking. An acute rise of left atrial and left ventricular filling pressures with concomitant rise in blood pressure has been described after surgical ASD closure.[10] Walker et al. reported an increased left ventricular ejection fraction (LVEF) determined by echocardiography, but no changes in heart rate or blood pressure, after percutaneous ASD closure.[3] These measurements were performed within 48 hours after ASD closure. Pascotto et al. also found an echocardiographically increased LVEF in 70 young patients 24 hours after ASD closure with the Amplatzer® septal Occluder.[4] Salehian et al. found an improvement of LV function, assessed by the myocardial performance index, almost 100 days after ASD closure.[11] Finally, Giardini et al. found an improvement of cardiopulmonary function due to an increase in left ventricular stroke volume and cardiac output six months after transcatheter ASD closure.[12]

These studies lack information about important haemodynamic parameters other than LV function, such as blood pressure, heart rate and cardiac output. Furthermore, using echocardiography, no immediate haemodynamic changes following closure were studied.

In our study, we used Finometer® and Modelflow® methodology. This enabled us to perform accurate beat-to-beat non-invasive finger pressure measurements and allowed us to investigate short-term haemodynamic changes. To our knowledge, this study is the first to describe immediate haemodynamic changes following percutaneous PFO and ASD closure.

In the PFO group no haemodynamic changes occurred. A PFO is usually characterized by a small, intermittent right-to-left shunt and not by a large shunt resulting in significant haemodynamic changes.

In the ASD subgroup SBP, MAP and SV increased instantly after percutaneous closure. This is what one would expect to happen, because device closure results in acute volume unloading of the right ventricle and redirection of the pulmonary venous return toward the left ventricle.

Study limitations

The first limitation of our study is that the Modelflow® model does not provide accurate absolute values of SV, CO and TPR without calibration. However, it is an accurate model to compare *changes* in haemodynamics between groups.[13] The second limitation is that we did not quantify the shunt fractions of the ASD and PFO groups before percutaneous closure. It would indeed be even more interesting to correlate haemodynamic changes with the amount of shunting. The third limitation is that we were not able to perform Finometer® measurements during the first seconds after closure. This was due to distortion of the Finometer® signal probably because of arrhythmias due to the manipulation of the catheters in the atria. However, with the method we used, we were able to gain information at a much shorter time after closure than any previous study. The fourth limitation is that all patients received anaesthetic medication, which probably influences haemodynamics. During the haemodynamic measurements, the anaesthetic treatment was stable in all patients. This enabled us to study sudden haemodynamic changes reliably.

Conclusions

Using non-invasive finger measurements, we found that stroke volume, mean blood pressure and systolic blood pressure increased after percutaneous closure of an ASD, whereas the percutaneous PFO closure had no effect on the measured haemodynamic variables.

r1 r2 r3 r4 r5 r6 r7 r8 r9 r10 r11 r12 r13 r14 r15 r16 r17 r18 r19 r20 r21 r22 r23 r24 r25 r26 r27 r28 r29 r30 r31 r32 r33

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Chapter 8

Case report

Late device thrombosis after atrial septal defect closure

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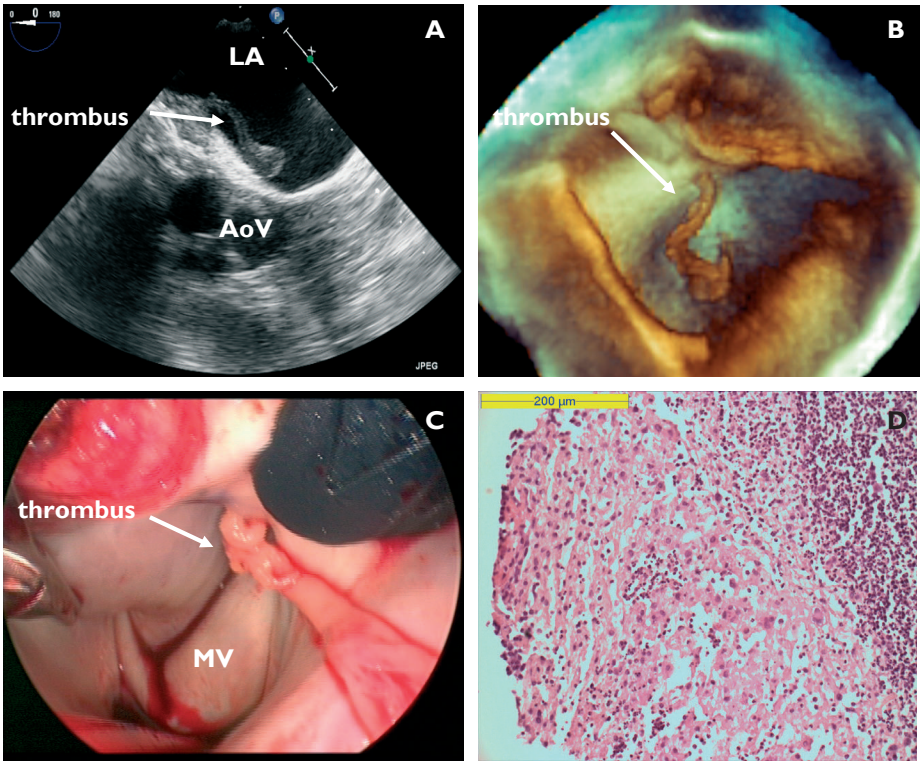
European Heart Journal (Accepted for publication)

A 62-year-old woman with a history of transcatheter atrial septal defect (ASD) closure using a Cardioseal/Starflex® device was admitted for recurrent transient ischemic attacks three years after closure. A transesophageal echocardiogram (TEE) revealed a large, mobile, thrombus-like structure attached to the left-atrial side of the device as a potential cardio-embolic source. There was no evidence of device malposition or arm fractures. Four months after initiation of oral anticoagulants, a TEE showed no resolution of the thrombus-like structure. The patient refused the recommended surgical exploration. Unfortunately, she was re-admitted for recurrent stroke two months later. Finally, she approved with exploration through minimal invasive port access surgery. During surgery, a structure of two centimeters covering the device was removed. The device was explanted, followed by primary ASD closure. Microscopic examination confirmed the structure to be a fresh fibrin thrombus with granulocytes. The patient recovered well. Treatment with oral anticoagulants was continued for at least six months.

Device thrombi have been described early after ASD closure. We report a symptomatic device thrombus at long-term follow-up using a Cardioseal/Starflex® device. These thrombi usually resolve under anticoagulation therapy. If they persist, surgery is recommended.



AoV, aortic valve; LA, left atrium; MV, mitral valve.

Panel A: TEE image of the thrombus attached to the left-atrial side of the device.

Panel B: Three-dimensional TEE image of the thrombus attached to the left-atrial side of the device.

Panel C: Intra-operative view of the thrombus attached to the left atrial septum.

Panel D: Microscopic image of the thrombus containing fibrin, erythrocytes and granulocytes (Haematoxylin-eosin stain).

Part three

Shunt closure and migraine

Chapter 9

Closure of a patent foramen ovale is associated with a decrease in prevalence of migraine: A prospective observational study

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Acta Cardiologica 2008; 63: 571-577

Abstract

Background: A causal relationship between migraine and a right-to-left shunt, due to a patent foramen ovale (PFO), has been suggested. In mainly retrospective studies, percutaneous closure of a PFO has been associated with a decrease in the prevalence of migraine.

Objective: In this prospective observational study we evaluated whether percutaneous closure of a PFO is associated with a decrease in the prevalence of migraine.

Methods: Between November 2003 and August 2005, we included 92 patients (age >16 years) who underwent a percutaneous closure of a symptomatic PFO, which was considered to be related to a paradoxical embolism. They received a headache questionnaire before and six months after closure. Two neurologists diagnosed migraine, according to the International Headache Criteria.

Results: Eighty-nine of 92 patients (97%, mean age 51.6±12.3 years, 63 men) completed the questionnaire immediately before PFO closure. The overall prevalence of migraine was 27.0%, for migraine without aura (MA-) 15.7%, and for migraine with aura (MA+) 11.2%. After more than six months of follow-up 84 of 89 patients (94%, mean age 52.1±12.0 years, 60 men) returned the questionnaire. The overall prevalence of migraine in this group decreased from 28.6% to 10.7% (P=0.001), for MA- from 16.7% to 8.3% (P=0.07), and for MA+ from 11.9% to 2.4% (P=0.02).

Conclusions: Percutaneous PFO closure is related to a decrease in the prevalence of migraine in this prospective observational study. However, randomized placebo controlled trials have to confirm these findings.

Introduction

The most common cause of a right-to-left shunt (RLS) is a patent foramen ovale (PFO). This is present in about 27% of the overall population.[1] However, the prevalence of a RLS in patients with migraine is between 50-60%.[2,3] A causal relationship between its presence and migraine has been proposed.[4] Migraine occurs in 10-12% of the general population.[5-7] A higher prevalence of migraine, especially migraine with aura, has been observed in patients with a RLS as compared to those without a shunt.[8] As reported in several trials, percutaneous closure of a symptomatic PFO might be associated with a decrease in the prevalence of migraine, especially migraine with aura.[8-13] A RLS is called symptomatic when it is related to certain disease manifestations, such as a paradoxical embolic event. However, most of these studies were retrospective,[8,9,11-13] which includes important methodological study limitations. The prospective studies by Morandi and Anzola were limited by their small patient numbers.[10,14]
In this prospective observational two-centre study we evaluated whether percutaneous PFO closure would be related to a reduction in the prevalence of migraine.

Methods

Patient selection

All patients (minimum age 16 years) who underwent a percutaneous closure of a symptomatic PFO in the St. Antonius Hospital, Nieuwegein, the Netherlands and the Gasthuisberg University Hospital, Leuven, Belgium between November 2003 and August 2005 were included in the study. The medical files of these patients were reviewed. All subjects gave informed consent. The local ethics committees of both centres approved the study.

PFO closure

Closure of PFO was performed under general anaesthesia (propofol) and continuous transesophageal echocardiography (TEE) monitoring. After accessing the right femoral vein, a bolus of 5000 U of heparin was administered. Sheaths up to 12 French were

used. The devices were implanted under fluoroscopic and echocardiographic guidance according to the standard technique as previously reported.[15] The choice of the device type was made in accordance to the clinical preference of the interventional cardiologist. All patients received an intravenous prophylactic dose of antibiotics one hour before and six hours after PFO closure (in most cases cefuroxim).

Within 24 hours after closure, a chest X-ray and a transthoracic echocardiogram (TTE) were performed. All patients were discharged on antiplatelet therapy (clopidogrel for at least four weeks and low-dose aspirin for at least six months). Prophylaxis against bacterial endocarditis was advised for a minimum of six months after the closing procedure.

Evaluation of migraine

As described previously[16], a structured questionnaire was composed in such a way that a neurologist could diagnose migraine with or without aura (MA+ or MA-, respectively), according to the criteria of the International Headache Society[17] (Figure 1).

We gave a questionnaire to all patients and requested to complete it before PFO closure. The same questionnaire was sent six months after closure, a prepaid envelope was enclosed. When patients did not return it, we phoned them once in order to obtain the headache questionnaire. Two neurologists, both blinded to the patients' files and time periods, diagnosed MA+ and MA-.

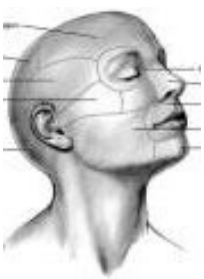
Headache characteristics

In addition to migraine prevalence, headache characteristics were analyzed in patients suffering from migraine before and after closure of the PFO. In this group comparison of three headache characteristics before and six months after PFO closure was performed. First, the duration of headache was compared. Second, headache severity, using the median severity score, and this score was measured on a scale ranging from 0 (no pain) to 10 (very severe pain). Third, the frequency of headache attacks was compared. Therefore, a scale ranging from 0 (no headache) to 6 (daily headache) was used (Figure 1).

Figure 1.

Headache Questionnaire

1. Do you often have a headache? Yes O No O
2. How frequently do you have a headache?
   - O never
   - O once a month
   - O several times a month
   - O once a week
   - O several times a week
   - O once a day
   - O several times a day
3. If you have a headache, how severe is this headache (scale from 0 to 10)? (indicate below)
   Minimal |——————|——————|——————|——————| Very severe
   0 5 10
4. Do you experience visual disturbances prior to or during the headache episodes?
   Yes O No O
5. Do you experience tingling in arms or legs before or during the headache episodes?
   Yes O No O
6. Do you have difficulties in speaking before or during the headache episodes?
   Yes O No O
7. Do you experience weakness (at one side of the body) before or during the headache episodes?
   Yes O No O
8. How long do the visual disturbances last? ……minutes
9. How long does the tingling last? ……minutes
10. How long do the speech disturbances last? ……minutes
11. How long does the weakness last? ……minutes
12. When you have a headache, do you experience:
    - Nausea? Yes O No O
    - Vomiting? Yes O No O
    - Increase in pain while walking? Yes O No O
13. When you have a headache, do you avoid:
    - Light? Yes O No O
    - Noise? Yes O No O
14. Is the headache throbbing? Yes O No O
15. Is the headache located on one side or both sides of the head?
    One O Two O
16. Can you continue your duties/activities during a headache episode?
    Yes O No O
17. How long does the headache last? ……minutes
18. Indicate with an arrow in this picture where the headache is mainly located.



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Complications and cryptogenic stroke recurrence

Complications during percutaneous PFO closure were analyzed in all patients. The incidence of cryptogenic stroke recurrence was obtained from the medical files of the patients. In order to obtain this information, patients were followed until their last outpatient visit.

Statistical analysis

Descriptive statistics were used to describe patient characteristics. Continuous variables with normal distribution are presented as mean ± standard deviation. Median, first and third quartiles (IQ1 and IQ3) were used when normal distribution was absent. Between groups comparison of continuous variables was done by the independent Student's *t* test. Categorical variables were compared by the Fischer exact test. The McNemar paired Chi-square test was performed to describe changes in proportions of patients with migraine. The Wilcoxon signed rank test was performed to compare migraine characteristics before and after PFO closure. Inter-observer reliability was evaluated by the Kappa coefficient. Relative reductions of migraine prevalence were expressed with 95% confidence intervals (CI). $P<0.05$ was considered to be statistically significant. All statistical analyses were performed by using SPSS software (SPSS Inc., version 11.5 for Windows; Chicago, IL,USA).

Results

Patient characteristics and migraine before closure

Ninety-two patients underwent percutaneous closure of a symptomatic PFO in our centres. Eighty-nine of 92 patients (97%, mean age 51.6±12.3 years, 63 men) completed the questionnaire before closure. The prevalence of migraine was 27.0%, MA- 15.7%, and MA+ 11.2%.

The patient characteristics, indication for closure, closure device types, and migraine prevalence are summarized in Table I.

Table I. Baseline characteristics of 89 patients who completed the questionnaire before PFO closure

	Number	Percentage (%)
Total	89	-
Men	63	71
Women	26	29
Mean age ± SD (y)	51.6 ± 12.3	
Indication for closure		
Stroke	81	91.0
Peripheral embolism	3	3.4
Other	5	5.6
Closure device type		
Amplatzer®	7	7.9
Cardioseal / Starflex®	42	47.2
Cardiastar®	38	42.7
Helex®	2	2.2
Occurrence of migraine		
Migraine total	24	27.0
MA -	14	15.7
MA +	10	11.2

SD, standard deviation; y, years; MA-, migraine without aura; MA+, migraine with aura.

