Closure of the interatrial septum: should we do it?

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Closure of the interatrial septum: should we do it?

Sluiting van het interatriale septum: moeten wij dat doen?

(met een samenvatting in het Nederlands)

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Aan Laura en Bram en …

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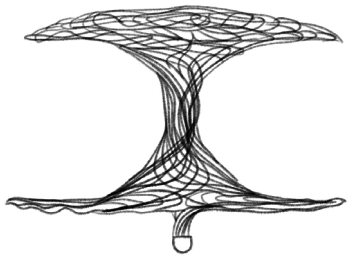

GENERAL INTRODUCTION

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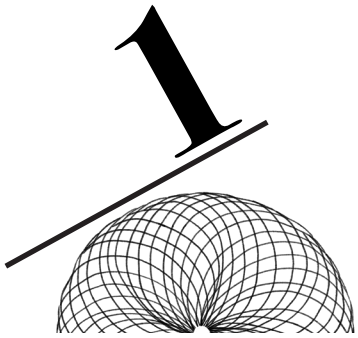

GENERAL INTRODUCTION AND OUTLINE OF THE THESIS

General introduction

Percutaneous closure of a patent foramen ovale (PFO) and atrial septal defect (ASD) is performed frequently. Especially PFO closure has been a subject for discussion but has proven its worth for cryptogenic stroke in patients less than 55 years of age. Closure is also performed for transient ischemic attack (TIA) and sometimes migraine with aura. However, the level of evidence is low for these indications. Many devices have been developed and improved over the years. Some showed to be effective and safe, whereas others are no longer used.
Cardiac imaging during these interventional procedures is essential. Transesophageal echocardiography (TEE) is the gold standard at this moment, but the technique keeps on developing to make it less invasive with a reduction in costs. The micro-probe TEE has been described for several percutaneous procedures for structural heart disease, but not for percutaneous ASD- and PFO closure.

Patent foramen ovale

The tunnel-like opening between the right and left atrium (RA and LA) is called the foramen ovale. This opening between the septum primum and septum secundum plays an important role in the fetal circulation. After birth, the left atrial pressure rises above the right atrial pressure due to a decrease in pulmonary vascular resistance. This causes the foramen ovale to close. Autopsy studies showed that this connection persists in about 27% of the population. This rises up to 50% in patients suffering cryptogenic stroke or transient ischemic attack (TIA) under the age of 55 years, based on echocardiographic findings [1, 2]. When the foramen ovale persists, a right-to-left shunt (RLS) can occur when the pressure in the right atrium exceeds that of the left atrium by Valsalva-like maneuvers such as coughing. A PFO is equally divided between sexes and decreases in prevalence by increasing age [3]. A paradoxical embolism can cross a PFO when an RLS occurs, resulting in an (cerebral) ischemic event. Other possible manifestations of a PFO are migraine, decompression illness or platypnoea syndrome [4-6].
A cryptogenic stroke is defined as a cerebral infarct of undetermined cause after adequate diagnostic investigation [7]. The most probable causes should be investigated and excluded; atrial fibrillation, carotid atherosclerosis, primary cerebrovascular disease and the presence of a coagulation disorders.
After exclusion of these probable causes, a transthoracic echocardiogram (TTE) with agitated saline should be performed to diagnose an RLS in young patients. Agitated saline consists of saline, the patients' blood and air (typically 5-10ml of saline/blood and 0,1-1ml air). These substances are mixed by repeated injection from one syringe to another through a three-way stopcock [8].

An RLS through a PFO is diagnosed when micro-bubbles are detected in the LA within four cycles after RA opacification, with or without a provocative (Valsalva) maneuver. After the RA is filled with agitated saline, the patient is asked to release the strain. The shunt size is measured and graded, based on the maximal amount of bubbles measured on a still frame in the LA. A minimal RLS is defined when 0-30 micro bubbles are present, a moderate RLS with 30-100 micro bubbles and a severe RLS with >100 micro bubbles [9].
Another important echocardiographic finding is an atrial septal aneurysm (ASA). An ASA is the bulging of the atrial septum involving the fossa ovalis region. Using echocardiography, an ASA is defined as more than 10 mm bulging of the atrial septum and is found in 1-2.5% of the general population based on large autopsy studies and population-based studies [3, 10]. The presence of a PFO in combination with an ASA seems to be associated with a larger risk of cryptogenic stroke with a higher annual event rate of 3.9% [1, 10-15].
Other anatomical findings that appear to give a higher risk of cryptogenic stroke are a long-tunnel PFO (≥10mm tunnel length), floppy interatrial septum, presence of a prominent Eustachian valve or Chiari's network and low-angle PFO ($\leq 10^0$ of PFO angle with inferior vena cava). However, only a scarce number of trials with a small population size have studied these anatomical findings [13].
Though, an RLS can be diagnosed by contrast TTE, the best way to visualize the interatrial septum anatomy is by transesophageal echocardiography (TEE). As mentioned above, several anatomical abnormalities can increase the risk of stroke in combination with a PFO and are therefore important to find. Mügge et al. found that TEE is superior to TTE in the diagnosis of ASA as ASA was often missed using TTE [12]. A TEE should therefore be performed not only in all patients with poor image quality on TTE, but in all patients with an RLS to identify high risk PFO's and to assess treatment strategy.
In patients younger than 55 years of age after suffering a cryptogenic stroke in the presence of a (high-risk) PFO, percutaneous closure should be considered.

Percutaneous PFO closure

The best treatment for patients <55 years old after suffering a cryptogenic stroke with a PFO has been a discussion for years. The first large randomized controlled trials (RCT) failed to show the benefit of percutaneous closure over optimal medical treatment because they included patients suffering TIA or without a proven stroke on imaging. Further, some used a proven inferior device and all trials were underpowered. More recent large RCT's showed that percutaneous closure should be preferred in selected patients over medical treatment alone [16-21]. The benefit of closure was even greater in patients with a high-risk PFO (defined as a PFO with at least a moderate RLS and/or the presence of an ASA).

PFO closure device

Julius Friedrich Cohnheim described the first association between stroke and inter-atrial connection in 1877 after necropsy on a young female [22]. It was until 1988 that Lechat et al. called attention for the higher prevalence of PFO in patients less than 55 years of age suffering a stroke [23]. The technique for the first percutaneous PFO closure in 1990 was derived from percutaneous ASD closure; the latter was described for the first time in 1976 [24, 25]. The first device that was used for PFO closure was the Rashkind Clamshell Occluder, which later evolved in the CardioSEAL and at last in the STARFlex device (Nitinol Medical Technologies, Amarillo, Texas, USA) [26]. Other devices were the Sideris Buttoned Device (Custom Medical Devices, Amarillo, Texas, USA), the Angel Wing device (Microvena Corp, Whitebear Lake, Minnesota, USA) and ASDOS (Sulzer Osypka, Germany) but all are already abandoned. The problem with these devices was that they were developed for ASD closure and thus missed the self-centering character of a PFO device [26]. The first self-centering device arrived in 1997 and was called the Amplatzer PFO Occluder (St Jude MedicalTM, Saint Paul, Minnesota, USA). The Amplatzer device was modified for PFO closure and firstly implanted in 1997 [27] and consists of a Nitinol wire mesh double disk with polyester fabric inside, both disks are connected by a small neck [26]. Since then, the Amplatzer device is one of the most extensively used devices and has proven to be safe and effective with a low complication rate (embolization, arrhythmia, recurrent TIA or stroke, device thrombus or pericardial effusion) and low residual shunt rate during follow-up [28-33]. The CardioSEAL device was a double square disk device that consisted of a Nitinol-Cobalt alloy and covered with Dacron but is no longer manufactured. The STARFlex device consisted of the same alloy and was also covered with Dacron. However, this device is also off market due to the increase risk of atrial fibrillation and thrombus formation [34]. For a while, it was thought that a bioabsorbable device would be the perfect device. The Dacron was replaced with an acellular porcine intestinal collagen layer matrix, mounted on the framework. This bioabsorbable device (BioSTAR, NMT Medical, Boston, MA) showed rapid endothelization and complete closure in animal models [35]. However, a relative high percentage of residual shunting was present six months after closure in humans [36]. The device was only partially bioabsorbable so the nitinol microsprings remained in-situ. Although the device is off market, many patients received this device worldwide and little is known about the long-term outcome of this specific device.

The Occlutech Figulla PFO device (Occlutech International AB, Helsingborg, Sweden) has a similar design to that of the Amplatzer device and consists of a unique braiding technique of nitinol wires forming two flexible retention discs that allows forming a single micro screw at the RA disc for connection in older generations and a ball, connected with a bioptome-like safety system in the newer Occlutech Figulla Flex II. There is no LA clamp, minimizing the amount of material implanted. It is a self-centering device

with high flexibility [37]. This device developed over the years and proved to be safe and effective during follow-up [2, 11, 38].
The Gore HELEX Septal Occluder (Helex, Gore, Flagstaff, AZ) consists of a Nitinol single wire frame covered with expanded polyetrafluoroethylene (ePTFE). The device was effective, but technically hard to implant and was replaced by the Gore Cardioform Septal Occluder (Helex, Gore, Flagstaff, AZ). This device consists of a Nitinol frame and is covered with ePTFE as well. The device has a low complication rate, but a relatively high residual shunt rate [16, 19, 39].

PFO and migraine

One of the most common and disabling neurological diseases is migraine. Migraine can be divided in migraine with- and without aura (MA and MA-). Within the normal population, the prevalence of overall migraine rises up to 18.5% and for MA 4.4% [40, 41]. There is a predominance in woman and the peak prevalence in woman is reached in the third decade of life and declines thereafter with age, while the curve for men is virtually flat [42]. Both genetic and environmental factors seem to play an important role in this complex disorder [43]. According to the criteria of the International Headache Society, migraine can be diagnosed using a structured headache questionnaire that is composed in such a way that a neurologist could diagnose and differentiate between MA and MA- [44, 45]. The diagnosis is based on headache characteristics and associated symptoms. A typical migraine attack is unilateral, throbbing and can last from 4- to 72 hours. It can be associated with nausea, vomiting and sensitivity to light, sound and movement. When transient focal neurological symptoms are present (usually visual) MA is present.
The presence of a PFO appears to be more frequent in patients with MA. MA arises at a younger age when severity of the RLS increases, especially if an ASA is also present [46].