Migraine characteristics

After more than six months of follow-up, we obtained a complete questionnaire in 84 of the 89 patients (94%, mean age 52.1±12.0 years, 60 men). The five patients, who did not return the questionnaire, were free of migraine before closure. In the 84 included patients the prevalence of migraine decreased significantly from 28.6% before to 10.7% after closure, a relative reduction of 63% (95% CI 33-79%, P=0.001). The prevalence of MA- changed from 16.7% before to 8.3% after closure, a relative reduction of 50% (95% CI 4-74%, P=0.07), and MA+ decreased significantly from 11.9% before to 2.4% after closure, a relative reduction of 80% (95% CI 20-95%, P=0.02). These data are shown in Figure 2.

In one patient (woman, 50 years of age) MA- changed into MA+. Two patients (both men, 49 and 58 years of age) developed MA- six months after an uncomplicated PFO closure.

Migraineurs were significantly younger than nonmigraineurs. There was no difference in gender nor in the use of possible prophylactic migraine medication between migraineurs and nonmigraineurs. Patient and headache characteristics and the use of medication before PFO closure in relationship to migraine are summarized in Table II. In the overall group of patients who suffered from migraine before and after PFO closure (n = 7) the median duration of headache attacks changed from 1.5 hours (IQ1: 0.1 - IQ3: 13.5 hours) before to 2 hours (IQ1: 0.3 - IQ3: 2 hours) six months after PFO closure (P=0.60). The median severity score was 6.5 (IQ1: 5 - IQ3: 8) before and 5 (IQ1: 4 - IQ3: 8) after PFO closure (P=0.36). The frequency of migraine attacks changed from 2 (IQ1: 2 - IQ3: 3) before to 2 (IQ1: 1 - IQ3: 4) after PFO closure (P=0.83). The Kappa coefficient for inter-observer reliability for migraine was 0.7 (P<0.001).

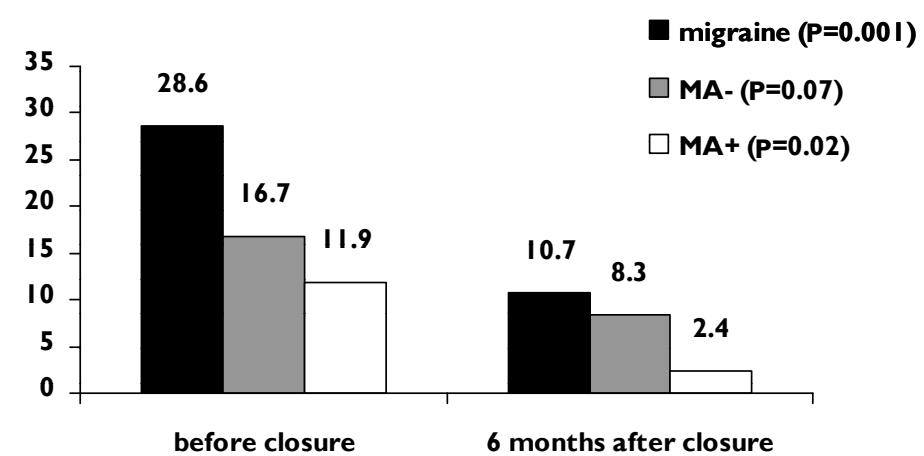

Figure 2. Prevalence of overall migraine, migraine without aura (MA-) and migraine with aura (MA+) before (left columns) and six months after (right columns) PFO closure.

Table II. Patient and headache characteristics and medication before PFO closure in relation to migraine

	Migraine	No migraine	P
Total, n (%)	24 (27.0)	65 (73.0)	
Male, n (%)	15 (23.8)	48 (76.2)	0.31
Female, n (%)	9 (34.6)	17 (65.4)	
Mean age ± SD (y)	45.2 ± 9.3	53.9 ± 12.5	0.003
Medication, n (%)[a]			
Acetylsalicylic acid	12 (57)	39 (66)	0.60
Clopidogrel	3 (14)	7 (12)	0.71
Dipyridamole	3 (14)	9 (15)	1.0
Coumadine	4 (19)	8 (13)	0.50
Low-molecular-weight heparin	0 (0)	6 (10)	0.33
Betablocker	3 (14)	10 (17)	1.0
Statin	8 (38)	18 (30)	0.59
ACE-inhibitor / AT2-receptor blocker	5 (24)	12 (20)	0.76
Calcium channel blocker	2 (10)	2 (3)	0.28
Headache characteristics			
Median duration, hours (IQ1-IQ3)[b]	1.8 (0.3 - 4.3)		
Median severity score, scale 0-10 (IQ1-IQ3)[c]	7 (5 - 7)		
Frequency of migraine attacks, n			
≥ once a month	17		
≥ once a week	7		

n, number; SD, standard deviation; y, years; ACE, angiotensin converting enzyme; AT2, angiotensin 2; IQ, inter-quartile.

[a]Data were available in 81 patients (of whom 21 suffered from migraine before PFO closure); [b]data were available in 22 patients; [c]data were available in 23 patients.

Complications and stroke recurrence

In all patients the percutaneous PFO closure was performed without major complications. In two patients minor complications occurred. One patient developed an inguinal haematoma, which required no surgical intervention. In the other patient the closure device did not unfold. During percutaneous removal of this device, it was lost in the inguinal subcutis, making minimal invasive surgery necessary. At a later stage another type of device could be placed successfully in this patient.

Two male patients developed a recurrent ischaemic event during follow-up. A 62-year-old patient developed a TIA three months after closure. The second patient, a 54-year-old patient, suffered from a stroke six months after PFO closure.

Discussion

Recently, we and others reported a prevalence of migraine of about 40% among patients with a symptomatic PFO.[4, 8] A reduction in the prevalence of migraine (ranging from 29-62%), particularly migraine with aura (ranging from 44-74%), has been described after percutaneous PFO closure.[8-13] These, mainly retrospective data, might suggest a causal relationship between the presence of a PFO and migraine.

In the present study we found a prevalence of migraine of 27% in patients who were referred for closure of a symptomatic PFO. This prevalence is higher than the prevalence of 10-12% reported for the general population.[5-7] After percutaneous PFO closure the overall prevalence of migraine decreased significantly to 11%. The reduction in the prevalence of migraine after closure appeared to be most pronounced in patients suffering from MA+, with a decrease from almost 12 to 2%, a relative reduction of 80%. Our prospective data are consistent with the findings of the previous retrospective studies.[8, 9, 11-13]

Pathophysiological mechanisms

To explain this relationship between RLS and migraine several pathophysiological hypotheses have been proposed. First, it is suggested that a particular genetic substrate might determine both atrial septum abnormalities and migraine.[18] Wilmshurst et al. found that the occurrence of atrial shunts was consistent with autosomal dominant inheritance in 20 probands with 71 relatives and that this was linked to the inheritance of migraine with aura in some families.[18] However, the suggestion of a genetic link between atrial shunts and migraine seems in contradiction with improvement of migraine after percutaneous PFO closure.

Second, it is hypothesized that in migraine, which is a form of neurovascular headache, trigger substances in the venous circulation could pass through the PFO. Normally,

these trigger substances are filtered in the lungs. In case of a PFO the RLS may permit these trigger substances to bypass the lung filter. In this condition, lower doses of trigger substances might be needed to induce migraine attacks. Micro-emboli or vaso-active chemicals such as serotonin are proposed as potential trigger substances.[4] These emboli may also explain the slightly increased risk of ischaemic stroke or transient ischaemic attack in patients suffering from MA+.[19] This increased risk might be explained by the elevated levels of platelet activation and platelet/leucocyte interaction in patients with migraine. The same interactions have been reported in the pathophysiology of ischaemic stroke.[20] The fact that the prevalence of PFO in patients with cryptogenic stroke is comparable with that among patients with migraine also supports this hypothesis.[21] How the aura in migraine is initiated is not well understood. Micro-thrombi might play an important role to initiate this cascade. In support of the hypothesis are the observations that aura is accompanied by mild hypoperfusion of the occipital cortex and that emboli seem to have a predilection to obstruct perfusion in this brain area.[22] Additionally, it has been shown that the incidence of subclinical brain infarction diagnosed with MR imaging is higher in patients with MA+ when compared to control subjects.[23] Moreover, the effect of shunt closure seems to be most pronounced in patients suffering MA+, which may support this finding. Finally, in support of the micro-thrombi hypothesis is the finding that treatment with high-dose aspirin or coumadin might prevent migraine attacks.[24, 25]

Prophylactic migraine medication

Recently, Wilmshurst et al. reported that the combination of clopidogrel for four weeks and aspirin for six months has been shown to be superior to aspirin alone for preventing migraine with aura in the first month after transcatheter closure of an atrial shunt.[26] However this study was performed in patients with either an atrial septal defect (ASD) or PFO. Additionally, Mortelmans et al. noticed no change in the prevalence of migraine before and after ASD closure in patients in whom the same drugs were used.[16] Nevertheless, whether clopidogrel results in a persistent reduction of migraine symptoms remains to be determined. Moreover, it has been reported that patients with migraine and PFO treated medically showed a non-significant

worsening of the overall migraine score compared to PFO closure after one year of follow-up.[14] In our study, almost all patients were treated with clopidogrel and low-dose aspirin after PFO closure, which might influence the occurrence of migraine. However, most patients received antiplatelet therapy before closure, because of a history of cryptogenic stroke. Moreover the effect of low-dose aspirin on migraine seems to be modest and comparable with placebo responder rates.[27] In addition, the clopidogrel was taken only for four weeks and we observed a significant decrease in the prevalence of migraine six months after closure. Therefore, the influence of clopidogrel or low-dose aspirin on the decrease in prevalence of migraine seems to be modest and can not explain the persistent and highly significant decrease in the prevalence of migraine after PFO closure.

Symptomatic vs. asymptomatic RLS

Recently, the results of the MIST (Migraine Intervention with Starflex Technology) trial were published. This is the first prospectively randomized, double-blind controlled study of the effect of percutaneous PFO closure on the prevalence of migraine. One hundred and fourty-seven English patients with severe therapy-resistant migraine with aura and a PFO were randomized to percutaneous closure or a so-called sham procedure. In this study, no significant reduction in the prevalence of migraine after PFO closure was found, although a significant reduction in headache days was seen in these patients with severe, therapy-resistant migraine.[28] Obviously, these results seem to be conflicting with the results of our study, in which a significant reduction of migraine is found after percutaneous PFO closure. An explanation might be the difference in study population. All patients included in our study suffered a symptomatic RLS; almost all (94%) had a history of a paradoxical embolic event due to the PFO. This might support the hypothesis of micro-thrombi bypassing the lung filter inducing a migraine attack. All patients in the MIST trial had an "asymptomatic" RLS; patients with paradoxical embolic events were excluded from this study.

Study limitations

An important limitation of our study might be selection bias. The patient population in our study was a selected cohort referred to our centres for PFO closure of a symptomatic RLS, mainly due to a paradoxical embolic event. We did not study a population without a previous neurologic event, like the MIST trial. Additionally, we should take into account the natural history of migraine in stroke patients, as described by Lapergue.[29] This study indicated that the frequency of migraine attacks following stroke starts to decrease before PFO closure. However, this study was performed in a small patient population and might include recall bias. Another limitation might be the male predominance in our study group in comparison with most studies of headache with female predominance. This might have affected the reported outcome. Finally, this study was limited because it is not a placebo-controlled design. The placebo effect in migraine therapy should be considered, but the reported changes in the prevalence of MA+ in our study (80%) seem to be larger than the reported placebo effect rates (20-40%).[30] However, one should take into account that placement of an intracardiac device may have a more profound placebo effect than medical therapies.

Conclusions

In this prospective observational study a high prevalence of migraine was found in patients with a symptomatic PFO, which significantly decreased six months after PFO closure.

Whether percutaneous PFO closure should be a new treatment in migraine remains to be determined. Prospective randomized trials need to be performed to answer this question.

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Chapter 10

Is a predominant left-to-right shunt associated with migraine? A prospective atrial septal defect closure study

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Catheterization and Cardiovascular Interventions 2009; 74: 1078-1084

Abstract

Background: A right-to-left shunt, as seen in patients with a patent foramen ovale, seems to be associated with migraine. An atrial septal defect (ASD), however, is characterized by a predominant left-to-right shunt (LRS). We prospectively evaluated the effect of percutaneous ASD closure on migraine.

Methods: All 70 consecutive patients (>16 years) who underwent a percutaneous ASD closure between November 2003 and December 2005 in one of the two participating centres were included in the study. Based on a standardized headache questionnaire, two independent neurologists diagnosed migraine with or without aura (MA+ and MA-, respectively) according to the International Headache Society criteria, before, six and twelve months after closure.

Results: Sixty-eight patients (97%; mean age 47.3±16.4 years; 22% men) agreed to participate in the study and completed the questionnaire. Before ASD closure, the overall prevalence of migraine was 34%, MA+ 22% and MA-12%.
At six months follow-up the headache questionnaire was completed by 63 patients (93%) and the prevalence of overall migraine decreased to 19%, MA+ to 8% and MA- to 11% (McNemar test, P=0.08, P=0.07 and P=1.0, respectively). At 12 months, the prevalence of migraine decreased further to 12%, MA+ to 5% and MA- to 7% (McNemar test, P=0.003, P=0.04 and P=0.29 versus at inclusion, respectively) based on a completed headache questionnaire of 57 patients (84%).

Conclusion: We found a high prevalence of migraine in patients with an ASD, and observed prospectively a reduction in the occurrence of migraine, especially migraine with aura, one year after percutaneous closure.

Introduction

The prevalence of migraine in the overall population is 10-12%, 6% in men and 15-18% in women.[1] In patients with migraine with aura, the prevalence of a right-to-left shunt (RLS) is almost two times higher compared to the general population.[2-4] Moreover, in patients with a cardiac or pulmonary RLS, the prevalence of migraine with aura seems to be higher when compared to those without a shunt.[5-10] Most cardiac RLS are related to a patent foramen ovale (PFO) which is present in one fourth of the population[11], whereas pulmonary RLS occur in patients with pulmonary arterio-venous malformations. Percutaneous closure of a PFO or a pulmonary arterio-venous malformation seems to be associated with a decrease in the occurrence of migraine.[5, 6, 12, 13] Therefore, a causal relationship between migraine and a RLS has been suggested, particularly in patients with migraine with aura.[3, 8]

Whereas a PFO is a persistent tunnel between the septum primum and septum secundum, an atrial septal defect (ASD) is a congenital heart defect in which a part of the inter-atrial septum is missing. An ASD is characterized by bidirectional shunting with a predominant left-to-right shunt (LRS), however, RLS may occur during a Valsalva maneuver or exercise. Recently, a relatively high prevalence of migraine, up to 30%, was found in patients with an unclosed secundum type ASD.[14] In this study, percutaneous ASD closure was initially not related to a decrease in prevalence of migraine.[14] However, the authors reported a significant decrease in migraine at later follow-up.[15] Because this study was limited to its retrospective design, we were interested to determine prospectively the effect of percutaneous ASD closure on the prevalence of migraine.

Methods

Patient selection

All patients (>16 years of age) scheduled for a percutaneous ASD closure at the University Hospital Gasthuisberg, Leuven, Belgium and at the St. Antonius Hospital, Nieuwegein, the Netherlands between November 2003 and December 2005, were

eligible to be included in the study. Patients with Down's syndrome or those who were not able to complete the Dutch questionnaire or to understand the written informed consent were excluded. The study protocol was approved by the ethics committees of the participating centres.

Patients' characteristics and the percutaneous ASD closure technique

Pre-, peri-, and postprocedural data (demographic, echocardiographic, and procedural parameters) were collected.

The percutaneous closing technique has already been extensively described in the literature.[16] Briefly, in both centres, the procedure was done under general anaesthesia under continuous transesophageal echocardiographic monitoring. In all patients balloon sizing was performed, and both Amplatzer® ASD occluders (AGA Medical Corporation, Golden Valley, MN, USA) and Cardioseal/Starflex® (NMT Medical, Inc., USA) devices were used for closure. The type of device was chosen by the interventional cardiologist depending on the anatomy and diameter of the defect. All patients received an intravenous prophylactic dose of antibiotics one hour before and six hours after percutaneous closure.

Within 24 hours after closure, a chest X-ray and a transthoracic echocardiogram (TTE) were performed. All patients were discharged on antiplatelet therapy: low-dose aspirin for six months and clopidogrel for at least four weeks. Prophylaxis against bacterial endocarditis was advised for a minimum of six months counting from the closing procedure. Late follow-up data were obtained by a phone call to the patients.

Evaluation of migraine

As described previously[16], a structured questionnaire was composed in such a way that a neurologist could diagnose migraine with or without aura (MA+ or MA-, respectively), according to the criteria of the International Headache Society.[17]

To diagnose migraine before closure, a headache questionnaire was given to all patients immediately before the closing procedure. To diagnose migraine at six and twelve months after ASD closure, the same questionnaire was sent to all patients included in the study; a prepaid envelope was enclosed. If patients did not return the

questionnaire within four weeks, they were phoned in order to obtain the headache questionnaire. Two neurologists, blinded to the patients' files and to the time period, diagnosed MA+ or MA-. The questionnaire also included the possibility to evaluate frequency, severity, and duration of migraine attacks. The frequency of headache attacks was reported by the patients in a score from 0 to 6, ranging from no headache to daily episodes. The severity of headache attacks was scored on a scale ranging from 0 (no pain) to 10 (very severe pain).

Statistical analysis

Descriptive statistics were used to describe the patients' characteristics. Continuous variables with normal distribution are presented as mean ± standard deviation. Median, first, and third quartiles (IQ1 and IQ3) or range (minimum - maximum) were used when no normal distribution was present. Proportions are presented as numbers and percentages. McNemar paired Chi-square test was performed to evaluate changes in prevalence of migraine before and after closure. Wilcoxon signed ranks test was done to compare related non-parametric variables. Inter-observer reliability was evaluated by the Kappa coefficient. All tests were two sided and $P<0.05$ was considered to be statistically significant. The statistical software package used for this analysis was SPSS for Windows version 12.0.

Results

Patients' and echocardiographic characteristics

Seventy patients were eligible for inclusion in the study, but in two the headache questionnaire could not be obtained. Finally, 68 patients (97%) were included (22.1% men, mean age 47.3±16.4 years). In only 7.4% of the patients the ASD was asymptomatic and the diagnosis was made by chance. In most patients the ASD was diagnosed because of dyspnoea and/or atrial arrhythmias (mostly atrial fibrillation). Up to 10% presented with a cryptogenic transient ischemic attack or stroke. These data are summarized in Table I.

The mean ASD diameter on echocardiography was 18.8±9.9 mm. In all patients the shunt was predominantly from left to right. Before ASD closure, right ventricular systolic pressure calculated from tricuspid valve regurgitation on Doppler was 31±10 mmHg. These data are also summarized in Table I.

Peri-procedural characteristics

In most patients (n = 62) the Amplatzer® ASD occluder (AGA Medical Corporation, Golden Valley, MN, USA) was used. Device characteristics are listed in Table I.

No severe complications occurred during and after the closing procedure. Residual shunting (including very small shunts), as diagnosed by a transthoracic echocardiogram (TTE) with contrast (agitated saline) within 24 hours after ASD closure was present in 22% of the patients. Residual shunting diagnosed with a contrast echocardiography at six months follow-up was reduced to 3.7%. All residual shunts were bidirectional, but predominantly left-to-right.

Prevalence of migraine before and after ASD closure

Before ASD closure 23/68 patients (33.8%) suffered from migraine, of which 15 patients (22.1%) suffered from MA+ and eight patients (11.8%) from MA-.

At six months follow-up 63/68 patients (92.6%) completed and returned the headache questionnaire. Three of the five patients who did not return the questionnaire suffered from migraine with aura at inclusion. The overall occurrence of migraine decreased from 33.8% before ASD closure to 19.0% six months after the closing procedure (McNemar test, P=0.08). The occurrence of MA+ and MA- decreased to 7.9% and to 11.1%, respectively (McNemar test, P=0.07 and P=1.0, respectively). In 12 patients who suffered from migraine before closure (seven patients with MA+ and five patients with MA-), migraine disappeared. In two patients MA+ changed into MA-. However, four patients who had no migraine before, developed migraine after the closing procedure: A 51-year-old man, who had a 16 mm Amplatzer® device implanted and a 55-year-old woman with a 34 mm Amplatzer® device developed MA+. A 54-year-old woman with a 28 mm Cardioseal/Starflex® device and a 48-year-old woman with a 24 mm Amplatzer® device developed MA-.

Table I. Patients' characteristics, reason of ASD detection, ASD characteristics and closure device characteristics.

	Number	Percentage (%)
Patients' characteristics		
Total	68	-
Men	15	22.1
Female	53	77.9
Mean age ± SD, (range) (y)	47.3 ± 16.4, (17-79)	
Reason of ASD detection		
Asymptomatic	5	7.4
Dyspnoea	38	55.9
Palpitations/atrial fibrillation	16	23.5
Syncope	1	1.5
Stroke/TIA	7	10.3
Peripheral embolism	1	1.5
ASD/echocardiographic characteristics		
Mean ASD diameter ± SD (mm)	18.8 ± 9.9	
Mean RVSP ± SD (mmHg)	31 ± 10	
Closure devices		
Amplatzer ASD occluder®	62	91.2
Median diameter (range) (mm)	24 (15-38)	
Cardioseal / Starflex®	6	8.8
Median diameter (range) (mm)	28 (28-33)	

SD, standard deviation; y, years; ASD, atrial septal defect; TIA, transient ischemic attack; mm, millimeters; RVSP: right ventricular systolic pressure.

At twelve months follow-up, 57/68 patients (83.8%) completed the headache questionnaire. Five of 11 patients who did not return the questionnaire suffered from MA+ before ASD closure. The overall prevalence of migraine at 12 months follow-up decreased to 12.3% (McNemar test, P=0.003). The prevalence of MA+ and MA- decreased to 5.3% and 7.0%, respectively (McNemar test, P=0.04 and P=0.29, respectively). In five patients who suffered from migraine (one MA+ and four MA-) at six months follow-up, migraine disappeared at twelve months. In a 55-year-old woman with a 34 mm Amplatzer® MA+ (before closure and at six months) changed into MA-. A 21-year-old woman with a 18 mm Amplatzer® device, who suffered from MA+ before closure and had no migraine at six months follow-up, developed MA- at

12 months follow-up. In a 20-year-old female with a 28 mm Amplatzer® device, who suffered from MA+ before closure, the aura disappeared at six months but returned after 12 months. Changes in migraine occurrence at six and twelve months follow-up are shown in Tables II and III and in Figure 1.

The inter-observer reliability to diagnose migraine was high (Kappa coefficient = 0.86, P<0.001).

Table II. Occurrence of migraine before and six months after ASD closure

N=63	6 months after ASD closure		
Before ASD closure	**no migraine (n=51)**	**MA+ (n=5)**	**MA- (n=7)**
No migraine (n=43)	39	2	2
MA+ (n=12)	7	3	2
MA- (n=8)	5	0	3

Values are numbers of patients

MA+, migraine with aura; MA-, migraine without aura.

Table III. Occurrence of migraine before and twelve months after ASD closure

N=57	12 months after ASD closure		
Before ASD closure	**no migraine (n=50)**	**MA+ (n=3)**	**MA- (n=4)**
No migraine (n=39)	38	1	0
MA+ (n=10)	6	2	2
MA- (n=8)	6	0	2

Values are numbers of patients

MA+, migraine with aura; MA-, migraine without aura.

Changes in migraine characteristics

In the overall group of patients who suffered from migraine before and respectively six (n=8) and 12 (n=6) months after ASD closure there were no significant changes in migraine characteristics (Tables IV and V).

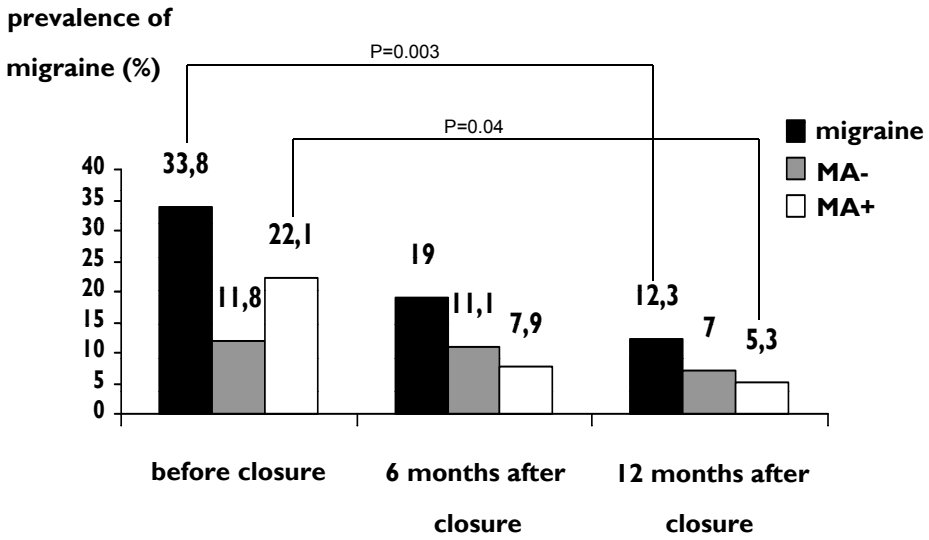

Figure 1. Prevalence of overall migraine, migraine without aura (MA-) and migraine with aura (MA+) before (left columns), six months after (middle columns) and twelve months after (right columns) ASD closure.

Residual shunting and migraine

There were two patients with residual shunting on echocardiography at six months follow-up. The first patient suffered from MA+ before ASD closure, which disappeared at six months follow-up. The second suffered from MA- before ASD closure which disappeared at twelve months follow-up. Hence, the presence of residual shunting appeared to be no predictor for persisting or new-onset migraine.

Table IV. Changes in migraine characteristics (frequency, severity and duration of headache attacks) in patients suffering from migraine before and six months after ASD closure (n = 8)

	before ASD closure	6 months after ASD closure	P
frequency median (IQ1-3) (scale 0-6)	2 (2-4)	3 (2-4)	0.74
severity median (IQ1-3) (scale 0-10)	6 (5.3-8)	6 (5-7.5)	0.25
duration median (IQ1-3) (hours)	24 (0.5-60)	24 (0.5-24)	1.0

IQ, interquartile

Table V. Changes in migraine characteristics (frequency, severity and duration of headache attacks) in patients suffering from migraine before and twelve months after ASD closure (n = 6)

	before ASD closure	12 months after ASD closure	P
frequency median (IQ1-3) (scale 0-6)	4 (2-5)	2.5 (1-4)	0.36
severity median (IQ1-3) (scale 0-10)	8 (6-9.3)	7 (6.5-8.3)	0.10
duration median (IQ1-3) (hours)	60 (12.3-60)	19.5 (4.9-51)	0.29

IQ, interquartile

Discussion

We found a relatively high prevalence of migraine in patients who were referred for percutaneous ASD closure. Additionally, a significant decrease in the prevalence of migraine, and particularly MA+, occurred at one year after percutaneous ASD closure.

ASD and migraine

The presence of a RLS is associated with an increased prevalence of migraine, as described earlier.[5-10] The transition of vasoactive substances or microemboli from the venous circulation into the systemic circulation seems to be the most assumed link between the presence of a RLS and migraine.[9] This hypothesis is enforced by the observation that percutaneous closure of a PFO is associated with a significant decrease in the prevalence of migraine attacks.[18] On the contrary, the MIST trial, the only prospectively randomized, double-blind controlled study of the effect of percutaneous PFO closure on the prevalence of migraine failed to confirm benefit on migraine from PFO closure.[19] In this trial, no significant reduction in the prevalence of migraine after PFO closure was found, although a significant reduction in headache days was seen in patients with severe, therapy-resistant migraine.[19] These results seem to be conflicting with the results of most other studies. An explanation for this might be the difference in study population of this trial compared with other studies. Additionally, the study was limited by inclusion of a high frequency of patients found not to have PFO during invasive evaluation, the occurrence of several adverse events and an unclear number of residual shunts after PFO closure. Additionally, the analysis phase was quite soon after implantation of the closure device.

However, whereas a PFO is considered as a variant of a normal inter-atrial septum, an ASD is defined as a real congenital heart defect. Moreover, in contrast with a PFO, an ASD is mainly characterized by a left-to-right shunt. The latter is frequently seen on transthoracic or transesophageal echocardiography with colour Doppler. However, during a Valsalva maneuver or exercise in an ASD, a right-to-left shunt can be detected with contrast echocardiography.[20] Therefore, the idea rose that also an ASD could be associated with an increased prevalence of migraine. Azarbal et al. found a migraine prevalence of 30% and MA+ prevalence of 17% in 23 ASD patients referred for transcatheter closure.[21] Mortelmans et al. reported a similar migraine prevalence of 30% and a MA+ prevalence of 11% in 75 patients before interventional ASD closure.[14]

In this study, we found a prevalence of up to 34% of migraine in ASD patients scheduled for closure. This observation is consistent with the hypothesis that RLS is associated with migraine. However, we have to take into account that our study population constituted a female predominance and a mean age of 47 years. The prevalence of migraine is higher among women and peaks in the fourth decade of life to 27%, thereafter decreasing with increasing age.[1]

ASD closure and migraine

As for PFO closure, it was interesting to investigate the effect of percutaneous ASD closure on the prevalence of migraine attacks. Two retrospective studies described the effect of percutaneous ASD closure. Azarbal et al. showed a substantial decrease in migraine from 30% before to 17% three months after closure. The decrease was even more pronounced for MA+: from 17% before to 4% after. However, the study was underpowered (n=23) to determine significant results.[21] Remarkably, Mortelmans et al. found no effect on the prevalence of migraine in 75 patients six months after percutaneous ASD closure; in contrast, several patients developed migraine initially after closure.[14] In support, recently, Rodés-Cabau et al. studied 185 migraine-free ASD and PFO patients scheduled for percutaneous closure. They reported that transcatheter ASD closure was associated with new-onset migraine with an incidence of 12% when compared with 0% after PFO closure. The first migraine episode occurred mostly within two weeks after the closing procedure and persisted in 2/3 of the cases

for more than two years.[22] These results suggest that ASD device implantation can act as a permanent trigger for migraine. However, the pathophysiologic basis of this observation remains unclear. Several hypotheses were formulated as microthrombus formation on the left-sided disk, transient nickel release, transient inflammation, platelet activation on the surface of the device with subsequent serotonin release, and others. However, most of these proposed mechanisms can be contradicted. Voet et al. recently reported no significant decrease in migraine prevalence in 71 patients who underwent ASD closure after 52 months follow-up. However, a significant reduction was noted in patients with new-onset migraine early after closure (n=7), where migraine disappeared in six patients (P=0.031). In the group with persistent migraine early after closure (n=13), another six patients became migraine-free (P=0.031).[15]
We currently found a significant reduction of 64% and 76% in the occurrence of migraine and MA+, respectively, at twelve months after ASD closure. These findings might support again the hypothesis that after ASD closure venous trigger substances can no longer bypass the lung filter, which might prevent migraine attacks. However, we could not show a significant decrease of migraine prevalence at six months after ASD closure. An explanation could be that, in support of the previously mentioned studies, new-onset migraine was higher at six months follow-up than twelve months follow-up. Residual shunting was minimal at six months (3.7%) and, therefore, could not explain the absence of beneficial effect.