Patients with MA appear to be at risk for stroke [47, 48]. A PFO, especially in combination with an ASA, is strongly associated with the occurrence of a cryptogenic cerebral event [1]. Therefore, a PFO might be the link between MA and stroke. However, this remains unclear due to the lack of evidence.
There are some hypothesis and possible explanations for the development of MA. However, the exact pathophysiology is still unknown. The micro-thrombi hypothesis is one of the theories that describes the possible association between a PFO and MA. It is possible that a migraine attack could be triggered by micro-thrombi from the venous circulation crossing a PFO into the systemic- and cerebral circulation. Normally, micro-thrombi from the venous circulation are filtered by the capillary system of the lungs. But, an RLS through a PFO can bypass that filter function [49]. There are studies

that support this hypothesis; a positive effect was found of ablation of atrial fibrillation on migraine symptoms and patients with new-onset migraine had an INR below the therapeutic range [50]. Warfarin lowered the Migraine Disability Assessment Score in another study [51]. There is a hypothesis that suggests that vasoactive agents cross the PFO into the systemic- and cerebral circulation creating vascular instability of the central nervous system causing migraine [52]. However, the evidence of this hypothesis is low.

Atrial septal defect

An atrial septal defect (ASD) is a relatively common cardiac defect and accounts for one third of all congenital heart diseases detected in adults [53, 54]. Essentially, an ASD is a deficiency of the septal tissue. The most common ASD (80% of all) is the secundum type ASD, which is located in the fossa ovalis region. The ostium primum type ASD (10% of ASD's) is located near the atrioventricular valves. The sinus venosous defect is a connection between the atrium (often superior of the septum) due to override of the embryologic sinus venosus and involves usually one of the pulmonary veins. The rarest of all is the unroofed coronary sinus; a connection between the coronary sinus and the left atrium [55].

An ASD causes a left-to-right shunt (LRS) due to the higher pressure in the LA compared to the RA. An RLS can occur transient when the pressure of the RA rises above that of the LA due to Valsalva-like maneuvers such as coughing or exercise.

An ASD is a congenital defect, but the diagnosis is often made in adults due to complications of the shunt, such as right ventricular dysfunction, arrhythmias, pulmonary hypertension or paradoxical embolism. However, many are diagnosed by coincidence. Most of the complications might be prevented by early closure.

Since 1976, when King and Mills described the first percutaneous ASD closure, the procedure and different closure devices have been described extensively in literature. Closure has proven to be safe and effective [2, 24, 29]. Today, one of the most widely used devices is the Amplatzer Septal Occluder with high closure rates and few implant complications. To improve implantation feasibility and lower the risk of device thrombosis, the Occlutech Figulla Septal ASD Occluder without a LA hub was made. Since then, three generations have been developed and have proven to be safe and effective during short- and mid-term follow-up [30, 31, 56]. Safety of a device based on a low complication rate, both peri-procedural and at long-term follow-up (embolization, pericardial effusion, arrhythmia's, recurrent cerebrovascular event, erosion). Efficacy of a device-closure is based on the presence or absence of a residual LRS on echocardiography. One of the possible complications after percutaneous ASD closure is erosion. The incidence has been estimated to be 0.1% using the Amplatzer device. None of the studies using the Occlutech device described cases of erosion [57]. It is possible that the

increased flexibility of the Occlutech device lowers the chance of erosion.
Other devices, such as the Cardioseal/Starflex and the Gore Helex/Cardioform Septal Occluder, also showed a high safety and efficacy profile, however, mainly during mid-term follow-up [32, 33, 58-60].

Embolization occurred with the Helex Septal Occluder in 1.5% and 0% when the Cardioform Septal Occluder is used, according to larger studies [59, 60]. Though device fracture was seen in 11.7% when using the Helex Septal Occluder, none of the patients had symptoms or needed further treatment [23]. There were no clinically significant residual LRS found in these patients during 60-months follow-up. There was a residual LRS in 7.2% of the patients using the Cardioform. However, there was only a clinically significant LRS in 0.4%. Device fracture was seen in 6.1% without the need for re-intervention [60]. Important to realize is that these studies also included children, making it difficult to compare these results with adult-only studies.

Transesophageal echocardiography versus micro-probe transesophageal echocardiography

Percutaneous interventions for structural heart disease can only be performed successfully when using cardiac image guiding. TEE proved to be safe for these procedures and important during ASD- and PFO closure [61-64]. Unfortunately, the TEE probe causes inconvenience for the patient due to its relatively large size making general anaesthesia in most cases necessary. Although very rare, trauma to the oropharynx, oesophagus and stomach can occur.
A smaller probe, the microprobe TEE (micro-TEE), was developed to overcome these downsides. Since 2009, micro-TEE showed to be safe and effective during percutaneous cardiac interventions in neonates and infants and more recently in adults as well [65-69]. The probe can be introduced through the nose or mouth.
Nijenhuis et al. studied the difference between TEE, micro-TEE and intracardiac echocardiography (ICE). Although image quality was comparable between micro-TEE and ICE, micro-TEE had a much wider field of view compared to ICE. Another important difference between TEE and micro-TEE is that micro-TEE has no three-dimensional view possibilities, which could help in sizing the defect and positioning the device. Besides the narrow field of view, ICE needs central venous access, which is much more invasive than micro-TEE with a higher complication rate [68].
Without general anaesthesia, spontaneous respiration is possible, lowering the risks for patients with pulmonary comorbidities, and decrease the hospitalization costs.
Although local anaesthesia seems to be ideal, there are some downsides as well. Because patients are awake, there is a higher chance of stress, anxiety and discomfort of the

procedure itself. Studies that compared general- and local anaesthesia during transcatheter aortic valve implantations (TAVI) found no difference in in-hospital and 30-days safety [70]. Comparing general anaesthesia and conscious sedation during TAVI procedures showed a reduction is hospitalization duration, but not in total costs [71]. Other, non-cardiac surgery studies did find a significant reduction in costs comparing local- and general anaesthesia [71, 73]. The safety and efficacy of micro-TEE compared to TEE during percutaneous ASD- and PFO closure has not been described in literature.

Aims and outline of the thesis

This thesis concerns percutaneous closure of an ASD and PFO, especially the long-term follow-up of the Occlutech device for ASD- and PFO closure is being discussed.
In chapter 2, the long-term efficacy of the bioabsorbable BioSTAR device for percutaneous PFO closure is examined. Chapter 3 discusses the efficacy and safety of the Occlutech PFO device during very long-term follow-up. The association between MA, PFO anatomy and shunt size is studied in chapter 4. We present our point of view on PFO closure comparing all large randomized trials in chapter 5 and show a case of re-closure of a PFO with two different devices in chapter 6.
The long-time follow-up of different devices after percutaneous ASD closure is studied in chapter 7. Chapter 8 contains the very long-term follow-up data of the Occlutech ASD device. In chapter 9, a rare case of a complete unroofed coronary sinus is presented. Finally, in chapter 10, we compare the use of TEE and micro-probe TEE guidance during percutaneous ASD- and PFO closure.

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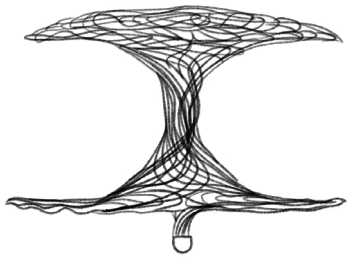
II

part II



PERCUTANEOUS PATENT FORAMEN OVALE CLOSURE

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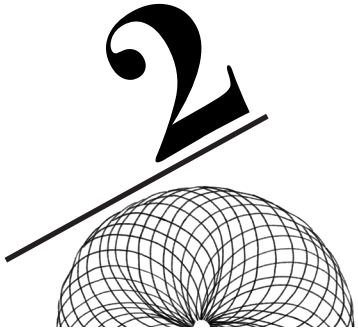

PERSISTENT HIGH RESIDUAL SHUNT RATE 2 YEARS AFTER PATENT FORAMEN OVALE CLOSURE USING A BIOABSORBABLE DEVICE

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A relatively high percentage of residual shunting was present 6 months after patent foramen ovale (PFO) closure using a bioabsorbable device [1]. The presence of moderate to severe residual shunt might increase the risk of cryptogenic stroke [2, 3]. Despite the fact that the device is currently off the market, many patients were treated worldwide, and little is known about the long-term efficacy and safety. We report the long-term safety and efficacy of the bioabsorbable device used for percutaneous PFO closure.

As reported previously, between November 2007 and January 2009, all consecutive patients who underwent a percutaneous closure of a symptomatic PFO with a bioabsorbable device (Biostar, NMT Medical, Boston, Massachusetts) were included [1]. Intracardiac echocardiography was used during most procedures. After discharge, routine follow-up was scheduled at 1, 6, 12, and 24 months, using contrast transthoracic echocardiography (cTTE). The residual shunt rate was classified as none, minimal, moderate, and severe, as described previously [1]. Continuous variables with normal distribution are presented as mean $\pm$SD. Residual shunt sizes at different time points were compared using the Wilcoxon signed rank test. Univariate statistical analysis, using a Cox proportional hazards model, was used to identify risk factors for residual shunting and adverse events after PFO closure. All statistical analyses were performed using SPSS software version 17.0 (SAS Institute, Cary, North Carolina).