Micro-thrombi and migraine

As mentioned earlier, only an association between MA+ and the presence of a shunt was found. In contrast to MA-, MA+ is initiated by cortical spreading depressions[23], a phenomenon of neuronal activation followed by suppression.[24] Coupled with these depressions are cerebral blood flow changes.[25] Micro-thrombi might play an important role to initiate this cascade. In support of the hypothesis are the observations that aura is accompanied by mild hypoperfusion of the occipital cortex and that emboli seem to have a predilection to obstruct perfusion in this brain area.[26] These emboli may also explain the slightly increased risk of ischemic stroke or transient ischemic attack in patients suffering from MA+.[27] The fact that the prevalence of PFO (with right-to-left shunting) in patients with cryptogenic stroke is comparable with that

among patients with migraine also supports this hypothesis.[28] Additionally, it has been shown that the incidence of subclinical brain infarction diagnosed with MR imaging is higher in patients with MA+ when compared with controls.[29] Finally, in support of the micro-thrombi hypothesis is the finding that treatment with high-dose aspirin or coumarin might prevent migraine attacks.[30, 31]

Congenital heart disease and migraine

Some authors hypothesized that a particular genetic substrate might determine both atrial septum abnormalities and migraine.[32, 33] Recently, several reports have been published that describe an increased prevalence of migraine in patients with a random congenital heart defect. Hermans et al. found an increased prevalence of MA+ in 80 patients with congenital heart disease with and without RLS compared with controls (respectively, 40% and 32.5% vs. 5%).[34] Additionally, Truong et al. found a three to four times higher prevalence of migraine in 395 adults with congenital heart disease compared with a sex-matched control population. They described an increasing prevalence of migraine in patients with no shunt (38%), a left-to-right shunt (44%), and a right-to-left shunt (52%).[35] Similarly, Hirth et al. found an increased prevalence of MA+ in both 29 cyanotic and 38 acyanotic patients with congenital heart disease of 59% and 42%, respectively.[36] However, they found a high prevalence of PFO in those with acyanotic congenital heart disease, which might explain the high prevalence of MA+ in this group. Finally, an increased prevalence of migraine has been described in patients with Marfan Syndrome.[37] All these reports suggest a genetic link between migraine and congenital heart defects and could be an alternative explanation for the relatively high prevalence of migraine in the ASD patients.

Limitations

First, although this was a two-centre study, the number of patients is low. This limited sufficiently powered statistical subanalyses. Second, a selection bias might be present. Only patients referred for percutaneous secundum type ASD closure were included in the study. Third, 16% of all patients were lost to follow-up, which could have influenced our long-term results. Fourth, almost all patients in this study were treated with clopidogrel and low-dose aspirin after ASD closure, which might influence

the occurrence of migraine. However, the effect of low-dose aspirin on migraine seems to be modest and comparable with placebo responder rates.[38, 39] In addition, clopidogrel was taken only for four weeks and aspirin for six months. We observed a significant decrease in the prevalence of migraine more than 12 months after ASD closure. Therefore, the influence of clopidogrel or low-dose aspirin on the decrease in prevalence of migraine seems to be modest and cannot explain the persistent and significant decrease in the prevalence of migraine after ASD closure. The most important limitation of this study was the absence of a placebo group. The placebo effect in migraine therapy should always be considered, but the reported changes in the prevalence of migraine in our study seem to be larger than the accepted placebo effect rates (20-40%).[40]

Conclusion

In conclusion, the prevalence of migraine in ASD patients is high, up to 35%. We report a reduction in the occurrence of migraine, especially migraine with aura, after percutaneous ASD closure. However, randomized controlled trials are still needed to draw substantial conclusions.

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Part four

General discussion

Chapter 11

General discussion

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Patent foramen ovale management

Patent foramen ovale and cryptogenic stroke: Risk of stroke recurrence and effect of medical (anti-thrombotic) therapy

High annual rates of recurrent stroke and death among medically treated cryptogenic stroke patients with PFO are reported, ranging from 1.5% to 12%, depending on the characteristics of the population studied.[1-6] The annual recurrent stroke and death rates among stroke and cryptogenic stroke patients with and without PFO are summarized in Table I. In the Lausanne study by Bogousslavsky et al., 41% of 340 patients with stroke or TIA were found to have a PFO.[1] Using conventional therapies, mostly aspirin or anticoagulation, the annual recurrence for stroke was 1.9% and the rate of stroke and death was 2.4%.[1] However, this study did not include comparison with a control group of patients who did not have an atrial septal abnormality. Therefore it is not suitable to answer the question whether the presence of a PFO increases the risk of recurrent stroke. Cujec et al. retrospectively analyzed a cohort of 90 cryptogenic stroke and TIA patients younger than 60 years of age. Those with PFO had a significantly higher annual rate of recurrent cerebral ischemic events than those without PFO: 12% versus 5%.[2] This finding was not reproduced in the prospective La Sapienza study by de Castro et al., who found no difference between the average risk of stroke or death in 160 cryptogenic stroke patients with or without PFO.[3] However, this study was limited because outcome determination was not blinded to the presence or absence of an atrial septal abnormality. In the prospective PICCS trial by Homma et al., 250 cryptogenic stroke patients with a mean age of 59 years, 39% of whom had a PFO, were treated with aspirin or warfarin.[4] Annual recurrent stroke and death rates were high. But there was no significant difference between patients with versus without PFO (annual event rates were 7.2% and 6.4% respectively). Mas et al. prospectively studied 581 cryptogenic stroke patients with a mean age of 43 years, 37% of whom had a PFO.[5] All patients were treated with aspirin. Annual stroke and death rates for patients with and without PFO were comparable, 1.5% and 1.8% respectively. However, the risk of stroke recurrence (not death) increased significantly in patients with both PFO and ASA.[5] This increased risk associated with PFO and ASA

was not found among patients with any stroke subtype in the PICCS trial.[4] However, in the latter study these data were not available for the cryptogenic stroke cohort alone. Regarding the efficacy of either warfarin or aspirin in preventing recurrent events, the Lausanne study reported that the type of treatment did not significantly affect the risk of stroke recurrence.[1] However, very few events occurred in this cohort. In the PICSS, no difference in the average annual rate of subsequent stroke or death was found between patients with PFO treated with warfarin versus aspirin.[4] However, the PICCS was underpowered to determine treatment effect. In contrast, Cujec et al. found in their retrospective study that warfarin was more effective than antiplatelet therapy for secondary stroke prevention.[2]

To summarize, among patients who have had a cryptogenic stroke and are treated medically, the risk of recurrent stroke or death is high. The presence of a PFO alone does not seem to portend a meaningfully increased risk. However, the presence of PFO and ASA together might indicate an increased risk of subsequent stroke.

Efficacy of percutaneous patent foramen ovale closure

Percutaneous PFO closure with an umbrella device is suggested to be an alternative or an additive to medical therapy for secondary prevention of (cryptogenic) stroke. Windecker et al. showed that in cryptogenic stroke patients with PFO, percutaneous PFO closure was at least as effective as medical treatment with antiplatelets or anticoagulants for preventing recurrent cerebrovascular events and even more effective in patients with complete PFO closure and a history of multiple cerebrovascular events.[7] Additionally, in a meta-analysis, Khairy et al. found that the one-year rate of recurrent neurological thrombo-embolism was 0-4.9% with transcatheter intervention as opposed to 3.8-12.0% with traditional medical treatment.[8] However, this review was limited because the treatment in the "medical" arm was not uniform and because this arm contained older patients, a male predominance, and a higher prevalence of diabetes and smoking compared to the "intervention" arm.

Table 1. Annual recurrent stroke and stroke/death rates in patients with (cryptogenic) stroke or TIA with and without PFO (and/or ASA)

Author	Year	Patients	FU (months)	Age (y)	IAS	N	Annual recurrent stroke/ death rate (%)	Annual recurrent stroke rate (%)
Bogousslavsky[1]	1996	All cause stroke or TIA	36	44	PFO	140	2.4	1.9
Cujec[2]	1999	Cryptogenic stroke or TIA	46	38	PFO	52		12[a]
				46	No PFO	38		5[a]
De Castro[3]	2000	Cryptogenic stroke	31	53	PFO	74	3.7	
				47	No PFO	86	4.5	
Mas[5]	2001	Cryptogenic stroke	38	40	PFO	216	1.5	
				40	ASA	10	0	
				40	PFO and ASA	51	3.8	3.8
				45	No PFO	304	1.8	1.1
Homma[4]	2002	All cause stroke	24	58	PFO	203	7.4	
				-	ASA	69	8.0	
				60	No PFO	398	7.7	
Homma[4]	2002	Cryptogenic stroke	24	-	PFO	98	7.2	
				-	No PFO	152	6.4	

FU, follow-up; y, years; IAS, inter-atrial septum; N, number; TIA, transient ischemic attack; PFO, patent foramen ovale; ASA, atrial septal aneurysm;
[a]Recurrent ischemic cerebral event rate (including TIA).
Patients were treated with [1]aspirin, warfarin or PFO closure, [2]aspirin, warfarin, neither or PFO closure, [3]aspirin, warfarin, both or neither, [4]aspirin or warfarin, [5]aspirin.

Differences in outcome and efficacy of transcatheter PFO closure have been reported.[9-30] Table II summarizes the results of several studies on transcatheter PFO closure.[9-30] In these studies annual recurrence rates of thrombo-embolic events of 0-5.3% have been reported after percutaneous PFO closure, which correlates to the review article by Khairy et al.[8] Recurrence rates were dependent on follow-up time, the definition and means of assessment of the clinical endpoints, and the types of devices used.[9-30] Residual shunting after PFO closure has been reported in 0-47%.[9-30] The high variability is probably due to differences in imaging techniques for detecting residual shunting with variable sensitivity, differences in the definition of residual shunting, differences in follow-up time and the use of different devices for PFO closure.

We found a 2.5% yearly recurrence rate of thrombo-embolic events (including stroke and TIA) during a mean follow-up of almost 2 years in 83 patients, who underwent percutaneous PFO closure in the St. Antonius Hospital, Nieuwegein, the Netherlands using the Amplatzer® and the Cardioseal/Starflex® device, with no differences between these devices.[16] Residual shunting was 6% six months after PFO closure. These results are comparable with previous reports. Additionally, we reported the largest series of PFO closures with the fourth generation Intrasept™ device from Cardia, Eagan, MN.[15] In our multicentre study, we found a 3.0% recurrence rate of thrombo-embolic events (including stroke and TIA) for a median follow-up time of almost one year with this device.[15] Residual shunting by the six months follow-up was 13%.

All these reports suggest that the percutaneous PFO closure is an effective procedure for preventing the recurrence of paradoxical thrombo-embolic events in cryptogenic stroke patients with PFO. It is suggested that transcatheter PFO closure is as effective or even better than medical therapy for this patient population.[7, 8] However, randomized clinical trials comparing medical treatment with transcatheter closure are still lacking. Until such studies are completed, both the AHA/ASA[6] and American College of Chest Physicians (ACCP) guidelines[31] recommend antiplatelet therapy for patients with ischemic stroke or TIA in the presence of a PFO (AHA/ASA, class IIA, level of evidence B; ACCP, grade 1A), unless indications exist for oral anticoagulants (AHA/ASA, class IIA, level of evidence C; ACCP, grade 1C). The AHA/ASA guidelines state that "insufficient data exist to make a recommendation about

PFO closure in patients with a first stroke and a PFO. PFO closure may be considered for patients with recurrent cryptogenic stroke despite optimal medical therapy (class IIB, level of evidence C)."[6] Currently, several prospective randomized trials (RESPECT, CLOSURE-1, Gore-REDUCE, PC-trial, CLOSE) comparing medical treatment with transcatheter PFO closure are underway and will hopefully delineate the correct indication for percutaneous PFO closure in the near future.

Efficacy of percutaneous patent foramen ovale closure in elderly

Most studies on transcatheter PFO closure focus on patients younger than 55 years of age with cryptogenic stroke. In 2007, however, Handke et al. reported an association between the presence of a PFO and cryptogenic stroke in older patients.[32] Little is known about the recurrence rate of thrombo-embolic events in older patients with cryptogenic stroke undergoing PFO closure. Kiblawi et al. found no significant differences in the rate of recurrent stroke or TIA in 184 patients older than 55 years of age (mean age 67 years) compared to 272 younger patients (mean age 41 years) after PFO closure with a Cardioseal Septal Occluder®.[33] Annual recurrence rates were 1.1% and 1.0% respectively during a mean follow-up of 17.8 months. Spies et al. compared the outcome of 423 patients older than 55 years of age (median age 63 years) and 632 younger patients (median age 42 years) undergoing PFO closure for paradoxical embolism using a variety of device types.[34] The annual incidence of recurrent thrombo-embolism was 1.8% for older patients after 20 months median follow-up time and 1.3% for younger patients after a median follow-up of 16 months. Thrombo-embolic event free survival was similar for both age groups.

In contrast, we found a significantly higher annual recurrent rate of stroke and TIA of 2.4% in 120 patients older than 55 years of age, who underwent PFO closure because of a cryptogenic thrombo-embolic event, compared to 0.6% in 215 patients younger than 55 years of age.[35] Additionally, age above 55 years was an independent predictor of recurrent stroke and TIA with an odds ratio of 3.8. The higher recurrent event rate we found in the older group might be explained by a reduced efficacy of PFO closure in this age group. We found that residual shunting, although not significantly, was slightly higher in the older group.[35] We and others reported that

residual shunting after PFO closure is a predictor for recurrent thrombo-embolic events.[30, 35, 36] Additionally, it could be that venous thrombogenesis is higher among older patients[37, 38] creating a higher chance of thrombo-embolism in the presence of residual shunting. Alternatively, the higher recurrent event rate in the older group might be due to underdiagnosed systemic atherosclerosis or to a higher incidence of asymptomatic and undetected atrial fibrillation (AF).[39] Moreover, there could be other confounding factors that cause a recurrent stroke or TIA, that were not covered in our study, especially in older patients. We compared the recurrence of events between younger and older patients after PFO closure. We did not compare them with a control group of patients treated with medication. The annual recurrence rate of stroke or TIA after medical treatment with aspirin or warfarin in elderly with a cryptogenic stroke and a documented PFO is 10%.[40] If we compare these results with the annual recurrence rate of stroke or TIA of 2.4% in our older age group, the results are actually quite beneficial. Hence, the transcatheter PFO closure might have beneficial effects in both younger and older patients with cryptogenic thrombo-embolism, but the higher recurrence rate in older patients might be attributable to other factors.

To summarize, our results suggest that elderly who have undergone transcatheter PFO closure because of a paradoxical embolic event have a worse outcome than younger patients. In the absence of a control group of patients treated with medication, it remains to be determined whether this is due to a reduced efficacy of PFO closure in the elderly or to this patient group carrying a higher risk of recurrent events independent of treatment. Our study confirms that we must carefully consider indications for PFO closure in patients older than 55 years. Unfortunately, being older than 60 years is a common exclusion criterion for most ongoing trials comparing medical treatment with anti-thrombotic agents and transcatheter PFO closure. Randomized trials including older patients with previous cryptogenic stroke are needed to develop treatment strategies in this patient group.

Safety of percutaneous patent foramen ovale closure

A systematic review by Khairy et al., in which peri-procedural complications of ten transcatheter PFO closure studies were divided into minor and major, showed a complication rate of 7.9 and 1.5%, respectively.[8] Complication rates of a number of transcatheter PFO closure studies, according to this classification, are summarized in Table II.[9-30] The classification scheme is described in Chapter 2 of this thesis. The total complication rate varies between 0-17.5%, whereas major complications were reported in 0-4.6%.[9-30] Differences between the reported complication rates can be explained by differences in the definition of complications, the fact that some only reported peri-procedural complications, the variation in follow-up period and the use of different closure devices.

We found a major complication rate of 1.2% and a total complication rate of 14.4% in 83 patients, who underwent percutaneous PFO closure in the St. Antonius Hospital, Nieuwegein, the Netherlands using the Amplatzer® and the Cardioseal/Starflex® device during a mean follow-up of almost two years, with no significant difference in complication rates between these devices.[16] These results are concordant with those previously reported. The relatively high total complication rate might be explained by the fact that we counted all episodes of paroxysmal AF as a complication (8.4%). With the Intrasept™ device, we found a major complication rate of 0.2% and a total complication rate of 14.1%, which mainly consisted of atrial fibrillation (6.2%).[15] Significantly, no arm fractures were found and the complication rate decreased substantially by the use of the Intrasept™ device when compared to older generation devices from the same manufacturer.[20] This is probably due to the technical improvement of the device.

To summarize, we and others consistently reported low complication rates after transcatheter PFO closure and thus the transcatheter PFO closure can be considered a safe procedure.

To further improve the safety of and overcome some "common" complications associated with percutaneous PFO closure, conventional closure devices are continuously improved. Additionally, other types of devices have been developed, for example the Biostar® device (NMT, Medical), which contains a totally biodegradable

matrix made of a porcine intestinal collagen layer, mounted on a nitinol framework.[41] It has been developed to avoid potential problems such as thrombosis, device fracture, erosion and inflammation which have been attributed to permanent synthetic implants[42-44] The Biostar® device was designed to induce a host connective tissue response and should lead to a more rapid and complete neo-endothelialisation. The collagen matrix is gradually resorbed over a period of about two years, leaving only the frame behind.[45, 46] We performed the first "head-to-head" comparison between the Biostar® device and the Cardioseal/Starflex® device, which is mounted on the same framework.[47] We found no significant differences between the devices regarding implantation success and complications. The efficacy of closure was comparable. The use of the bioabsorbable device, however, tended to be associated with a higher percentage of moderate shunting. Of course, we are still waiting for the long-term results of this new device.

Recently, other catheter techniques to close a PFO without a permanent implant have been developed. These include the application of radiofrequency energy[48], PFO closure by means of a suture[49] and the implantation of a flat, self-expanding stent that is designed to be positioned within the PFO tunnel.[50] The efficacy of these new techniques remains to be seen. However, all these developments will hopefully improve the outcome and safety of interventional PFO closure in the future.

Table II. Outcome, complications and efficacy of percutaneous PFO closure

Author	Year	Device type	N	Age (y)	FU (months)	Complications (%) Total	Major	Residual shunting Imaging	(%)	Annual recurrent TE (%)
Windecker[30]	2000	Multiple	80	52	19	10	3.8	TEE (6 m)	27	3.4
Wahl[27]	2001	Multiple	152	50	20	7.9	4.6	TEE (6 m)	21	5.3
Bruch[12]	2002	Multiple	66	48	20	0	0	TEE (12 m)	0	0
Martin[17]	2002	Multiple	110	47	28	7.3	4.5	TTE (12 m)	34	0.9
Schrader[19]	2003	Multiple	457	49	20	8.8	0.9	TEE (12 m)	6	1.8
Onorato[18]	2003	Multiple	256	48	19	9.8	0.8	TEE (12 m)	2	0.8
Schwerzmann[20]	2004	Total	100	50	24	9.0	1.0	TEE (6 m)	20	3.5
		STAR	50	50	26	16.0	2.0		34	-
		Amplatzer	50	50	23	2.0	0		6	-
Braun[11]	2004	Multiple	307	43	24	3.6	0.7	TEE (24 m)	4	0.8
Alameddine[9]	2004	Multiple	272	51	-	8.1	1.5	TEE/ICE (0 m)	21	1.8
Spies[22]	2006	Cardia	403	49	13	8.2	0.2	TEE (6 m)	11	2.0
Slavin[21]	2007	Total	131	52	30	7.6	1.5	TEE (2 m)	8	0
		Cardioseal	30	-	-	-	-		5	-
		Amplatzer	101	-	-	-	-		12	-
Spies[24]	2008	Intrasept	247	53	14	1.6	0.4	TEE (6 m)	13	2.3
Wahl[28]	2008	Multiple	825	51	-	5.9	0.4	TEE (6 m)	12	0.1
Balbi[10]	2008	Multiple	128	46	32	5.5	2.3	TCD (6 m)	18	0.6
Kutty[14]	2008	Cardioseal	216	50	25	-	2.3		-	3.4
Spies[23]	2008	Total	795	51	26	11.3	0.9	TEE (6-12 m)	8	1.4
		Cardia	405	49	36	13.6	1.0		9	1.1
		Intrasept	301	52	15	7.6	1.0		7	2.5
		Amplatzer	89	52	20	1.3	0		8	1.3
Taaffe[25]	2008	Total	660	49	1	6.9	0.3	TEE (1 m)	-	0.2
		Amplatzer	220	47	-	7.7	0.5		35	0
		Helex	220	51	-	7.7	0.5		47	0.5
		Cardioseal	220	50	-	5.5	0		38	0
Luermans[16]	2008	Total	83	49	23	14.4	1.2	TTE (6 m)	6	2.5
		Amplatzer	20	-	23	5.0	0		15	5.2
		Cardioseal	63	-	23	17.5	1.6		4	1.6
Luermans[15]	2008	Intrasept	430	51	10	14.1	0.2	TEE/TTE/TCD (6 m)	13	3.0
Von Bardeleben[26]	2009	Multiple	357	51	46	3.9	0.3	TEE (12 m)	5	0.7
Wahl[29]	2009	Amplatzer	620	51	36	0.6	0.6	TEE (6 m)	9	0.8
Cifarelli[13]	2009	Multiple	202	45	36	2.0	0.5	TTE/TCD (6 m)	4	1.5

N, number; y, years; FU, follow-up; TE, thrombo-embolism; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography; TCD, transcranial Doppler; ICE, intracardiac echocardiography; m, months.

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Patent foramen ovale closure and migraine

A relationship between the presence of a right-to-left shunt (RLS), as seen in patients with PFO, and migraine with aura (MA+) has been proposed.[51] Therefore, several researchers studied the effect of percutaneous PFO closure on the occurrence of migraine.[52-69] These reports are summarized in Table III.[52-69] In retrospective studies, in patients who underwent percutaneous PFO closure because of a paradoxical embolic event, the prevalence of migraine decreased from 22-57% before closure to 14-30% after closure.[53, 55, 57, 62, 63, 66, 69] The prevalence of MA+ decreased from 13-43% before closure to 5-24% after closure.[53, 55, 57, 62, 63, 66, 69] Of note, Schwerzmann et al. did not find a reduction in migraine prevalence, though they did observe a reduction in the frequency of migraine attacks after PFO closure.[66] However, these studies were limited by their retrospective character.[53, 55, 57, 62, 63, 66, 69] We conducted the largest prospective observational study and found an overall prevalence of migraine of 27% and MA+ of 11% in 89 patients with a history of paradoxical embolism and PFO, which significantly decreased to 11% and 2% respectively six months after percutaneous PFO closure.[60] Table III lists the results of other prospective observational studies on this topic.[52, 54, 61, 64, 65, 67, 68] However, the inclusion criteria applied in these studies were different from most retrospective reports: patients that suffered from migraine with or without clinical or subclinical cerebral ischemic events undergoing PFO closure were selected.[52, 54, 61, 64, 65, 67, 68] Also in these patients a reduction in the prevalence of migraine and MA+ of 24-100% was observed after PFO closure.[52, 54, 61, 64, 65, 67, 68] All these reports confirm a high prevalence of migraine, especially MA+, in patients with a PFO along with a significant decrease of migraine prevalence and/or attacks after PFO closure. However, all these studies yield methodological restrictions because of a nonrandomized, observational character. In 2008, the results of the MIST (Migraine Intervention with Starflex Technology) trial were published.[70] It was the first randomized, double-blind controlled study of the effect of percutaneous PFO closure on the prevalence of migraine. One hundred and forty-seven patients with severe, therapy-resistant migraine with aura and a PFO were randomized to percutaneous closure or a so-called sham procedure. Six months after the PFO closure, no significant reduction in the prevalence of migraine was found, although on

exploratory analysis, a significant reduction in headache days was observed.[70] These results seem to be in conflict with the results of previous studies. This might be explained by the different study population of this trial compared to other studies. The patients in the observational studies mostly suffered a symptomatic RLS: almost all had a history of a paradoxical embolic event due to the PFO. Conversely, all patients in the MIST trial had an "asymptomatic" RLS: patients with paradoxical embolic events were excluded. Moreover, the MIST trial was limited by inclusion of a high frequency of patients found not to have PFO during invasive evaluation, the occurrence of several adverse events and an unclear number of residual shunts after PFO closure. Additionally, the analysis phase was quite soon after implantation of the closure device. Therefore, the MIST study failed to refute the concordant findings of the observational studies.

To explain the relationship between RLS and migraine several pathophysiological hypotheses have been proposed. First, micro-thrombi or emboli could pass through the PFO and enter the systemic and cerebral circulation and trigger a migraine attack. The RLS may permit these micro-thrombi to bypass the lung filter. Indeed, this "thrombi-hypothesis" could be the link between migraine and ischemic stroke. This hypothesis is supported by the finding that migraine patients, especially patients with MA+, have a higher life-time risk for an ischemic cerebral event compared to the general population.[71-73] Additionally, it has been shown that the incidence of subclinical brain infarction diagnosed with MR imaging is higher in patients with MA+ when compared to controls.[74-76] This increased risk might be explained by the elevated levels of platelet activation and platelet/leucocyte interaction in patients with migraine. The same interactions have been reported in the pathophysiology of ischemic stroke.[77] The fact that the prevalence of PFO in patients with cryptogenic stroke is comparable with that among patients with migraine also supports this hypothesis.[78] As mentioned earlier, only an association between MA+ and the presence of RLS has been described. In contrast to MA-, MA+ is initiated by cortical spreading depressions.[79] Coupled with these depressions are cerebral blood flow changes.[80] Micro-thrombi might play an important role in initiating this cascade. In support of this hypothesis, aura is accompanied by mild hypoperfusion of the occipital cortex

and emboli seem to have a predilection to obstruct perfusion in this brain area.[75, 81] Finally, in support of the micro-thrombi hypothesis is the finding that treatment with high dose aspirin or coumadin might prevent migraine attacks.[82, 83]

A second pathophysiological hypothesis is that vaso-active substances in the venous circulation might trigger a migraine attack if they reach the brain in sufficient concentrations.[51] Normally, the trigger substances are filtered and detoxified in the lungs. The presence of RLS permits the substances to bypass the lung filter. Alternatively, chronic RLS might reduce the threshold for migraine generation in the brain.[84] It is postulated that in the presence of RLS, micro-bubbles activate platelets and this might liberate 5-hydroxytryptamine, which plays an important role in the pathogenesis of migraine.[82-85] Third, it is suggested that a particular genetic substrate might determine both atrial septum abnormalities and migraine. Wilmshurst et al. found that the occurrence of atrial shunts was consistent with autosomal dominant inheritance in 20 probands with 71 relatives and that this was linked to the inheritance of migraine with aura in some families.[86] However, the suggestion of a genetic link between atrial shunts and migraine seems in contradiction with improvement of migraine after percutaneous PFO closure.

To summarize, there seems to be an association between the presence of a right-to-left shunt through a PFO and migraine with aura. The most plausible pathophysiological hypothesis for this association is the passage of micro-thrombi through a PFO, which cause a migraine attack. The percutaneous PFO closure seems to be associated with a decrease in the occurrence of migraine with aura.

Table III. Prevalence of migraine and migraine with aura before and after the percutaneous PFO closure

Author	Year	FU (months)	N	before closure		after closure		P (M)	P (MA)
				M (%)	MA (%)	M (%)	MA (%)		
Retrospective									
Wilmshurst[69]	2000	17	37	57	43	30	24	< 0.05	< 0.05
Post[62]	2004	6	66	39	18	16	5	< 0.05	< 0.05
Schwerzmann[66]	2004	24	215	22	17	20	15	NS	NS
Azarbal[53]	2005	3	66	45	30	17	8	-	-
Reisman[63]	2005	9	162	35	24	14	11	-	-
Giardini[57]	2006	20	131	-	27	-	5	-	< 0.05
Dubiel[55]	2008	38	191	24	13	18	8	-	-
Retrospective, only migraine patients included									
Jesurum[58]	2008	18	77	100	71	46	10	-	-
Prospective									
Giardini[56]	2006	58	38	-	34	-	3	-	-
Luermans[60]	2008	6	89	27	11	11	2	< 0.05	< 0.05
Prospective, only migraine patients included									
Morandi[61]	2003	6	17	100	47	71	12	< 0.05	< 0.05
Anzola[52]	2006	12	50	100	66	64	14	< 0.05	< 0.05
Rigatelli[64]	2007	11	10	100	100	0	0	-	-
Rigatelli[65]	2009	10	20	100	100	-	-	-	-
Wahl[68]	2009	32	17	100	82	76	59	-	-
Chessa[54]	2009	6	42	100	66	74	50	-	-
Vigna[67]	2009	16	53	100	43	66	19	-	-

FU, follow-up; N, number; M, migraine; MA, migraine with aura.
In all studies patients with paradoxical embolism were included, except: [69]patients with paradoxical embolism or decompression illness; [52,58,61,64]patients with migraine and paradoxical embolism; [65,68]patients with migraine only; [54]patients with migraine with and without cerebral events; [67]patients with migraine and subclinical brain infarction. [63]Only migraineurs were followed. [65]No migraine prevalence reported, only migraine burden.

r1 r2 r3 r4 r5 r6 r7 r8 r9 r10 r11 r12 r13 r14 r15 r16 r17 r18 r19 r20 r21 r22 r23 r24 r25 r26 r27 r28 r29 r30 r31 r32 r33

Atrial septal defect management

Efficacy of percutaneous atrial septal defect closure

The first transcatheter device closure of an ASD was described by King and Mills in 1976.[87, 88] The technique has been continuously improved and has, to a large extent, replaced the surgical ASD closure. The percutaneous closure of a secundum type ASD is nowadays widely practiced, but the transcatheter approach is applicable only in secundum type ASD's. The ideal lesion for percutaneous closure is considered to be a defect of less than 30 mm in diameter with a rim of tissue around the defect of at least 5 mm to prevent obstruction of the coronary sinus, right pulmonary veins, vena cavae or atrioventricular valves. More than 50% of ASD's meet these criteria.[89, 90] There have been numerous reports describing the efficacy of transcatheter ASD closure.[91-110] Table IV summarizes the results of most of these studies.[91-110] Using predominantly the Amplatzer® ASD occluder and the Cardioseal® device, we and others found that the percutaneous ASD closure can be performed with a high success rate. As presented in Table IV, residual shunting during follow-up after ASD closure has been reported in 0-46%.[91-110] These differences can be explained by the variation in follow-up time, the definition of residual shunting and the use of different imaging modalities to diagnose residual shunting. We found residual shunting, as diagnosed by a contrast TTE and including very small shunts, in 14% of 133 adult patients who underwent percutaneous ASD closure with the Amplatzer® and the Cardioseal/Starflex® device.[110] No differences were observed between the two devices used in our study.