Percutaneous PFO closure with the bioabsorbable device was performed in 62 consecutive patients (55% women; mean age: 47.7$\pm$11.8 years). Ninety-four percent of the patients had experienced a cryptogenic stroke or transient ischemic attack (TIA) and were referred by a neurologist. Eight patients (12.9%) had a history of supraventricular tachycardia (SVT). These data were previously reported [1]. In summary, device implantation was successful in 60 patients (96.8%), and there were complications in 2 patients (3.2%). A minimal vascular surgical intervention was needed to retrieve the device at the femoral vein in both. A small groin hematoma was present in 6 patients (9.7%). There were no procedure-related deaths, major adverse cardiac events, or stroke between discharge and 2-year follow-up. In 7 patients (11.3%), new SVTs were diagnosed in the first month after closure, and 1 (1.6%) was diagnosed between 1- and 6-month follow-up. Patients with known rhythm disorders did not report an increase in SVT episodes after PFO closure. A TIA recurred in 2 patients, both within the first year after closure. No device-related complications or recurrent ischemic cerebral events occurred between 12- and 24-month follow-up.

One day after closure, a residual shunt was present in 60% (36 of 60 patients): minimal in 31.7%, moderate in 20%, and severe in 8.3% of patients. At 12-month follow-up, in total, 25% of patients (14 of 56 patients) had a residual shunt: minimal in 17.9%, moderate in 5.4%, and severe in 1.8% (p=0.76 compared with 6-month follow-up as reported previously) [1]. The 4 patients missing from this follow-up had no residual shunt at 6months. At 24-month follow-up, 30.9% (17 of 55 patients) had a residual shunt (21.8% minimal, 9.1% moderate, and 0.0% severe; p=0.37) compared with

12-month follow-up. At 24-month follow up, cTTE was not performed in 4 patients, and 1 patient was lost to follow-up. Three of these 4 patients were the same as described at 12-month follow-up. The other 2 patients had no residual shunt at 12-month follow-up. All these patients had no new symptoms or complications at 24-month follow-up. Between 12- and 24-month follow-up, the residual shunt size remained the same in 8 patients and both increased and decreased by 1 level in 1 patient. Three patients with a minimal residual shunt at 12-month follow-up had no shunt at 24-month follow-up. However, 6 patients without a shunt at 12-month follow-up experienced a minimal residual shunt at 24-month follow-up. No predictors of residual shunt could be identified. Efficacy data are shown in Figure 1.

The bioabsorbable device has a high residual shunt rate of 30%, even 2 years after closure. This implies that this device was insufficient for percutaneous closure of a PFO, and long-term follow-up seems to be necessary.

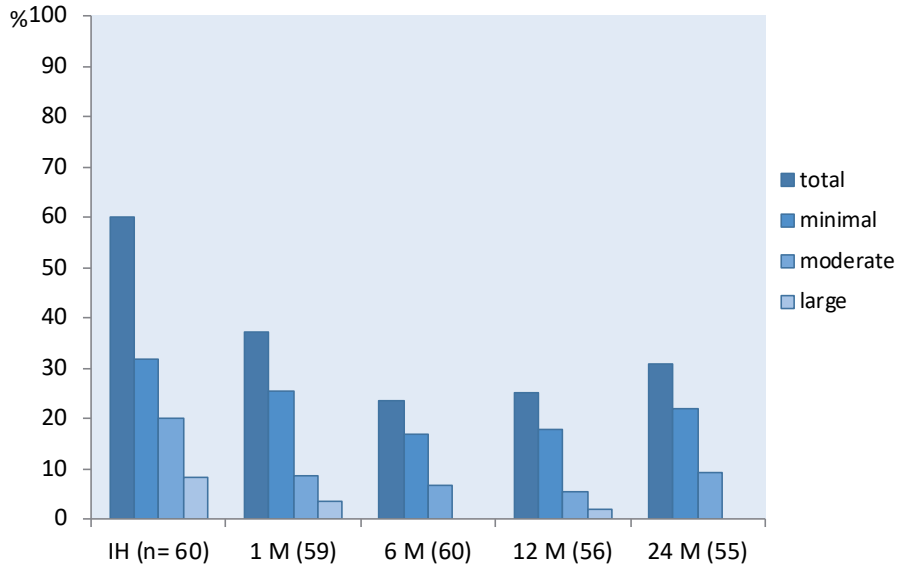

Figure 1. Percentage of residual shunting diagnosed by cTTE during follow-up

During follow-up, contrast transthoracic echocardiography (cTTE) was used to grade residual shunting as none, minimal, moderate, or severe. One day after closure, a residual shunt was present in 60%: minimal in 31.7%, moderate in 20%, and severe in 8.3%. At 12-month follow-up, 25% of patients had a residual shunt: minimal in 17.9%, moderate in 5.4%, and severe in 1.8% (p =0.76 compared with 6-month follow-up). At 24-month follow-up, 30.9% had a residual shunt: minimal in 21.8%, moderate in 9.1%, and severe in 0.0% (p=0.37 compared with 12-month follow-up). A high residual shunt rate is still present 2 years after closure using a bioabsorbable device. Long-term follow-up seems to be necessary. IH . in hospital; M . months.

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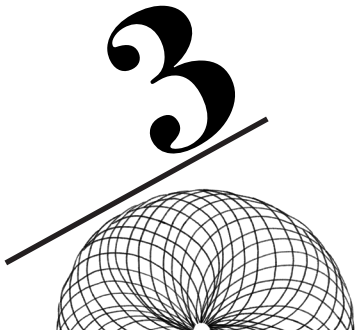

PERCUTANEOUS PATENT FORAMEN OVALE CLOSURE USING THE OCCLUTECH FIGULLA DEVICE: MORE THAN 1300 PATIENT-YEARS OF FOLLOW UP

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Abstract

Objective: To evaluate the safety and efficacy of the Occlutech patent foramen ovale (PFO) closure device at long-term follow-up (FU).

Background: The Occlutech Figulla Occluder device has been proven safe and effective six-months after percutaneous PFO closure. We describe the safety and efficacy after more than 1300 patient-years of FU.

Methods: All consecutive patients who underwent PFO closure between October 2008 and December 2015 were included. All complications, residual stroke and transient ischemic attack (TIA) were registered. Residual right-to-left shunt (RLS) was diagnosed using contrast transthoracic echocardiography and graded as minimal, moderate or severe.

Results: In total, 250 patients (mean age 53.5±10.7 years, 46.8% female) underwent percutaneous PFO closure using the Occlutech device. The mean FU was 5.9±1.8 years, a total of 1345 patient-years. TIA or stroke was the main indication for closure (89.6%). The initial success rate, defined as successful implantation, was 100%, no major complications occurred. Minor complications were inguinal haematoma in 16 patients (6.4%), pericardial effusion without the need for intervention in 1 patient (0.4%) and a supraventricular tachycardia in 1 patient (0.4%). A moderate or large shunt at one-year follow up was present in 5.9%. A cerebrovascular vascular event occurred in 2.0% at 1-year follow-up (four TIA, one stroke) and in 7.4% at long-term FU (nine TIA, eight stroke). The total cerebrovascular event rate (TIA and CVA) was 0.02% per patient-year of FU, with a stroke rate of 0.01%.

Conclusion: The Occlutech device appears to be safe at long-term follow-up with a very low annual cerebrovasculair event rate and a low moderate to large shunt rate at 1-year FU.

Introduction

Patent foramen ovale (PFO) is a common intracardiac finding that is detected in 27% of the general population and it's prevalence rises up to 50% in patients suffering cryptogenic stroke or transient ischemic attack (TIA) under the age of 55 years [1, 2]. Percutaneous PFO closure has proven to be safe and effective using different devices, including the Occlutech Figulla device [2, 3].
Three randomized controlled trials (RCT) were published in 2017 comparing percutaneous PFO closure using multiple devices versus medical treatment in patients suffering a cryptogenic cerebral event. All three RCT's showed a significant benefit for percutaneous closure over medical treatment [4-6].
Though, the short- and mid-term follow-up (FU) showed good results for safety and efficacy, little is known about the long-term FU using the Occlutech Figulla device. We describe the safety and efficacy of percutaneous PFO closure using this device after more than 5 years FU.

Methods

Population

All consecutive patients between October 2008 and December 2015 who underwent percutaneous PFO closure in the St. Antonius Hospital, Nieuwegein, were included. In all, the Occlutech Figulla device (Occlutech®) was implanted. Firstly, the neurologist screened all patients with a stroke or TIA, including vascular imaging of the cerebral and carotid arteries, laboratory tests and at least 48 hr of cardiac rhythm monitoring. When no cause was found (cryptogenic stroke/TIA), the patient was referred to the cardiologist. Next, a cTTE was performed at the outpatient clinic in combination with a visit to the interventional cardiologist or congenital cardiologist both specialized in PFO closure. If necessary, a transoesophageal echocardiogram was performed. When a PFO was diagnosed, percutaneous closure was discussed with the patient. This study was approved by the local ethical committee (registration number R&D/Z16.054).

Device

The Occlutech Figulla PFO device consists of a unique braiding technique of nitinol wires forming two flexible retention discs that allows forming a single microscrew at the right atrial disc for connection. There is no left atrial clamp, minimizing the amount of material implanted. It is a self-centering device with high flexibility [7]. Figure 1 shows the Occlutech device during fluoroscopy and TEE.

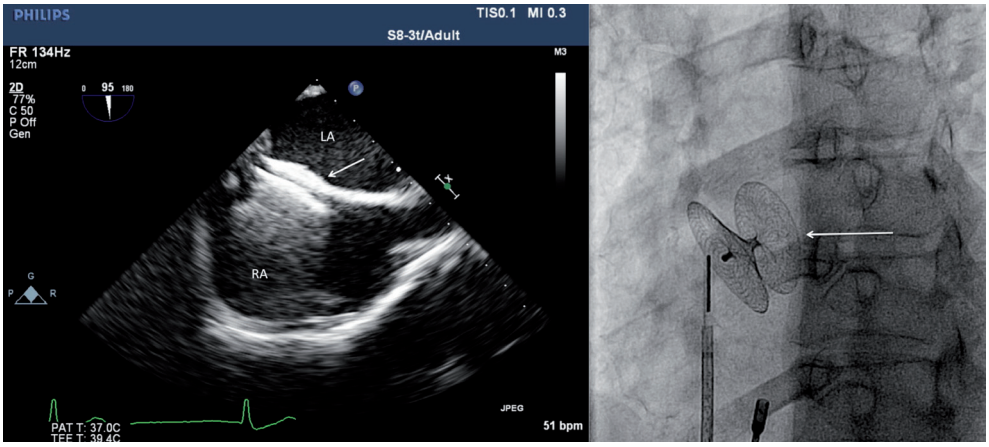

Figure 1: The Occlutech Figulla PFO device positioned between the interatrial septum during transesophageal echocardiography and fluoroscopy.