An improvement in symptoms and exercise tolerance has been reported in patients undergoing percutaneous ASD closure.[95, 103, 104, 107, 111] We also found an improvement in NYHA functional class after ASD closure in 133 adult patients.[110] This finding is compatible with the reduction in left atrial volume and improvements in right and left ventricular function and functional capacity that have been described after ASD closure.[112-116] In support, using the Finometer®, which enables beat-to-beat haemodynamic measurements, we found that stroke volume, mean blood pressure and systolic blood pressure increased immediately after percutaneous closure of an

ASD.[117] These haemodynamic changes were not observed in the control group of patients undergoing PFO closure.[117]
To summarize, nowadays the transcatheter ASD closure is the treatment of choice in patients with sizable and/or symptomatic secundum type ASD's. It can be performed with a high success rate, a low rate of residual shunting and it results in improvement of symptoms and cardiac function.

Safety of percutaneous atrial septal defect closure

The complications that can occur during and after ASD closure are mostly the same as those for percutaneous PFO closure. As summarized in Table IV, numerous studies have reported total complication rates of 0-48.1% and major complication rates of 0-17.2% of transcatheter ASD closure.[91-110] We found major complications in 6.0% of 133 patients who underwent percutaneous ASD closure using the Amplatzer® or the Cardioseal/Starflex® device between 1996 and 2008 in the St. Antonius Hospital, Nieuwegein, the Netherlands.[110] We reported a total embolization rate of 3.7%, which is comparable with embolization rates of 0-7.4% reported in several studies.[91-110] We found a higher major complication rate, however, in patients with Cardioseal/Starflex® compared to patients with Amplatzer® devices (17.2 vs. 2.9%), due to a higher embolization rate (13.8 vs. 1.0%).[110] Moreover, in univariable analysis, the implantation of a Cardioseal/Starflex® device (OR 6.0) and a larger device diameter (OR 1.1) were found to be predictors of major complications.[110] In contrast, Butera et al. found a non-significant difference in embolization rate between these two devices.[91] They reported embolization in three (2.5%) out of 121 patients who received the Cardioseal/Starflex® device compared to one (0.7%) out of 153 patients who received an Amplatzer® device.[91] An explanation for the high embolization rate using the Cardioseal/Starflex® devices in our study could be the larger diameter of the ASD and the closure device in these patients. These diameters seem to be larger in our study compared to others who used the Cardioseal/Starflex® device.[91, 104] Moreover, the Cardioseal/Starflex® devices that embolized or migrated in our study were part of the first 30% of all transcatheter ASD closing procedures performed in our centre during the study period. We have to take into account a learning curve and

the fact that closing techniques and some closure devices are continuously improved. During the last 70% of all procedures in our centre, only one device (Amplatzer®) embolized. Nowadays, we preferably use the Amplatzer® device in patients with large ASD's and only consider Cardioseal/Starflex® devices in patients with small defects.
A minor complication rate of 0-37% has been reported for transcatheter ASD closure in numerous studies.[91-110] This variance is probably the result of differences in follow-up time, the definition of complications and the types of devices used. In our study, minor complications occurred in 10.5%[110], which is comparable with earlier reports.[91-110] Taking into account the longer follow-up period of three and a half years in our study compared to others, our results are even more beneficial. We found no differences in the occurrence of minor complications between the types of devices used. In our study new-onset AF was the most frequent complication (9.8%) after ASD closure.[110] Spies et al. found an incidence of 12% of new-onset AF in 240 patients after ASD closure during a median follow-up of 20 months.[118] The annual incidence was 4.1%[118] compared to an annual incidence of 2.9% in our study.
To summarize, during long-term follow-up percutaneous ASD closure in adults is safe when using the Amplatzer® device. Larger Cardioseal/Starflex® devices might be related to a higher embolization rate.

Atrial septal defect closure and migraine

Only three retrospective studies have described the effect of percutaneous ASD closure on the occurrence of migraine.[53, 119, 120] These studies are summarized in Table V. In patients who underwent percutaneous ASD closure, the prevalence of migraine was 29-31% before and 17-27% after ASD closure. The prevalence of MA+ was 11-17% before and 4-15% after closure. Azarbal et al. showed a substantial decrease in migraine prevalence from 30% before to 17% three months after closure. The decrease was even more pronounced for MA+: from 17% before to 4% after. However, the study was underpowered (n=23) to determine significant results.[53] Mortelmans et al. found no effect on the prevalence of migraine in 75 patients six months after percutaneous ASD closure, but the frequency of migraine attacks in patients with pre-existing migraine decreased significantly.[119] However, several patients, mostly with relatively larger Amplatzer® devices, developed MA+ initially after ASD closure.[119]

Table IV. Outcome, complications and efficacy of percutaneous ASD closure

Author	Year	Device type	N	Age (y)	FU (months)	Complications (%) Total	Major	Residual shunting (%)	TE (%)
Chan[92]	1999	Amplatzer	100	13	3	5.0	1.0	1	0
Pedra[104]	2000	Cardioseal	50	10	10	24.0	0	46	0
Losay[99]	2001	Amplatzer	44	45	6	13.6	2.3	5	2.3
Oho[102]	2002	Amplatzer	35	13	-	2.9	0	3	0
Chessa[93]	2002	Total	417	27	-	7.7	3.4	-	2.4
		Amplatzer	258	27	-	8.1	3.1	-	0.4
		Cardioseal	159	27	-	6.9	3.8	-	0
Kannan[96]	2003	Amplatzer	45	34	16	28.9	2.2	4	0
Fischer[94]	2003	Amplatzer	236	5	28	1.7	0.4	6	0
Staniloae[107]	2003	Amplatzer	117	50	19	8.5	1.7	9	0
Hildick-Smith[95]	2004	Amplatzer	64	51	21	20.3	3.1	-	1.6
Butera[91]	2004	Total	274	20	-	4.7	2.2	2	0
		Amplatzer	153	20	16	3.9	1.3	0	0
		Cardioseal	121	21	24	5.8	3.3	4	0
Masura[101]	2005	Amplatzer	154	12	78	0	0	0	0
Tomar[108]	2006	Amplatzer	430	20	-	10.9	1.4	-	0
Post[105]	2006	Total	65	46	14	16.9	6.2	20	1.5
		Amplatzer	36	46	6	13.9	0	19	0
		Cardioseal	26	46	22	38.5	15.4	25	0
		ASDOS	3	46	54	0	0	0	33.3
Patel[103]	2007	Amplatzer	113	58	36	3.5	0	11	0
Spies[106]	2007	Amplatzer	170	47	13	9.4	1.2	23	1.2
Wilson[109]	2008	Amplatzer	222	-	22	10.9	1.4	9	0.5
Law[97]	2009	Cardioseal	27	9	25	48.1	11.1	4	0
Majunke[100]	2009	Amplatzer	650	46	36	9.5	1.7	4	0.8
Li[98]	2009	Amplatzer	191	25	6	6.3	2.1	7	0
Luermans[110]	2010	Total	133	47	41	16.5	6.0	14	2.3
		Amplatzer	104	47	32	11.6	2.9	11	1.9
		Cardioseal	29	47	73	34.4	17.2	22	3.4

N, number; y, years; FU, follow-up;TE, thrombo-embolism after ASD closure.

In support, Rodés-Cabau et al. studied 185 migraine-free ASD and PFO patients scheduled for percutaneous closure. They reported that transcatheter ASD closure was associated with new onset migraine with an incidence of 12% as compared to 0% after PFO closure. The first migraine episode occurred mostly within two weeks after the closing procedure and persisted in 2/3 of cases for more than two years.[121] These results suggest that ASD device implantation can act as a permanent trigger for migraine, though the pathophysiologic basis of this observation is unclear. Several hypotheses were formulated, including microthrombus formation on the left sided disk, transient nickel release, transient inflammation, platelet activation on the surface of the device with subsequent serotonin release and others.[69, 119, 120, 122-124] In the study by Voet et al. no significant decrease in migraine prevalence in 71 patients who underwent ASD closure after 52 months follow-up was found. However, a significant reduction was noted in patients with new-onset and persistent migraine early after closure.[120] We performed the only prospective observational study so far on the effect of ASD closure on migraine. In 68 patients, the prevalence of migraine and MA+ was 34% and 22% respectively before ASD closure. We found a significant reduction of 64% for the prevalence of migraine and 76% for MA+ twelve months after ASD closure (Table V).[125]

Table V. Prevalence of migraine and migraine with aura before and after the percutaneous ASD closure

Author	Year	FU (months)	N	before closure		after closure		P (M)	P (MA)
				M (%)	MA (%)	M (%)	MA (%)		
Retrospective									
Azarbal[53]	2005	3	23	30	17	17	4	-	-
Mortelmans[119]	2005	29	75	29	11	27	15	NS	NS
Voet[120]	2008	52	71	31	11	23	9	NS	NS
Prospective									
Luermans[125]	2009	12	68	34	22	12	5	< 0.05	< 0.05

FU, follow-up; N, number; M, migraine; MA, migraine with aura.

These reports show that the prevalence of migraine in patients with ASD is higher than for the general population. Additionally, whereas some report an initial aggravation or development of migraine after ASD closure, our prospective study shows a decrease in the prevalence of migraine at longer follow-up.

Pathophysiologically these findings can be explained as follows: first, an ASD is characterized by predominant left-to-right shunting. However, during a Valsalva maneuver or exercise, a RLS can be detected with contrast echocardiography.[126] Thus in patients with ASD, the same pathophysiological processes can occur as in patients with RLS through a PFO. As described above, the increase in RLS during Valsalva might cause migraine trigger substances to bypass the lung filter and enter the cerebral circulation. Second, several studies reported an increased prevalence of migraine in patients with a random congenital heart defect. Hermans et al. found an increased prevalence of MA+ in 80 patients with congenital heart disease with and without RLS compared to controls (respectively 40% and 32.5% vs. 5%).[127] Additionally, Truong et al. found a three to four times higher prevalence of migraine in 395 adults with congenital heart disease compared to a sex-matched control population. They described an increasing prevalence of migraine in patients with no shunt (38%), a left-to-right shunt (44%), and a right-to-left shunt (52%).[128] Similarly, Hirth et al. found an increased prevalence of MA+ in both 29 cyanotic and 38 acyanotic patients with congenital heart disease of 59% and 42%, respectively.[129] However, they found a high prevalence of PFO in those with acyanotic congenital heart disease, which might explain the high prevalence of MA+ in this group. An increased prevalence of migraine has also been described in patients with Marfan Syndrome.[130] All these reports suggest a genetic link between migraine and congenital heart defects that could be an alternative explanation for the relatively high prevalence of migraine in the ASD patients. Finally, in patients with congenital heart defects, RLS might be accompanied by hypoxaemia. Hypoxaemia may lead to increased haemoglobin levels. A positive correlation between haemoglobin level and the prevalence of migraine has been reported.[131] Hermans et al. confirmed the association between migraine and rising haematocrit levels.[127] Migraine, due to augmented haemoglobin levels, might be caused by the activation of blood compounds and the endothelium due to shear stress. Therefore, hyperviscosity could be another explanation for the high prevalence of MA+ observed in patients with congenital heart disease and an obligate RLS, which results in secondary polyglobulia.[127]

To summarize, a high prevalence of migraine, especially migraine with aura, has been described in patients with an ASD. The pathophysiological basis for the association of

migraine (with aura) and an ASD might be incidental right-to-left shunting or a genetic basis. We found a significant reduction of migraine (with aura) after percutaneous ASD closure.

Limitations and recommendations for the future

Limitations

First, it is difficult to compare the results of the studies that describe the efficacy and safety of percutaneous PFO and ASD closure because of differences of the size of the study population, the definition and means of assessment of clinical endpoints, the follow-up duration and the closure devices used. Second, almost all patients were referred for percutaneous closure of an inter-atrial septal defect, which induces a selection bias. Third, the results of the studies on the effect of cardiac shunt closure on migraine are disputable because shunt closure was carried out for indications other than migraine, such as a paradoxical embolic event. Extrapolating those results to migraine patients without a history of a paradoxical embolic event is questionable. Fourth, these studies have a limited value by their non-randomized, non placebo-controlled design. The placebo effect in migraine therapy should indeed be considered, but the reported changes in the prevalence of migraine in our studies seem to overrule the reported placebo effect rates of 20-40%.[132] We are, however, aware that placement of an intracardiac device may have a more profound placebo effect than drug treatment on health perception. Fifth, we applied headache questionnaires to diagnose migraine, which might induce a recall bias. Sixth, almost all patients were treated with clopidogrel and low-dose aspirin after transcatheter closure, which might influence the occurrence of migraine. But the effect of low-dose aspirin on the occurrence migraine seems to be modest and comparable with placebo responder rates.[133, 134] In addition, clopidogrel was taken only for four weeks and aspirin for six months. Therefore the influence of clopidogrel or low-dose aspirin on the decrease in prevalence of migraine seems to be modest and cannot explain the persistent and significant decrease in the prevalence of migraine we found after PFO and ASD closure.

Recommendations for further research

Our data do not answer the important remaining question of how transcatheter PFO closure compares to medical treatment with anti-thrombotic agents for prevention of recurrent thrombo-embolism in patients with paradoxical embolic events. Randomized trials that compare transcatheter closure with medical therapy are needed. The results of ongoing randomized trials (RESPECT, CLOSURE-1, Gore-REDUCE, PC-trial, CLOSE) will hopefully answer this question in the near future. Unfortunately, a common exclusion criterion for most ongoing trials is age above 60 years. Randomized trials that include older patients are needed to develop management strategies in this patient group.

There seems to be an association between migraine and a right-to-left shunt. The pathophysiological basis for this association needs to be further clarified and a randomized clinical trial with appropriate inclusion criteria and clinical endpoints needs to be performed to determine the effect of percutaneous shunt closure on migraine.

Conclusions

The percutaneous closure of a patent foramen ovale is effective and safe in patients with paradoxical embolic events using different device types. Patent foramen ovale closure seems to be related with less beneficial outcome in elderly with previous paradoxical embolic events. The percutaneous closure of an atrial septal defect is effective and safe, especially when using the Amplatzer® device, and results in haemodynamic and symptomatic improvement. There is evidence for an association between a right-to-left shunt and migraine. Shunt closure might be associated with an improvement of migraine. It is, however, too early to recommend primary percutaneous shunt closure in the treatment of migraine and large randomized trials are needed.

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Chapter 12

Summary

Samenvatting

Dankwoord

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Summary

A cardiac right-to-left shunt through a patent foramen ovale (PFO) or an atrial septal defect (ASD) allows paradoxical embolism and seems to be associated with cryptogenic stroke and migraine. The transcatheter closure of inter-atrial shunts by means of the delivery of an "umbrella" device is nowadays widely practised in the treatment of patients with symptomatic shunts. Shunt closure has also been associated with a decrease in the prevalence of migraine.
Aims of this thesis were to:

1. study the efficacy and safety of transcatheter PFO and ASD closure, using different types of closure devices.
2. evaluate the effect of transcatheter PFO and ASD closure on the occurrence of migraine.

Part one of this thesis, encapsulating **chapter 1**, offers an introduction. An overview of atrial septal abnormalities (PFO, atrial septal aneurysm and ASD) and their association with cryptogenic stroke and migraine is given.

Part two of the thesis concerns the efficacy and safety of percutaneous PFO and ASD closure.

In **chapter 2** the efficacy and safety of percutaneous PFO closure using the fourth generation Intrasept™ device (Cardia, Eagan, MN, USA) is studied. All 430 patients who underwent a PFO closure with the Intrasept™ device between July 2002 and September 2006 were included in this multi-centre study. The indications for closure were cryptogenic stroke (69.8%), TIA (23.5%), peripheral embolism (3.3%), and other (3.5%). The recurrence of thrombo-embolic events was 0.5% for stroke and 2.5% for TIA during a median follow-up time of 0.8 years. Peri-procedural complications of PFO closure were reported in 11.5% of cases. In only 0.2% major peri-procedural complications occurred. No severe complications occurred during mid-term follow-up. We found a higher prevalence of residual shunting within six months after PFO closure in patients who suffered a recurrent thrombo-embolic event (36.4%)

compared to patients who did not (12.5%). In conclusion, the percutaneous closure of a symptomatic PFO with the fourth generation Intrasept™ device is safe and effective in the prevention of recurrent paradoxical thrombo-embolic events.

In **chapter 3** we compared the efficacy and safety of PFO closure using the new bioabsorbable Biostar® device (NMT Medical, Boston, USA) with the non-bioabsorbable Cardioseal/Starflex® device from the same manufacturer. Between June 2003 and July 2008, 37 patients received a Biostar® device and 44 patients a Cardioseal/Starflex® device in the St. Antonius Hospital, Nieuwegein, the Netherlands. Within six months follow-up, two patients who received a bioabsorbable device suffered a recurrent TIA. There were no significant differences in short-term complications between both groups. Overall, atrial arrhythmias occurred in 19%, with no difference between both groups. At six months follow-up, a residual shunt was present in 28% (17% minimal, 11% moderate) using the bioabsorbable device compared to 29% (27% minimal, 2% moderate) using the non-bioabsorbable device. In conclusion, there is no significant difference in safety and efficacy at six months between the bioabsorbable and non-bioabsorbable device. However, the use of the bioabsorbable device tends to be associated with a higher percentage of moderate residual shunting after PFO closure.

In **chapter 4** the efficacy and safety of percutaneous PFO closure during mid-term follow-up in a single centre using two types of devices is studied. Between May 1998 and November 2006 83 patients underwent percutaneous PFO closure in the St. Antonius Hospital, Nieuwegein, the Netherlands. The Cardioseal/Starflex device® (NMT Medical, Boston, USA) was used in 63 patients and the Amplatzer PFO occluder® (AGA Medical Corporation, Golden Valley, MN, USA) in 20 patients. Indications for PFO closure were cryptogenic stroke (59.0%), TIA (33.7%), peripheral embolism (2.4%) and other (4.8%). Stroke recurred in 1.2% and TIA in 3.6% during a mean follow-up of 1.9 years. Peri-procedural complications occurred in 12%. In only 1.2% major peri-procedural complications occurred. The mid-term complication rate was 2.4% and only consisted of minor complications. During follow-up, a residual right-to-left shunt was present in 5.7%. No significant differences in outcome, complications or residual shunting could be documented between the two types

of devices. In conclusion, the percutaneous closure of a PFO seems to be a safe and effective procedure to prevent the recurrence of paradoxical thrombo-embolic events during mid-term follow-up, using these types of devices.

In **chapter 5** the efficacy and safety of percutaneous PFO closure in older patients is studied. Comparative statistics were performed between 120 patients older than 55 years of age (mean age 63 years) and 215 patients younger than 55 years of age (mean age 43 years), who underwent percutaneous PFO closure because of a paradoxical embolic event in two referral centres between May 1998 and January 2008. The prevalence of hypertension, diabetes, hyperlipidemia and coronary and peripheral artery disease was higher in the older group. During a mean follow-up period of 4.0 years we found a significantly higher annual recurrence rate of stroke or TIA in the elderly (2.4%) compared to the younger (0.6%) after PFO closure. By multivariable analysis, age >55 years was an independent predictor of recurrent stroke or TIA (odds ratio 3.8). There was no significant difference in the occurrence of complications related to PFO closure between the two groups and residual shunting was only slightly higher in the older group (12.1%) compared to the younger (7.7%). In conclusion, the percutaneous PFO closure appears to be effective for secondary prevention of cryptogenic stroke in younger patients but seems to be related with less beneficial outcome in elderly.

In **chapter 6** the efficacy and safety of percutaneous ASD closure in adults using two types of devices is studied during long-term follow-up. We included 133 patients who underwent percutaneous ASD closure in the St. Antonius Hospital, Nieuwegein, the Netherlands between November 1996 and January 2008. The Amplatzer® ASD occluder (AGA Medical Corporation, Golden Valley, MN, USA) was used in 104 and the Cardioseal/Starflex® device (NMT Medical, Boston, USA) in 29 patients. During a mean follow-up of 3.4 years the occurrence of major complications was significantly higher in patients with Cardioseal/Starflex® compared to patients with Amplatzer® devices (17.2 vs. 2.9%) due to a higher embolization rate (13.8 vs. 1.0%). By univariable analysis, the implantation of a Cardioseal/Starflex® device (odds ratio 6.0) and a larger device diameter (odds ratio 1.1) were found to be predictors of the occurrence of

major complications. Minor complications occurred in 10.5%, recurrent thromboembolism in 2.3% and residual shunting at six months was 13.9% without differences between the two devices used. NYHA class improved significantly from 1.8 before to 1.2 after ASD closure without differences between the devices. In conclusion, during long-term follow-up, percutaneous ASD closure in adults is safe and effective when using the Amplatzer® device. Larger Cardioseal/Starflex® devices are possibly related to a higher embolization rate.

In **chapter 7** the immediate haemodynamic effects of percutaneous closure of inter-atrial shunts are studied, using non-invasive finger pressure measurements. We included 15 patients who underwent percutaneous PFO closure and 10 patients who underwent percutaneous ASD closure in the St. Antonius Hospital, Nieuwegein, the Netherlands. By using the Finometer® for non-invasive measurement and calculation of haemodynamics, we found that after PFO closure none of the haemodynamic parameters changed significantly, whereas immediately after ASD closure the systolic and mean pressures and stroke volume increased and the heart rate decreased significantly. The changes in stroke volume differed significantly between the PFO and ASD patients. In conclusion, using non-invasive finger pressure measurements, we found that stroke volume, mean and systolic blood pressure increased immediately after percutaneous closure of an ASD in adults, whereas the percutaneous PFO closure had no effect on haemodynamic characteristics.

In **chapter 8** a case of late thrombosis on an ASD closure device is described.

Part three of the thesis concerns the effect of percutaneous closure of inter-atrial shunts on the occurrence of migraine.

In **chapter 9** the effect of percutaneous PFO closure on the occurrence of migraine is studied in a prospective observational design. We included 92 patients who underwent percutaneous PFO closure because of a symptomatic PFO in two referral centres between November 2003 and August 2005. They received a standardized headache questionnaire before and six months after PFO closure. Two neurologists,

blinded to the patients' files and time periods, diagnosed migraine according to the International Headache Criteria. Before closure, we found an overall prevalence of migraine of 27%, for migraine with aura 11%, and for migraine without aura 16% based on a completed questionnaire of 89 patients. After more than six months follow-up 84 of 89 patients (94%) returned the questionnaire. The overall prevalence of migraine in this group decreased significantly from 29% to 11%. The prevalence of migraine with aura decreased significantly from 12% to 2%. In conclusion, percutaneous PFO closure seems to be related to a decrease in the prevalence of migraine.

In **chapter 10** we prospectively evaluated the effect of percutaneous ASD closure on the occurrence of migraine. We included 70 patients who underwent percutaneous ASD closure between November 2003 and December 2005 in two referral centres. Standardized headache questionnaires were sent to all patients before and after ASD closure. Two neurologists, blinded to the patients' files and time periods, diagnosed migraine according to the International Headache Criteria. Before ASD closure, the overall prevalence of migraine was 34%, migraine with aura 22% and migraine without aura 12% based on a completed questionnaire in 68 patients. At 12 months follow-up, the prevalence of migraine and migraine with aura decreased significantly to respectively 12% and 5% based on a completed headache questionnaire in 57 patients (84%). In conclusion, we found a high prevalence of migraine in patients with an ASD and observed prospectively a reduction in the occurrence of migraine, especially migraine with aura, one year after percutaneous closure.

Part four of this thesis, encapsulating **chapter 11**, offers a general discussion. First, the management of patients with a PFO and a paradoxical embolic event is discussed, stressing on the transcatheter PFO closure. Second, an overview of the literature about the effect of transcatheter PFO closure on the occurrence of migraine is given. Third, an overview of reports about transcatheter ASD closure is given. Fourth, the effect of percutaneous ASD closure on the occurrence of migraine is discussed. Finally, the limitations of the studies described in this thesis are summarized and recommendations for further investigations are given, followed by the conclusions of this thesis.

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Samenvatting

Een cardiale rechts-links shunt door een patent foramen ovale (PFO) of een atriumseptum defect (ASD) kan leiden tot paradoxale embolisatie en is geassocieerd met het cryptogeen herseninfarct en migraine. Tegenwoordig wordt het percutaan sluiten van inter-atriale shunts door middel van het via katheterisatietechnieken plaatsen van een sluitingsdevice (een "parapluutje") steeds vaker toegepast ter behandeling van patiënten met symptomatische shunts. Het sluiten van dergelijke shunts is ook gerelateerd aan een afname van de prevalentie van migraine.
Doelstellingen van deze thesis waren:

1. het onderzoeken van de effectiviteit en veiligheid van percutane sluiting van het PFO en het ASD, gebruik makend van verschillende typen sluitingsdevices.
2. het onderzoeken van het effect van percutane PFO en ASD sluiting op het vóórkomen van migraine.

In **Deel één (hoofdstuk 1)** van deze thesis, de inleiding, wordt een overzicht gegeven van atriumseptum afwijkingen (het PFO, het atriumseptum aneurysma en het ASD) en hun associatie met het cryptogeen herseninfarct en migraine.

In **Deel twee** van deze thesis wordt de effectiviteit en veiligheid van percutane sluiting van het PFO en het ASD onderzocht.

In **hoofdstuk 2** wordt de effectiviteit en veiligheid van percutane PFO sluiting door implantatie van het vierde generatie Intrasept™ device (Cardia, Eagan, MN, USA) onderzocht. Alle 430 patiënten, die een PFO sluiting door middel van implantatie van dit device ondergingen tussen juli 2002 en september 2006, werden geïncludeerd in dit onderzoek, dat werd uitgevoerd in meerdere verwijzingscentra. De indicaties voor sluiting van het PFO waren cryptogeen herseninfarct (69.8%), TIA (23.5%), perifere embolisatie (3.3%) en andere indicaties (3.5%). Tijdens de 0.8 jaar na sluiting ontwikkelden 0.5% van de patiënten een recidief herseninfarct en 2.5% een recidief TIA. Rondom de sluitingsprocedure traden complicaties op bij 11.5% van de patiënten, waarvan slechts 0.2% een ernstige complicatie was. Er traden tijdens de verdere

studieperiode geen ernstige complicaties op. Binnen zes maanden na PFO sluiting was er sprake van een hogere prevalentie van residuele rechts-links shunt bij patiënten die een recidief thrombo-embolie doormaakten (36.4%) dan bij patiënten zonder recidief (12.5%). Concluderend: percutane sluiting van een PFO met het vierde generatie Intrasept™ device is veilig en effectief ter preventie van recidief paradoxale thrombo-embolieën.

In **hoofdstuk 3** wordt de effectiviteit en veiligheid van percutane PFO sluiting, gebruik makend van het nieuwe bioabsorbeerbare Biostar® device (NMT Medical, Boston, USA) vergeleken met het niet bioabsorbeerbare Cardioseal/Starflex® device van dezelfde fabrikant. In het St. Antonius Ziekenhuis in Nieuwegein werd tussen juni 2003 en juli 2008 bij 37 patiënten een Biostar® device geïmplanteerd en bij 44 patiënten een Cardioseal/Starflex® device. Tijdens de zes maanden na sluiting ontwikkelden twee patiënten met een Biostar® device een recidief TIA. Er was geen verschil in het optreden van complicaties op de korte termijn tussen de groepen. Atriale ritmestoornissen traden op bij 19% van de patiënten, zonder verschil tussen beide groepen. Er was sprake van een residuele shunt, zes maanden na sluiting, bij 28% (bij 17% een minimale shunt en bij 11% een matige shunt) van de patiënten met een Biostar® device vergeleken met 29% (bij 27% een minimale shunt en bij 2% een matige shunt) van de patiënten met een Cardioseal/Starflex® device. Concluderend: er is geen significant verschil in de effectiviteit en veiligheid na zes maanden tussen het bioabsorbeerbare en het niet-bioabsorbeerbare device. Echter, het gebruik van het bioabsorbeerbare device neigt een hogere prevalentie van een matige residuele shunt na PFO sluiting met zich mee te brengen.

In **hoofdstuk 4** wordt de effectiviteit en veiligheid van percutane PFO sluiting op de middellange termijn in één verwijzingscentrum, gebruik makend van twee typen sluitingsdevices, onderzocht. Tussen mei 1998 en november 2006 ondergingen 83 patiënten een percutane PFO sluiting in het St. Antonius Ziekenhuis in Nieuwegein. Het Cardioseal/Starflex device® (NMT Medical, Boston, USA) werd gebruikt voor PFO sluiting bij 63 patiënten en de Amplatzer PFO occluder® (AGA Medical Corporation, Golden Valley, MN, USA) bij 20 patiënten. De indicaties voor PFO

sluiting waren cryptogeen herseninfarct (59.0%), TIA (33.7%), perifere embolie (2.4%) en andere indicaties (4.8%). Tijdens de 1.9 jaren na PFO sluiting was er sprake van een recidief herseninfarct bij 1.2% van de patiënten en van een recidief TIA bij 3.6%. Complicaties rondom de procedure traden op bij 12% van de patiënten. Slechts bij 1.2% betrof dit een ernstige complicatie. Gedurende de verdere studieperiode traden nog bij 2.4% van de patiënten complicaties op, die niet ernstig waren. Er was sprake van een residuele shunt na PFO sluiting bij 5.7% van de patiënten. Er waren geen significante verschillen in de uitkomst en het optreden van complicaties en residuele shunts tussen de beide sluitingsdevices. Concluderend: percutane PFO sluiting lijkt een effectieve en veilige procedure ter voorkoming van recidief paradoxale thrombo-embolieën op de middellange termijn, gebruik makend van deze devices.

In **hoofdstuk 5** wordt de effectiviteit en veiligheid van percutane PFO sluiting bij oudere patiënten onderzocht. Er werd vergelijkende statistiek verricht tussen 120 patiënten ouder dan 55 jaar (met een gemiddelde leeftijd van 63 jaar) en 215 patiënten jonger dan 55 jaar (met een gemiddelde leeftijd van 43 jaar), die percutane PFO sluiting ondergingen vanwege een paradoxale thrombo-embolie in twee verwijzingscentra tussen mei 1998 en januari 2008. De prevalentie van hypertensie, diabetes mellitus, hyperlipidemie, coronairlijden en perifeer vaatlijden was hoger in de oudere leeftijdsgroep. Tijdens de vier jaren na PFO sluiting was er een significant hoger jaarlijks recidiefpercentage van herseninfarct of TIA in de oudere leeftijdsgroep (2.4%) vergeleken met de jongere leeftijdsgroep (0.6%). Bij een multivariate analyse bleek een leeftijd hoger dan 55 jaar een onafhankelijke voorspeller van recidief herseninfarct of TIA met een odds ratio van 3.8. Er was geen verschil in het optreden van complicaties gerelateerd aan PFO sluiting tussen de beide leeftijdsgroepen. Het percentage van residuele shunts na PFO sluiting was niet significant hoger in de oudere leeftijdsgroep (12.1%) vergeleken met de jongere groep (7.7%). Concluderend: percutane PFO sluiting blijkt effectief in de secundaire preventie van cryptogeen herseninfarct bij jongere patiënten. Echter, percutane PFO sluiting lijkt gerelateerd aan een minder gunstige uitkomst bij oudere patiënten.