Closing procedure

Local anaesthesia and intracardiac echocardiography (ICE) or TEE was used during the procedure as described previously by Van den Branden et al [3]. Depending on the morphology of the PFO, device size was chosen by the interventional cardiologist. The initial success rate was defined as successful implantation.

Follow-up

All complications were registered. At discharge, routine follow-up was scheduled at 1, 6, 12 and 24 months, using cTTE in rest and after a provocative Valsalva manoeuvre. After the right atrium was filled with agitated saline, the patient was asked to release the Valsalva. A right-to-left shunt (RLS) through a PFO was diagnosed when micro bubbles were detected in the left atrium within four cycles after right atrial opacification. The size of the RLS was classified by the number of bubbles in the left ventricle on a still frame and graded as minimal (<30 bubbles), moderate (30-100 bubbles), and large (>100 bubbles). Successful closure was defined as the presence of no RLS at FU. Long-term FU information was obtained by interviewing patients by telephone.

Statistical analysis

Descriptive statistics were used for patients' characteristics. Continuous variables with normal distribution are presented as mean ± standard deviation. All statistical analyses were performed using SPSS software (version 24.0 for Windows). The cerebrovascular event rate was assessed using the Kaplan-Meier curves analysis. It was defined as the date of closure to the occurrence of a cerebrovascular event. Further, the cerebrovascular event rate was calculated and presented as percentage per patient-year FU.

Results

Patient characteristics

Between October 2008 and December 2015, percutaneous PFO closure was performed in 250 patients (mean age 53.5 ± 10.7 years, 46.8% female) using the Occlutech device. The main indication for closure was TIA or stroke (89.2%). Besides peripheral emboli (4.8%) and migraine (1.2%), other less common indications were: decompression disease, persistent hypoxemia and a reclosure after using the bioabsorbable device. Baseline characteristics and indication for closure are summarized in Table 1.

Table 1. Baseline characteristics

Number	250
Age (years)	53.5 ± 10.7
Female, n (%)	117 (46.8%)
BMI (kg/m^2)	25.8 ± 4.0
Systolic blood pressure (mmHg)	129.7 ± 14.4
Diastolic blood pressure (mmHg)	79.8 ± 7.9
Risk factors and co-morbidities, n (%)	
Smoking	55 (22.0%)
Diabetes	8 (3.2%)
Arterial hypertension	65 (26.0%)
Hypercholesterolemia	73 (29.2%)
CAD	6 (2.4%)
History of SVT	7 (2.8%)
Indication for closure, n (%)	
Cryptogenic TIA/stroke	224 (89.6%)
Peripheral emboli	12 (4.8%)
Migraine	3 (1.2%)
Other	11 (4.4%)
TTE characteristics, n (%)	
RLS after Valsalva	250 (100%)
Spontaneous RLS	102 (40.8%)
Floppy/ASA	130 (52.0%)
Follow-up (years)	5.9±1.8

Data are presented as mean ± SD or number (percentage)
BMI, Body Mass Index, CAD, coronary artery disease; SVT, supraventricular arrhythmia; TIA, transient ischemic attack; RLS, right-to-left shunt; ASA, atrial septal aneurysm

Procedural outcome

Most procedures were performed under local anaesthesia (98.4%) and ICE monitoring (98%). All devices were implanted successfully and no procedural complications occurred. In-hospital complications occurred in 18 patients (7.2%). In total, 16 patients (6.4%) had a minimal inguinal haematoma. No surgery or blood transfusion was necessary. One patient (0.4%) suffered a new-onset supraventricular tachycardia (SVT) and one patient (0.4%) had pericardial effusion without the need for intervention.

Follow-up

Long-term FU data were available in 228 patients (91.2%). During a mean follow up of 5.9 years, a total of 1345 patient-years, a TIA occurred in 13 patients, a rate of 0.01% per patient-year. Nine patients suffered a stroke; a stroke rate of 0.01% per patient-year. In total, the annual rate of a thrombo-embolic event during follow up after percutaneous PFO closure was 0.02% per patient-year. The Kaplan-Meier curve regarding the cerebrovascular event rate is shown in Figure 2.

Within the first 12-months, recurrent thrombo-embolic events occurred in five patients (2.0%, four TIA). cTTE showed a residual RLS in two of these patients (one minimal and one moderate). The patient with the moderate RLS was a 48-year old female with a recurrent TIA 4 months after closure and was already using oral anticoagulation. At 12-months FU, this patient suffered multiple TIA's, without a residual RLS or device thrombus. A recurrent stroke occurred in one patient (0.4%). This 64-year old patient was already using double antiplatelet therapy at that moment and had no RLS or device thrombus. None of these patients had a history of SVT, nor did occur at later FU.

Data regarding residual shunting and new SVT are summarized in Table 2. The closure was successful in 67.9% 1 year after closure, with a moderate or large shunt in 5.9%. Within the first 12 months, two patients (0.9%) died. One patient was known with pulmonary hypertension, pulmonary fibrosis and emphysema and died due to secondary complications of these diseases. Latest cTTE showed no residual RLS. The other patient died of an unknown cause, however, the partner was contacted and mentioned that the patient died due to a cause; that was unrelated to the closure. However, because no autopsy was performed, a device related cause could not be fully excluded.

After the first year, nine patients suffered a TIA (3.9%) and eight patients a stroke (3.5%). In two of these patients (one TIA, one stroke) the neurologic event was probably caused by a dissection of the carotid artery. One patient, without a residual RLS at FU, suffered a TIA after non-cardiac surgery. In the other cases, no cause was found. Though, a minimal residual RLS was found in two patients (one TIA, one stroke), none was found in the others. The mean duration to onset of TIA after closure was 2.5 $\pm$ 1.7 years and duration to onset of stroke was 4.1 $\pm$ 2.4 years. None of these patients had a history of SVT.

New-onset SVT's occurred in six patients (2.6%). In total, four patients (1.8%) died at long-term FU (all within 30 months). Three died due to a malignancy and one to

an unknown cause. As no autopsy was performed on the patient who died from an unknown cause, a device related cause could not be excluded. In total, 14 patients (5.6%) were lost to FU.

The thrombo-embolic event rate and new-onset SVT rate are presented in Table 2.

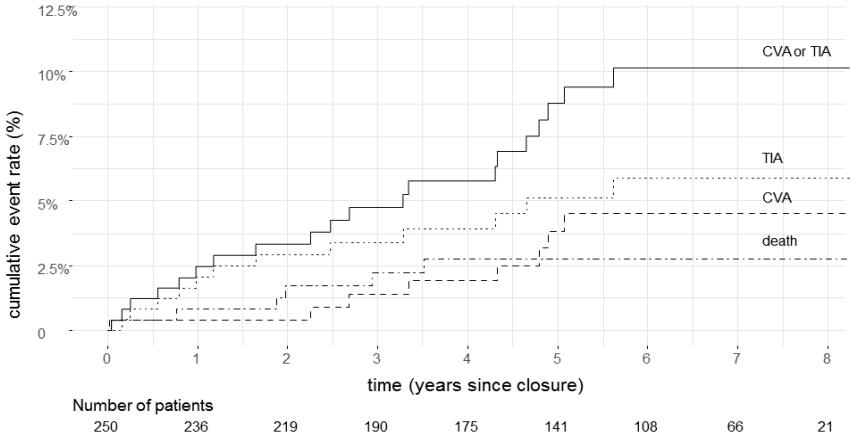

Figure 2: Kaplan Meier of cerebrovascular events after patent foramen ovale closure using the Occlutech device.

Table 2. Efficacy and safety during follow-up

	≤12 months follow-up	>12 months follow-up
Number, n	250	228
Complications, n (%)		
TIA	4 (1.6%)	9 (3.9%)
Stroke	1(0.4%)	8 (3.5%)
SVT	9 (3.6%)	6 (2.6%)
TTE available, n	187 (82.0%)	0
RLS, n (%)		
No shunt	127 (67.9%)	-
Minimal	49 (26.2%)	-
Moderate	8 (4.3%)	-
Severe	3 (1.6%)	-

TIA, transient ischemic attack; SVT, supraventricular tachycardia; TTE, transthoracic echocardiography; RLS, right-to-left shunt

Discussion

Percutanous PFO closure using the Occlutech device is safe and effective during a follow up of more than 1,300 patient-years with a low rate of cerebrovascular events.

Complications

The complication rate after percutaneous PFO closure with the Occlutech device varies between 0% and 15% [2, 7, 8]. Krizanic et al. described successful percutaneous PFO closure in 35 patients without any major complications [7]. Saguner et al. described periprocedural complications in three patients (15%) [8]. The relatively wide range in complication rate of these studies is probably due to the small population size. Recently, two large RCTs and one long-term FU study of an earlier published trial were published showing a major peri-procedural event rate up to 5.9%, though, none of the studies used the Occlutech device [6, 9, 10]. Our study showed no major peri-procedural events, proving that implantation of the Occlutech device is safe.

Recurrent thrombo-embolic events

In literature, the recurrent thrombo-embolic event rate is different between studies (0.0-5.0%) [2, 6, 8-11].

Aytemir et al. described PFO closure in 221 patients using the Occlutech device in 57%, but also the BioSTAR in 9.5%, with a median FU of 30 months [11]. Three patients suffered a recurrent TIA (1.3%) and one patient a recurrent stroke (0.45%). It is unclear which device was used in these specific patients. This is important because the BioSTAR has proven to be insufficient for closure [12]. There was one patient (5%) with a recurrent TIA 10 minutes after implantation in the study by Saguner et al. and none in a study by Krizanic et al. with 6-months FU [2, 8]. Both studies had a smaller population and a shorter FU time when compared to our study making it difficult to compare.

The more recent published trials have a longer FU time and are therefore more comparable to our results. However, different devices were used. Mas et al. described 238 patients that underwent percutaneous PFO closure within the CLOSE trial of whom only 15 patients (6.3%) received the Occlutech PFO device. There were no recurrent strokes, but eight patients (3.4%) suffered a recurrent TIA after closure. It is unclear which devices were used in these patients. In total, 6.0% suffered a stroke in de medical treatment group [9].

There were six patients (1.4%) in the study by Sondergaard et al. who suffered a recurrent clinical ischemic stroke after closure and 5.4% in the medical treatment group during a median FU of 3.2 years after PFO closure using the Helex septal occluder/Cardioform septal occluder [10].

The long-term FU study of the RESPECT trial by Saver et al. using the Amplatzer

device described a recurrent stroke in 18 patients (3.6%) and in 5.8% in the medical treatment group [6].
As described above, in our study nine patients (3.9%) suffered a recurrent stroke after almost 6 years of follow up (1,345 patient years), resulting in a low annual stroke rate of 0.01% per patient year. This is comparable to the closure group in the trials mentioned above. The medical treatment group in these trials show a significant higher stroke rate (5.4-6.0%) when compared to our closure group (3.9%). Moreover, the follow up time in our study was significantly higher in comparison to the studies mentioned above. None of the patients with a cerebrovascular event at FU had a moderate or severe RLS at 12-months FU. A minimal shunt was found in just one patient suffering a stroke after closure. This makes it unlikely that these events were related to (unsuccessful) PFO closure.

Residual right-to-left shunts

In literature, the residual shunt rate after PFO closure ranges from 8% to 21% [13-15]. Little is known about the residual shunt rate when using the Occlutech device, especially at long-term FU.
There were no residual shunts observed at FU in the study by Aytemir et al. using only color-Doppler to evaluate the residual shunt, which probably underestimated the shunt rate [2]. Saguner et al. found a residual shunt rate of 39% (minimal + moderate) at 6-month FU. Two of these patients needed re-closure with a second device [8]. Krizanic et al. found a moderate residual shunt was present in 3.7% at 6 months FU [7]. A more recent study by Hildick-Smith et al. described 100 patients that received the Occlutech device and found at least a moderate shunt of 20.7% at 6-months FU [15].
When minimal and moderate shunts are excluded in our study, a residual severe RLS was present in 1.6% 12 months after closure. However, we found a minimal residual RLS in 26.2% of the patients at 12 months follow up. This is a relatively large number of patients when compared to literature. Shah et al. described percutaneous PFO closure in 880 patients using the Amplatzer PFO Occluder. There was a residual RLS in 8.4% at 11-months FU. However, only patients with a previous residual RLS underwent cTTE at FU [16]. Though, it is possible that the Valsalva manoeuver was not performed correctly during the first study and that an RLS can be found later at FU. Cheli et al. described 120 patients after percutaneous PFO closure using the Amplatzer PFO Occluder. All patients underwent contrast transcranial Doppler at FU. There was a residual RLS in 29% at 1 year and 17% at 5-years FU [17]. These results are comparable to our findings. A potential cause of a higher residual RLS rate after closure using the Occlutech compared to the Amplatzer device could be the different device design or difference in technique to diagnose the residual shunt. The smaller amount of material of the Occlutech device could be associated with less defect closure. The more flexible structure could create more mobility between the device and the interatrial septum.

We found an overall RLS rate of 32.1% at 12-months FU. After excluding minimal shunts, the residual RLS rate 1 year after closure is 5.9%. Unfortunately, no data were available about the residual RLS rate at long-term FU.

Arrhythmias

New onset supraventricular arrhythmias are a relatively common complication after PFO closure, especially when compared to medical therapy, and the incidence rises up to 6.6% in literature [6, 9, 10].

Aytemir et al. described three patients (1.3%) who developed a supraventricular arrhythmia at FU using the Occlutech device [11]. There were none in the study by Saguner et al. and one (1.1%) in the study by Hildick-Smith et al. [8, 15]. In the more recent trials, SVTs occurred between 0.6% and in 6.6% [6, 9, 10].

In all studies, new onset SVTs were diagnosed according to patient's symptoms or during routinely physical examination or ECG at the outpatient clinics, making it hard to know the exact incidence. In our study, new onset SVTs were found in 15 patients (6.6%) of which 6 (2.6%) occurred more than 2 years after closure. When compared to literature, our findings are, though within a wide range, similar.

Limitations

There are several limitations in our study. First, it was an observational single center study, not comparing the Occlutech device to other devices. Second, we used contrast TTE at FU for detecting residual shunts while TEE is the gold standard. Furthermore, no data about residual RLS were available at long-term FU. As 5.6% of the patients were lost to FU, it is unclear whether the event rate is actually higher. Finally, our patients were referred for percutaneous closure creating a possible selection bias.

Conclusion

At long-term FU, the Occlutech device appears to be safe for percutaneous PFO closure with a very low annual cerebrovascular event rate and a low moderate to large shunt rate at 1-year FU.

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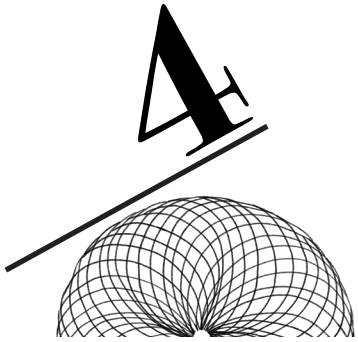

PATENT FORAMEN OVALE WITH ATRIAL SEPTAL ANEURYSM IS A STRONGLY ASSOCIATED WITH MIGRAINE WITH AURA: A LARGE OBSERVATIONAL STUDY

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Abstract

Background: A patent foramen ovale (PFO) with atrial septal aneurysm (ASA) has been identified as a risk factor for cryptogenic stroke. Patients with migraine with aura (MA) appear to be at risk for silent brain infarction, which might be related to the presence of a PFO. However, the association between MA and PFO with ASA has never been reported. We examined this association in a large observational study.

Methods and Results: Patients (>18 years) who underwent an agitated saline transesophageal echocardiography (cTEE) at our outpatient clinics within a timeframe of four years were eligible to be included. Before cTEE they received a validated headache questionnaire. Two neurologists diagnosed migraine with or without aura according to the International Headache Criteria.

A total of 889 patients (mean age 56.4 ± 14.3 years, 41.7% women) were included. A PFO was present in 23.2%, an isolated ASA in 2.7%, and a PFO with ASA in 6.9%. The occurrence of migraine was 18.9%; the occurrence of MA was 8.1%. The prevalence of PFO with ASA was significantly higher in patients with MA compared to patients without migraine (18.1% versus 6.1%; OR 3.72, 95% CI 1.86-7.44, $P<0.001$). However, a PFO without ASA was not significantly associated with MA (OR 1.50, 95% CI 0.79-2.82, $P=0.21$). Interestingly, a PFO with ASA was strongly associated with MA (OR 2.71, 95% CI 1.23-5.95, $P=0.01$).

Conclusion: In this large observational study, PFO with ASA is significantly associated with MA only. PFO closure studies should focus on this specific intra-atrial anomaly.

Key Words: Cerebrovascular disorders, echocardiography, heart septal defects

Introduction

Migraine is a common neurological disorder and has been acknowledged as one of the most important causes of disability burden.[1] The prevalence of migraine in the population is 18.5% and for migraine with aura (MA) 4.4%.[2] The peak prevalence for woman is reached in the third decade of life and thereafter declines with age, while the prevalence for men is virtually flat.[3] Migraine seems to be a complex disorder in which both genetic and environmental factors play an important role.[4]

The patent foramen ovale (PFO) is a slitlike inter-atrial opening which is present in about 27% of the general population.[5] It is one of the major causes of a cardiac right-to-left shunt (RLS). An atrial septal aneurysm (ASA) is a congenital bulging of the atrial septum involving the fossa ovalis region. An ASA has been found in 1-2.5% of the general population in large autopsy studies and population-based studies using echocardiography.[5, 6]

The presence of PFO and ASA has been associated with cryptogenic stroke.[7, 8] Patients with migraine with aura (MA) appear to be at risk for stroke[9, 10], which might be related to the presence of a PFO. However, the association between MA and PFO with ASA has never been reported. [4]

We investigated the association of the presence of PFO with ASA with the occurrence of MA in patients who underwent an agitated saline transesophageal echocardiography (cTEE) at our outpatient clinics.

Methods

Study design and population

All consecutive patients (>18 years) who underwent a cTEE at the outpatient departments of the University Hospital Gasthuisberg, Leuven, Belgium and the St. Antonius Hospital, Nieuwegein, the Netherlands within a timeframe of four years were eligible to be included in the study. All patients received a Dutch headache questionnaire for the diagnosis of migraine. The following patients were excluded: patients who did not undergo an agitated saline examination; patients who did not complete the headache questionnaire or patients with an atrial septal defect (ASD). The patients' medical history was retrieved from the medical records. Informed consent was obtained from all patients and the ethical committees of the participating centers approved the study.

Transesophageal echocardiography

An ultrasonography system with a 5-MHz transducer was used for transesophageal echocardiography (TEE) examinations. The agitated saline examination was performed by injection of a bolus of agitated saline solution into a peripheral vein with and without

a provocative manoeuvre during TEE. A RLS through a PFO was diagnosed when micro bubbles were detected in the left atrium within four cycles after right atrial opacification with or without a provocative maneuver. The provocative maneuver, was performed by asking the patient to stop breathing, close their mouth and nose, and strain. After the right atrium was filled with agitated saline, the patient was asked to release the strain. The shunt size was measured as previously published and graded as no – minimal – moderate or large, based on the maximal amount of bubbles measured on a still frame. [11] An atrial septal aneurysm (ASA) was defined as a bulging of the atrial septum of at least 10 mm beyond the plane of the atrial septum into either the right or left atrium. Experienced, independent physicians who were unaware of the presence of migraine performed and reviewed the echocardiographic examinations.