In **hoofdstuk 6** wordt de effectiviteit en veiligheid op de lange termijn van percutane ASD sluiting bij volwassenen onderzocht, gebruik makend van twee typen sluitingsdevices. Er werden 133 patiënten geïncludeerd, die een percutane ASD sluiting ondergingen in het St. Antonius Ziekenhuis in Nieuwegein tussen november 1996 en januari 2008. De Amplatzer® ASD occluder (AGA Medical Corporation, Golden Valley, MN, USA) werd geïmplanteerd bij 104 patiënten en het Cardioseal/ Starflex® device (NMT Medical, Boston, USA) bij 29 patiënten. Gedurende de 3.4 jaren na sluiting traden ernstige complicaties significant vaker op bij patiënten met een Cardioseal/Starflex® device dan bij patiënten met een Amplatzer® device (17.2 vs. 2.9%). Dit was het gevolg van het vaker emboliseren van de Cardioseal/Starflex® devices vergeleken met de Amplatzer® devices (13.8 vs. 1.0%). Bij een univariate analyse bleken de implantatie van een Cardioseal/Starflex® device (odds ratio 6.0) en een grotere device diameter (odds ratio 1.1) voorspellers van het optreden van ernstige complicaties. Niet-ernstige complicaties traden op bij 10.5%, recidief thrombo-embolieën bij 2.3% en een residuele shunt zes maanden na ASD sluiting trad op bij 13.9% van de patiënten zonder verschillen tussen de gebruikte devices. De NYHA functionele klasse verbeterde significant van 1.8 voor tot 1.2 na ASD sluiting, ook zonder verschillen tussen de devices. Concluderend: percutane ASD sluiting bij volwassenen is veilig en effectief op de lange termijn bij het gebruik van het Amplatzer® device. Het gebruik van de grotere Cardioseal/Starflex® devices is mogelijk gerelateerd aan meer embolisaties.

In **hoofdstuk 7** worden de onmiddellijke haemodynamische effecten van percutane sluiting van inter-atriale shunts onderzocht, gebruik makend van niet-invasieve vingerdruk metingen. Er werden 15 patiënten die een percutane PFO sluiting ondergingen en 10 patiënten die een percutane ASD sluiting ondergingen in het St. Antonius Ziekenhuis in Nieuwegein geïncludeerd. Bij deze patiënten werden met behulp van de Finometer®, op non-invasieve wijze, haemodynamische veranderingen gemeten en berekend. Na PFO sluiting werden geen significante haemodynamische veranderingen waargenomen. Echter, onmiddellijk na ASD sluiting was er sprake van een significante toename van de systolische en gemiddelde bloeddruk, een significante toename van het slagvolume en een significante afname van de hartfrequentie. Er was

een significant verschil in de verandering van het slagvolume tussen de PFO en de ASD patiënten. Concluderend: gebruik makend van niet-invasieve vingerdruk metingen was er sprake van een toename van de systolische en gemiddelde bloeddruk en het slagvolume onmiddellijk na sluiting van een ASD bij volwassenen, terwijl percutane PFO sluiting geen effect had op de haemodynamische karakteristieken.

In **hoofdstuk 8** wordt een casus beschreven van late thrombose op een ASD sluitingsdevice.

Deel drie van deze thesis betreft het effect van percutane sluiting van inter-atriale shunts op het vóórkomen van migraine.

In **hoofdstuk 9** wordt het effect van percutane PFO sluiting op het vóórkomen van migraine onderzocht in een prospectieve, observationele studie. Er werden 92 patiënten geïncludeerd, die een percutane PFO sluiting ondergingen in twee verwijzingscentra tussen november 2003 en augustus 2005. De indicatie tot sluiting was in bijna alle gevallen een paradoxale embolie. Alle patiënten ontvingen een gestandaardiseerde hoofdpijnvragenlijst voor en zes maanden na PFO sluiting. Twee neurologen, die geblindeerd waren voor de patiëntendossiers en tijdsperioden, diagnosticeerden migraine volgens de internationaal geldende criteria. Voor PFO sluiting vulden 89 patiënten de vragenlijst in. De prevalentie van migraine voor sluiting was 27%, de prevalentie van migraine met aura was 11% en de prevalentie van migraine zonder aura was 16%. Meer dan zes maanden na sluiting stuurden 84 van de 89 patiënten (94%) de hoofdpijnvragenlijst terug. In deze groep nam de prevalentie van migraine significant af van 29% tot 11%. De prevalentie van migraine met aura nam significant af van 12% tot 2%. Concluderend: percutane sluiting van een PFO lijkt gerelateerd aan een afname van de prevalentie van migraine.

In **hoofdstuk 10** wordt in een prospectieve studie het effect van percutane ASD sluiting op het vóórkomen van migraine onderzocht. Er werden 70 patiënten geïncludeerd, die een percutane ASD sluiting ondergingen in twee verwijzingscentra tussen november 2003 en december 2005. Alle patiënten ontvingen een

gestandaardiseerde hoofdpijnvragenlijst voor en na ASD sluiting. Twee neurologen, die geblindeerd waren voor de patiëntendossiers en tijdsperioden, diagnosticeerden migraine volgens de internationaal geldende criteria. Voor ASD sluiting vulden 68 patiënten de vragenlijst in. De prevalentie van migraine voor sluiting was 34%, de prevalentie van migraine met aura was 22% en de prevalentie van migraine zonder aura was 12%. Twaalf maanden na sluiting stuurden 57 patiënten (84%) de hoofdpijnvragenlijst terug. De prevalentie van migraine en migraine met aura nam significant af tot respectievelijk 12% en 5%. Concluderend: wij vonden een hoge prevalentie van migraine bij patiënten met een ASD en een significante afname van migraine, met name migraine met aura, één jaar na percutane ASD sluiting.

Deel vier (hoofdstuk 11) van deze thesis omvat de discussie. Ten eerste wordt de behandeling van patiënten met een PFO en een paradoxale thrombo-embolie besproken, met nadruk op percutane PFO sluiting. Ten tweede wordt een overzicht gegeven van de literatuur die verschenen is over het effect van percutane PFO sluiting op het vóórkomen van migraine. Ten derde wordt een overzicht gegeven van de literatuur die is verschenen over percutane ASD sluiting. Ten vierde wordt het effect van percutane ASD sluiting op het vóórkomen van migraine besproken. Tenslotte worden de beperkingen genoemd van de studies die in deze thesis zijn beschreven en worden er suggesties gegeven voor toekomstig onderzoek, gevolgd door de conclusies van deze thesis.

Dankwoord

Mijn dank is groot aan éénieder die op welke wijze dan ook aan de totstandkoming van dit proefschrift heeft bijgedragen. In het bijzonder wil ik noemen:

Alle patiënten die hebben willen meewerken aan dit onderzoek en die de moeite hebben genomen hoofdpijnvragenlijsten in te vullen. Zonder hen geen onderzoek.

Prof. Dr. N.M. van Hemel, geachte promotor, dankzij uw inspanningen aan het einde van het traject is het uiteindelijk tot een concreet proefschrift gekomen. Uw inhoudelijke commentaren en kritieken in de vorm van "NvH'tjes" zijn bij het schrijven van de inleiding en de discussie van grote waarde geweest. Ik dank u voor de begeleiding en de organisatie van mijn promotie.

Prof. Dr. W.I.H.L. Budts, geachte promotor, de oorspronkelijke ideeën met betrekking tot dit onderzoek alsmede een groot deel van de data komen van u en ik ben blij dat Marco ze heeft meegenomen naar Nieuwegein en mij ervan heeft laten proeven. Bedankt voor al uw goede ideeën en de intensieve begeleiding bij het schrijven van de manuscripten. Uw commentaren waren altijd snel en scherp. Bedankt ook voor de gegeven mentale ondersteuning voor de verdediging.

Dr. H.W.M. Plokker, geachte co-promotor, beste Thijs, dit proefschrift was er niet geweest zonder jouw hulp. Nog vrijwel voor er überhaupt een manuscript geschreven was, had jij al een overzichtelijk en afgebakend pad richting een proefschrift samen met mij uitgestippeld. Gedurende het bewandelen van dit pad was jij altijd vlot met commentaren, die vaak en gelukkig eindigden met de bemoedigende woorden "goed werk, jongens." Aan het eind van het pad wist jij de juiste mensen bij elkaar te brengen om tot dit resultaat te komen. Je bezit charisma, mores, didactische vaardigheden en een gevoel voor humor die voor mij in het onderzoek maar nog meer in de opleiding tot cardioloog verrijkend zijn.

Dr. M.C. Post, geachte co-promotor, beste Marco, jou ben ik zonder enige twijfel de meeste dank verschuldigd. Ik weet nog goed dat je in 2005 de "echoput" binnenkwam. Je was destijds druk bezig met je eigen proefschrift. Er waren echter nog vele aanvullende onderzoeksideeën en je zocht iemand om die samen met jou uit te werken. Dat was het begin van onze samenwerking. Je hebt me sinds die tijd met een aanstekelijk enthousiasme begeleid en je hebt ontzettend veel tijd gestoken in het gezamenlijk invoeren en analyseren van data, het meeschrijven van manuscripten, het maken van posters en dat tot in alle details. Ik heb enorm veel bewondering voor je "goedheid", je geduld en je gave met betrekking tot het doen van onderzoek waarin je een ware octopus lijkt. Allerbeste Marco, ik ben trots op ons werk en ik dank je voor alles!

De leden van de beoordelingscommissie Prof. Dr. F.L. Moll, Prof. Dr. Y. van der Graaf, Prof. Dr. P.A.F.M. Doevendans, Prof. Dr. M.J. Schalij en Prof. Dr. V. Thijs, u allen wil ik danken voor het kritisch beoordelen van het proefschrift.

De neurologen Prof. Dr. V. Thijs en Dr. W.J. Schonewille, u dank ik voor het analyseren van de vele hoofdpijnvragenlijsten.

Hans Kelder, jou wil ik graag danken voor het geven van tips en het beantwoorden van mijn vragen op het gebied van de statistiek.

De medewerkers van het centraal medisch archief en het "poli"-archief van het St. Antonius Ziekenhuis in Nieuwegein, bedankt voor het altijd zo vlot opzoeken van de gevraagde patiëntenstatussen.

Sonia Rens, secretaresse van de afdeling Cardiologie van het Leuvense Ziekenhuis Gasthuisberg, u wil ik ook hartelijk danken voor het opzoeken van de Leuvense patiëntendossiers.

De medewerkers van de hartfunctieafdeling, en dan met name de echolaboranten en de echo-beoordelaars, mijn collegae, veel dank voor het vervaardigen en beoordelen van de ontelbare echo's en het geven van "bubbles".

De medewerkers van het Secretariaat Cardiologie van het St. Antonius Ziekenhuis, ik dank jullie voor de gegeven administratieve ondersteuning.

De verpleegkundigen van de afdeling Cardiologie in het St. Antonius Ziekenhuis, jullie hulp bij het verzamelen van de hoofdpijnvragenlijsten van de patiënten waardeer ik enorm.

De leden van de Maatschap Cardiologie van het St. Antonius Ziekenhuis, ik ben zeer dankbaar voor de mogelijkheid en de tijd die ik heb gekregen voor het doen van onderzoek naast mijn opleiding tot cardioloog. Dr. W. Jaarsma, mijn opleider, wil ik in dit kader in het bijzonder danken. Daarnaast wil ik Dr. M.J. Suttorp en Dr. J.M. ten Berg graag hartelijk danken voor het zo succesvol sluiten van de inter-atriale septumdefecten en voor het reviewen van de manuscripten.

De leden van de Maatschap Interne Geneeskunde van het St. Antonius Ziekenhuis, u allen dank ik voor de ruimte die mij gegeven werd voor het doen van onderzoek naast mijn vooropleiding. In het bijzonder dank ik Dr. D.H. Biesma, de opleider in die tijd, voor de gegeven tijd. Ook Dr. P.H.Th.J. Slee wil ik hier noemen. Peter, omdat ik je lang niet gesproken heb, wil ik je via deze weg nog uitdrukkelijk danken voor de inspirerende rol die je hebt gespeeld tijdens mijn vooropleiding. Je bezieling zal ik nooit vergeten. Dr. W.J.W. Bos, dank voor het idee van en de begeleiding omtrent het "finometer-manuscript." Gelukkig zagen de Scandinaviërs er uiteindelijk iets in.

Liesbeth Hoegen Dijkhof, jou wil ik graag danken voor het realiseren van de "onderzoekstijd" die ik hard nodig had in de eindfase, en dat in tijden van "assistentenschaarste."

Atticus, thank you for your valuable comments on the introduction and general discussion.

Eefke, bedankt voor je creativiteit in het ontwerp van de afbeelding op de kaft, misschien was ik wat lastig maar het resultaat mag er zijn. Ik citeer je: "The cover was inspired on "Day & Age" by "the Killers", however our "umbrellas" are healers, not killers."

Collega-assistenten Cardiologie, het hebben van plezier in je werk en het onderzoek is gefundamenteerd op de inhoud daarvan maar misschien nog meer op de omstandigheden waaronder je dat kunt doen: de sfeer. Voor de bepaling van dat laatste zijn jullie grotendeels verantwoordelijk. Dank voor alles wat ik met jullie kan delen en voor de lach. Maar let wel, de gaatjes zijn nu gesloten, dus jullie moeten nu echt met iets anders komen.

Vrienden en vriendinnen, jullie zijn verantwoordelijk voor de ontspanning en de steun die ik nodig had tijdens dit werk. De gedachte dat ik wat meer tijd ga hebben om jullie te zien vervult mij met vreugd. Guido, Coen en Frans, mijn allerbeste kameraden: we hebben al veel meegemaakt samen. De befaamde maandagavonddiners in Maastricht vormen de basis voor de stevige vier-eenheid die nu bestaat. Ik denk dat juist ons verschillend karakter ons verbindt en ik hoop, maar weet, dat dat altijd zo zal blijven.

Coen en Frans, mijn geneeskundebroeders, mijn paranimfen, de wetenschap dat jullie op deze dag achter mij staan doet me goed.

Jo en Fien, lieve "schoonouders in spe", het is altijd een genot om bij jullie "thuis te komen" in het zuiden van het land. Daar waar de wortels liggen smaakt toch alles beter. Bedankt voor jullie interesse maar bovenal warmte.

Lieve Jaimie, grote zus, ik heb het gevoel dat we de laatste jaren steeds meer naar elkaar toe groeien. Ik ben enorm trots op wat je doet maar nog meer om wie je bent. Jouw kijk op de dingen in het leven en jouw manier van doen is altijd net dat beetje anders en dat maakt je Jaimie, mijn zus.

Lieve papa en mama, zonder de steun, zorg en liefde die jullie mij geven, had ik dit nooit volbracht. Dit boekje is voor jullie.

De laatste woorden zijn voor mijn allerliefste Christel, klein van stuk maar de allergrootste voor mij. Ik vind het moeilijk de juiste woorden te vinden om iemand die zo dicht bij me staat als jij te bedanken. Het belangrijkste is denk ik dat je er altijd was en bent. En schatje, het is eindelijk af, de computer gaat voorlopig uit, de studiekamerdeur dicht en kom, we gaan iets leuks doen.

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