Diagnosis of migraine

As described previously [12], a structured headache questionnaire was composed in such a way that a neurologist could diagnose MA and migraine without aura (MA-), according to the criteria of the International Headache Society.[13] All patients received the Dutch questionnaire before undergoing cTEE. Two independent neurologists, who were blinded to the patients' files and cTEE results, diagnosed MA and MA-. When there was not a perfect agreement, both neurologists discussed the case to reach consensus.

In addition, in patients with MA, headache characteristics were analysed by means of the headache questionnaire. First, the duration of headache was recorded. Second, headache severity was measured on a scale ranging from 0 (no pain) to 10 (very severe pain). Third, the frequency of headache attacks was noted.

Statistical analysis

Descriptive statistics were used to describe patient characteristics. Continuous variables were tested on normality and presented as mean ± standard deviation. Median, first and third quartiles (IQ1 and IQ3) were used when normal distribution was absent. Percentages were used to report categorical variables. Univariate and multivariate logistic-regression analyses were used to estimate the unadjusted and adjusted odds ratios (OR) and the corresponding 95% confidence intervals (CI). In the multivariate analyses the most significant, clinical relevant univariate variables were included. Kruskal Wallis tests were performed to analyze any association between headache characteristics and the atrial septal anatomic variables in patients with MA. Inter-observer reliability for the diagnosis of migraine was evaluated by calculating the Kappa coefficient. The Mann-Whitney test was performed to analyse any association between having a PFO with ASA and the degree of right-to-left shunting.

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 22.0 for Windows).

Results

Patient characteristics

Within the time frame, 2349 patients underwent a TEE at the outpatient departments of the participating centers. Patients who did not fully complete the headache questionnaire or did not understand the Dutch questionnaire (1190), patients who did not undergo an agitated saline examination (213), and patients with an ASD (57) were excluded. In total 889 (38%) patients (mean age 56.4±14.3 years, 41.7% women) were included in the present study. A flowchart of the patient inclusion is depicted in Figure 1. The patient characteristics are summarized in Table 1.

A PFO was found in 23.2% of the cases; the prevalence of an isolated ASA was 2.7%. The prevalence of other atrial septal abnormalities and the occurrence of migraine are shown in Table 1. The Kappa coefficient for inter-observer reliability for the diagnosis of migraine was 0.77 (P<0.001).

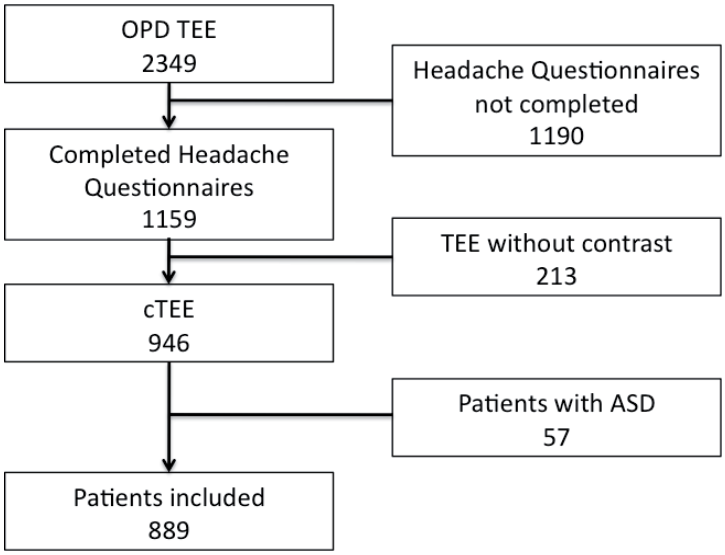

Figure 1. Flowchart of Patient Inclusion.

OPD, outpatient department; TEE, transesophageal echocardiography; cTEE, transesophageal echocardiography with agitated saline; ASD, atrial septal defect.

Table 1. Patient Characteristics, Inter-atrial Septal Anatomy and Occurrence of Migraine (MA and MA-).

	Patient Population (n=889)
Patient Characteristics	
Age (years) ± SD	56.4 ± 14.3
Women, n (%)	371 (41.7)
Mean BMI (kg/m^2) ± SD	26.2 ± 4.5
History	
Stroke or TIA (%)	34.7
CAD (%)	14.2
Diabetes (%)	7.5
Hypertension (%)	34.0
Hypercholesterolaemia (%)	34.3
Smoking (%)	31.4
Atrial fibrillation (%)	32.8
Medication	
Aspirin (%)	32.8
Warfarin (%)	31.6
Betablocker (%)	42.0
Indication for TEE	
Suspicion of endocarditis (%)	3.1
Evaluation of valve abnormalities/prosthesis (%)	18.9
Evaluation of cardio-embolic source (%)	45.1
Evaluation of atrial thrombi pre-PVI/ECV (%)	20.2
PFO on cTTE (%)	8.5
Other (%)	4.2
Inter-atrial Septal Anatomy	
No PFO, no ASA, n (%)	659 (74.1)
Isolated PFO, n (%)	145 (16.3)
Isolated ASA, n (%)	24 (2.7)
PFO with ASA, n (%)	61 (6.9)
Migraine	
Migraine, n (%)	168 (18.9)
Migraine without aura, n (%)	96 (10.8)
Migraine with aura, n (%)	72 (8.1)

n, number; SD, standard deviation; BMI, body mass index; kg/m^2, kilograms per square meter; TIA, transient ischemic attack; CAD, coronary artery disease; TEE, transesophageal echocardiography; PVI, pulmonary vein isolation; ECV, electrical cardioversion; PFO, patent foramen ovale; cTTE, agitated saline transthoracic echocardiography; ASA atrial septal aneurysm

Migraine with aura

In univariate analysis, the presence of PFO with ASA, compared to the absence of an atrial septal anomaly, was associated with MA (OR 3.72, 95% CI 1.86-7.44, *P*<0.001). A PFO without ASA was not significantly associated with MA (OR 1.50, 95% CI 0.79-2.82, *P*=0.21), nor was an isolated ASA (OR 1.48, 95% CI 0.33-6.63, *P*=0.61) (Table 2).

Additionally, in univariate analysis, female sex and a younger age were found to be associated with MA (Table 2). Though, atrial fibrillation and hypercholesterolemia were significant in univariate analysis as well, both are not clinical relevant for migraine with aura and were therefore left out multivariate analysis. In an adjusted multivariable model, PFO with ASA appeared to be strongest associated with MA (OR 2.71, 95% CI 1.23-5.95, *P*=0.01). Aside from the combination of PFO and ASA, both female sex (OR 2.44, 95% CI 1.37-4.34, *P*=0.002) and age (OR 0.94, 95% CI 0.92-0.96, *P*<0.001) were independently associated with MA. There were no missing values in multivariate analysis.

Migraine without aura

Between patients with MA- and patients without migraine, no significant difference was found between the presence of an isolated PFO (13.5% vs. 16.4%, *P*=0.50), isolated ASA (5.2% vs. 2.4%, *P*=0.14) or PFO with ASA (4.2% versus 6.1%, *P*=0.45) (Table 2). Additionally, in univariate analysis, female sex, a younger age and using a betablocker were found to be associated with MA-. Importantly, atrial septal anatomy was not associated with MA-. Though, using atrial fibrillation was significant in univariate analysis as well, it is not clinical relevant for migraine and was therefore left out multivariate analysis. In an adjusted multivariable model, female sex (OR 1.83, 95% CI 1.13-2.97, P=0.01) and age (OR 0.97, 95% CI 0.95-0.99, P<0.001) were independently associated with MA-. There were 74 missing values in multivariate analysis (9.1%).

Factors associated with migraine, with and without aura by inter-atrial septal anatomy

Between patients with MA and MA-, having a PFO with ASA was associated with MA (18.1% vs. 4.2%, *P*=0.004). No significant difference was found between MA and MA- and isolated PFO (19.4% vs. 13.5%, *P*=0.15) and isolated ASA (2.8% vs. 5.2%, *P*=0.66).

Additionally, in univariate analysis, also younger age was associated with MA. (Table 2) In an adjusted multivariable model, having a PFO with ASA was the only factor associated with MA (OR 4.34, 95% CI 1.10-17.1, P=0.04).

Table 2. Factors associated MA and MA-, Univariate Analysis

	No migraine	MA	MA-	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Patient Characteristics				MA vs no migraine		MA- vs no migraine		MA vs MA-	
Total	721	72	96	-	-	-	-		
Age (years) ± SD	58.5 ± 13.6	44.4 ± 14.1	49.6 ± 13.2	0.93 (0.92 – 0.95)	<0.001	0.96 (0.94 – 0.97)	<0.001	0.97 (0.95 - 1.00)	0.02
Women, n (%)	269 (37.3)	48 (66.7)	54 (56.3)	3.36 (2.01 – 5.61)	<0.001	2.16 (1.41 – 3.32)	<0.001	1.56 (0.83 - 2.93)	0.17
BMI (kg/m^2) ± SD	26.4 ± 4.2	26.7 ± 6.7	24.7 ± 4.3	1.02 (0.94 – 1.10)	0.71	0.90 (0.82 – 0.97)	0.01	1.07 (0.98 - 1.17)	0.12
History									
Stroke or TIA (%)	33.8	40.3	37.2	1.32 (0.79 – 2.21)	0.87	1.16 (0.73 – 1.85)	0.53	1.14 (0.59 - 2.19)	0.70
CAD (%)	16.1	3.0	8.2	0.16 (0.04 – 0.67)	0.01	0.47 (0.21 – 1.04)	0.06	0.34 (0.07 - 1.71)	0.19
Diabetes (%)	7.7	4.5	8.1	0.56 (0.17 – 1.85)	0.34	1.06 (0.47 – 2.42)	0.88	0.53 (0.13 - 2.13)	0.37
Hypertension (%)	37.3	16.4	22.1	0.33 (0.17 – 0.64)	0.01	0.48 (0.28 – 0.81)	0.006	0.69 (0.30 - 1.58)	0.42
Hypercholesterolaemia (%)	37.0	19.4	25.6	0.41 (0.22 – 0.77)	0.005	0.59 (0.35 – 0.98)	0.04	0.70 (0.32 - 1.52)	0.44
Smoking (%)	29.6	29.4	42.6	0.99 (0.45 – 2.18)	0.98	1.76 (0.93 – 3.34)	0.08	0.56 (0.22 - 1.44)	0.25
Atrial fibrillation (%)	37.2	13.4	14.0	0.26 (0.13 – 0.54)	<0.001	0.27 (0.15 – 0.51)	<0.001	0.96 (0.38 - 2.43)	1.00
Medication									
Aspirin (%)	32.9	38.1	28.6	1.26 (0.74 – 2.14)	0.40	0.82 (0.50 – 1.35)	0.43	1.54 (0.77 - 3.08)	0.29
Warfarin (%)	34.7	10.9	22.6	0.23 (0.10 – 0.51)	<0.001	0.55 (0.32 – 0.94)	0.03	0.42 (0.17 - 1.07)	0.08
Betablocker (%)	44.3	35.9	28.6	0.71 (0.41 – 1.20)	0.20	0.50 (0.31 – 0.83)	0.007	1.40 (0.70 - 2.81)	0.38
Inter-atrial Septal Anatomy									
No PFO, no ASA, n (%)	542 (75.2)	43 (59.7)	74 (77.1)	Reference	-	Reference	-	Reference	-
Isolated PFO, n (%)	118 (16.4)	14 (19.4)	13 (13.5)	1.50 (0.79 – 2.82)	0.21	0.81 (0.43 – 1.50)	0.50	1.85 (0.80 - 4.31)	0.15
Isolated ASA, n (%)	17 (2.4)	2 (2.8)	5 (5.2)	1.48 (0.33 – 6.63)	0.61	2.15 (0.77 – 6.01)	0.14	0.69 (0.13 - 3.70)	0.66
PFO with ASA, n (%)	44 (6.1)	13 (18.1)	4 (4.2)	3.72 (1.86 – 7.44)	<0.001	0.67 (0.23 – 1.91)	0.45	5.59 (1.72 - 18.2)	0.004

MA, migraine with aura; MA-, migraine without aura OR, odds ratio; CI, confidence interval; SD, standard deviation; n, number; BMI, body mass index; kg/m^2, kilograms per square meter; TIA, transient ischemic attack; CAD, coronary artery disease; PFO, patent foramen ovale; ASA, atrial septal aneurysm.

Coumadin

A subgroup analysis was performed excluding all patients using coumadin or with a history of atrial fibrillation. A total of 527 patients (59.3%) were included in this subgroup analysis. Only a PFO with ASA was more often found in patients suffering MA compared to MA- (18.2% vs. 5.5%, P=0.02). No significant difference was found in the presence of an isolated PFO (20.0% vs. 15.1%, *P*=0.27) or isolated ASA (3.3% vs. 5.5%, *P*=0.77).

PFO size

A moderate- and severe shunt rate was found in 12.0% and 12.0% for MA and 5.7% and 0% for MA-, respectively (p=0.007). The shunt rate differs significantly between MA and patients without migraine (p=0.03). A significantly higher shunt rate was found in patients with a PFO with ASA when compared to patients with an isolated PFO (p=0.015). (Table 3)

Table 3. PFO grade in patients with M-, MA- and MA.

	Grade 0	Grade 1	Grade 2	Grade 3
M-	80,6%	6,8%	7,0%	5,6%
MA-	88,6%	5,7%	5,7%	0,0%
MA	60,0%	16,0%	12,0%	12,0%
Isolated PFO	-	44.4%	35.2%	20.4%
PFO with ASA	-	20.7%	37.9%	41.4%

PFO, patent foramen ovale; M-, no migraine; MA-, migraine without aura; MA, migraine with aura; ASA, atrial septal aneurysm. PFO grade: maximum number of microbubbles counted in the left ventricle in one still frame. Grade 0 (no microbubbles), grade 1 (1-29 microbubbles), grade 2 (30–100 microbubbles) and grade 3 (>100 microbubbles).

Headache characteristics

The headache characteristics (duration, severity, and frequency of headache attacks) of all patients with MA (n=72) in relation with the inter-atrial septal anatomy are summarized in Table 4. In this group, we found no correlation between the MA characteristics and the anatomical variables.

Table 4. Characteristics of Headache Attacks in Relation with Inter-atrial Septal Anatomy in Patients with MA (n=72)

	No PFO, no ASA	Isolated PFO	Isolated ASA	PFO with ASA	*P*
	n=43	n=14	n=2	n=13	
Median duration, hours (IQ1-IQ3)	4 (1-24)	1.5 (0.8-4)	36 (0.25-72)	24 (1.4-24)	0.51
Median severity score, scale 0-10 (IQ1-IQ3)	7 (5-8)	7.5 (6-8)	6.5 (5-8)	7 (6-8)	0.62
Frequency of migraine, n of patients					0.37
≥ once a month	21	9	0	7	
≥ once a week	22	5	2	6	

MA, migraine with aura; n, number; PFO, patent foramen ovale; ASA, atrial septal aneurysm; IQ, inter-quartile.
Kruskal Wallis tests were performed to compare headache characteristics between groups.

Discussion

To our knowledge this is the first observational study reporting a strong association between the presence of a PFO with ASA and the occurrence of MA in a large patient population referred for TEE.

Association between PFO and MA, the role of ASA

Current literature remains discordant as to whether a linkage exists between PFO and MA. In many observational studies, an association between PFO and the occurrence of MA has been found.[14] However, other studies found no association between migraine with or without aura and the presence of a PFO. [15-17]
The discordant findings between the positive and negative studies might be explained in different ways. Firstly, in the observational studies most patients suffered a symptomatic PFO, which means a history of a cryptogenic cerebral ischemic event. In the negative studies, patients with these "high-risk" PFO's were excluded, which could have influenced their findings. Secondly, one of the factor that was strongest associated with the occurrence of a cryptogenic cerebral event is the presence of a combination of a PFO with an ASA.[8] Patients with MA appear to be at risk for stroke, which might be related to the presence of a PFO.[9, 10] We therefore hypothesized that the link between the association of PFO and MA might be the ASA. The negative studies did not identify this specific anomaly, which might have influenced their observational results. Indeed, the presence of a PFO and/or ASA can only be clearly demonstrated by TEE, and not by transthoracic echocardiography (TTE) or transcranial Doppler (TCD) as used in the

negative studies.[18]
More recently, two prospective trials were published. The MIST trial compared percutaneous PFO closure and a sham procedure in 147 patients. No improvement of migraine was found after closure. The PRIMA trial compared percutaneous PFO closure and pharmacological treatment in 107 patients and did show a lower frequency of MA in the percutaneous closure group. The difference in outcome between these trials was probably due to the patient selection and follow-up time. [19-20]
Interestingly, in the current study, we found no significant association between PFO without ASA, diagnosed by TEE, and MA. This is comparable with the negative studies. However, PFO with ASA was strongly independent associated with MA (OR 2.7).
Moreover, we only found an association between the presence of PFO with ASA and the occurrence of MA. No association was found with MA-. Secondly, the shunt size was significantly higher in patients suffering MA.

Pathophysiological mechanism

The exact pathophysiology for MA is yet unknown. A plausible explanation for the association between PFO and MA seems to be the "micro-thrombi hypothesis." This hypothesis suggests that, in the presence of PFO, micro-thrombi or emboli originating in the venous circulation might enter the systemic and cerebral circulation and trigger a migraine attack. By shunting from right to left through the PFO these micro-thrombi might bypass the lung filter.[21] In situ micro-thrombus formation secondary to stasis of blood in the PFO tunnel might be another source of migraine triggering substances. Another study supporting the micro-thrombi hypothesis is the study by Mohanty et al. describing the positive effect of AF ablation on migraine symptoms. Further, they described that cases with new migraine had a subtherapeutic INR, which supports the theory that micro-thrombi could be associated with migraine.[22] After exclusion of patients using coumadin or with a history of atrial fibrillation, the presence of a PFO with ASA was still associated with MA in our study.
Bhaskar et al. conclude that cortical spreading depression is the physiological substrate of MA and probably also for MA-.[23] Because the exact pathophysiology is not clear, the micro-thrombi hypothesis is still one of the many hypotheses for the cause of MA. Though, no studies actually prove the micro-thrombi hypothesis, several case reports have been published showing benefit of Warfarin in patients suffering MA. [24-25] As mentioned before, we did not find a significant association between PFO without ASA and MA in our study. A possible explanation is our finding that PFO's with an ASA have a higher degree of right-to-left shunting supporting our findings that only the presence of PFO with ASA was significantly associated with the occurrence of MA.
In support of this theory and to clarify it, we believe there might be a parallel between the pathophysiology of the association between PFO with ASA and MA on one hand and PFO with ASA and cryptogenic stroke on the other. Paradoxical embolism of thrombus

through a PFO implies to be the most likely pathophysiologic mechanism in young patients with cryptogenic stroke.[26] Moreover, a stronger association with cryptogenic stroke has been reported for PFO with ASA as compared to PFO alone.[8] Additionally, it has been observed that in cryptogenic stroke patients the risk of recurrent stroke increased significantly in patients with PFO and ASA when compared to patients with only a PFO or ASA.[27] The observation that MA patients have a higher life-time risk for an ischemic cerebral event compared to the general population supports the parallel even more.[9]

In support of the micro-thrombi hypothesis is the finding that treatment with high dose aspirin or oral anticoagulants might prevent migraine attacks.[28, 29] We also found a protective effect of coumadin on the occurrence of MA in univariate analysis. However, there was no significant difference in coumadin use between the MA and MA- group (p=0.08), probably based on the small sample size. But both groups were underpowered and different, which makes it difficult to make any conclusions.

A relatively high prevalence of CAD, hypertension, hypercholestrolaemia and AF was found. The reason is probably that there are more men with higher age in this population. We also found that there is less migraine in patients with higher age, as well as the frequency of a PFO. These findings are in line with earlier studies. [3, 30, 31]

Limitations

The first limitation of our study is selection bias. All patients were referred to the cardiologic outpatient department for undergoing cTEE for different indications, including referral for ruling out a cardio-embolic source. This might have influenced the prevalence of PFO and ASA. However, we found a prevalence of PFO and isolated ASA of respectively 23% and 2.7%, which is comparable with that in the general population. [5, 6] Secondly, this study was limited because of a relatively high rate of exclusion of patients, partially because they did not undergo an agitated saline examination. When patients experienced too much discommodity during TEE, we decided to abandon the agitated saline examination. However, this is inherent to the semi-invasive character of TEE. A larger group was excluded because they did not fully complete the survey or master the Dutch language. This could cause a bias, also because it is not clear whether only patients with a history of headache agreed to participate. Earlier TTE- or TEE data of these patients was not available. Therefore, comparing the patients that did not undergo TEE to those who did, was not possible.

Conclusion

Only a PFO with ASA is significantly associated with MA in this large observational study. Further PFO studies should focus on this specific intra-atrial anomaly.

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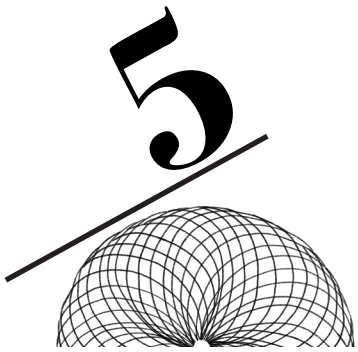

POINT OF VIEW: PERCUTANEOUS CLOSURE OF A PATENT FORAMEN OVALE AFTER CRYPTOGENIC STROKE

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Abstract

A patent foramen ovale (PFO) is a common intracardiac finding that is located between the left and right atrium. It can cause right-to-left shunting and has a high prevalence in patients who suffer a cryptogenic stroke. Earlier trials did not show superiority of percutaneous PFO closure with standard medical therapy over standard medical therapy alone in the treatment of cryptogenic stroke. Interestingly, several meta-analyses show positive results regarding closure, suggesting underpowering of the individual trials. Recently, two large prospective trials and one long-term follow-up study showed benefit of percutaneous closure over standard medical therapy in treatment of cryptogenic stroke. A larger right-to-left shunt or the presence of an atrial septal aneurysm were predictors for a recurrent event. Therefore, percutaneous PFO closure after cryptogenic stroke should be recommended over antiplatelet therapy alone in patients younger than 55 years of age with a high-risk PFO.

Introduction

Patent foramen ovale (PFO) is a common intracardiac finding that is located between the left and right atrium and is found in about 25% of the population. In patients with a cryptogenic stroke or transient ischaemic attack (TIA) the prevalence rises up to 50% [1].

Large case-control studies showed an association between PFO and cryptogenic stroke, especially in patients younger than 55 years of age [2]. Several observational studies described a reduction in recurrent neurological events after percutaneous PFO closure with standard medical therapy (later mentioned as percutaneous PFO closure) compared with lifelong medical therapy [3-4]. A few years ago, three prospective randomised trials failed to show superiority of percutaneous PFO closure. Long-term follow-up was lacking though. These trials differ in patient selection and type of device used. [5-7]. However, several meta-analyses showed a benefit of percutaneous PFO closure suggesting underpowering of the individual studies [8, 9]. Recently, two large randomised controlled trials and one long-term follow-up study of an earlier trial were published. We discuss these trials in this point of view article and give our recommendation about the optimal treatment for cryptogenic stroke in the presence of a PFO.

Earlier trials: clinical outcome and predictors for recurrence of stroke

Three prospective randomised trials have been published studying the difference between medical therapy and percutaneous PFO closure in patients who suffered from a cryptogenic stroke or TIA. A summary of these trials is shown in Table 1.

The first trial, CLOSURE-1 ("Evaluation of the STARFlex Septal Closure System in Patients with a Stroke and/or Transient Ischemic Attack due to Presumed Paradoxical Embolism through a Patent Foramen Ovale"), was published in 2012 and included 909 patients who presented with a cryptogenic stroke or TIA. At least a moderate right-to-left shunt (RLS) or an atrial septal aneurysm (ASA) was present in 52.9% and 36.6%, respectively. The STARFlex device (NMT Medicals) plus antiplatelet therapy (clopidogrel for 6 months and aspirin for 2 years) were used in the closure group and oral anticoagulation (OAC), aspirin or both in the medical therapy group at the discretion of the principal investigator. The primary endpoint, the composite of stroke/TIA during 2-year follow-up, death from any cause during the first 30 days, and death from neurologic cause between 31 days and 2 years, was reached in 5.5% after closure and in 6.8% in the medical therapy group (adjusted hazard ratio (HR), 0.78; 95% confidence interval (CI), 0.45-1.35; p=0.37). Subgroup analysis showed no predictors for recurrent stroke/TIA [5].

Table 1.

	CLOSURE 1	PC	RESPECT	Gore REDUCE	CLOSE
Patients (n)	909	414	980	664	663
Mean age (years)	45.9±9.5	44.5±10.1	45.9±9.9	45.2±9.4	43.3±10.4
Male (%)	51.8	49.8	54.7	60.1	58.9
Moderate or large RLS (%)	52.9	65.6	75.2	81.3	100.0
ASA (%)	36.6	23.7	35.6	20.4*	32.8
Treatment					
Type of medical therapy	Aspirin, OAC or both	Antiplatelet, OAC or both	Antiplatelet or OAC	Antiplatelet	Antiplatelet or OAC
Oral anticoagulation (%)	34.0	31.0	25.0	0.0	28.2
Type of closure device	STARFlex	Amplatzer PFO	Amplatzer PFO	Helex septal occluder/ Cardioform septal occluder	Any ICC approved device
Follow-up					
Mean follow-up time (months)	44.0	49.0	31.0	38.4	63.6
Effective closure (%)	86.1	95.9	93.5	75.6	93.0
Drop-out medical therapy (%)	0.87	15.2	17.2	14.8	5.1
Drop-out closure device (%)	10.1	3.9	9.2	8.8	8.8
Adverse events medical therapy					
Major bleeding (%)	1.1	1.4	1.9	2.7	2.1
Atrial fibrillation (%)	0.7	1.0	1.5	0.4	0.9
Adverse events closure device					
Major procedural complication (%)	3.2	1.5	0.6	2.5	5.9
Non procedural major bleeding (%)	2.6	0.5	1.6	0.9	0.8

Atrial fibrillation (%)	5.7	2.9	3.0	6.6	4.6
<u>Endpoints medical therapy</u>					
Stroke (%)	3.1	2.4	3.3	5.4	6.0
TIA (%)	4.1	3.3	-	-	-
Death (%)	0.0	0.0	1.2	0.0	0.0
<u>Endpoints closure device</u>					
Stroke (%)	2.9	0.5	1.8	1.4	0.0
TIA (%)	3.1	2.5	-	-	-
Death (%)	0.0	1.0	0.6	0.5	0
Conclusion	No significant benefit for closure	No significant benefit for closure	No significant benefit for closure	Significant benefit for closure	Significant benefit for closure

The PC trial ("Using the Amplatzer PFO Occluder with Medical Treatment in Patients with Cryptogenic Embolism") was published in 2013 and included 414 patients who suffered a cryptogenic stroke, TIA or a peripheral thromboembolic event. At least a moderate RLS was present in 65.6% and an ASA in 23.7%. The closure group received an Amplatzer device (St. Jude Medical), clopidogrel for 1-6 months and aspirin for at least 6 months. Medical therapy consisted of antiplatelet therapy, OAC, or both, at the discretion of the treating physician. During mean follow-up of 4.0 years, the primary endpoint (composite of death, non-fatal stroke, TIA or peripheral embolism) occurred after closure and after medical therapy, in 3.4% and 5.2%, respectively (HR 0.63, 95%CI:0.24-1.62; p=0.34). Subgroup analysis found no predictors for recurrent stroke/TIA [6].

Finally, the RESPECT trial ("Randomised Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment"), published in 2013, randomised 980 patients with cryptogenic stroke to closure (Amplatzer device, St. Jude Medical, plus aspirin and clopidogrel for 1 month, followed by aspirin alone for 5 months) or to medical therapy (aspirin, clopidogrel or warfarin). At least a moderate RLS was present in 75.2% and an ASA in 35.6%. After a mean follow-up of 2.6 years, the primary endpoint (composite of recurrent fatal and non-fatal ischaemic stroke, death from any cause within 30 days after implantation or 45 days after randomisation) was reached in the closure and medical therapy group in 3.4% and 5.2%, respectively (HR 0.49, 95%CI:0.22-1.11; p=0.08). Subgroup analysis showed a benefit for closure in presence of larger RLS (HR 0.18, 95%CI:0.04-0.81; p=0.01) or ASA (HR 0.19, 95%CI:0.04-0.87; p=0.02) [7].

None of these three trials showed superiority of percutaneous closure over medical therapy. However, the trials had study limitations and are difficult to compare. Firstly, the dropout rate was high, based on crossover to closure. Secondly, different devices were used for percutaneous closure. The CLOSURE-1 trial used the STARFlex device, which is already off the market due to poorer efficacy and safety data. Both the PC and the RESPECT trial used the Amplatzer device, which has proven to be safe and effective. Thirdly, different primary endpoints were used: the CLOSURE-1 and PC trials used stroke and TIA as endpoint, the RESPECT trial only stroke. Patient selection was different between trials. For instance, the CLOSURE-1 trial included patients without a proven stroke on imaging, where the PC trial also included patients with a peripheral embolism. Long-term medical therapy was different between trials as well, based on physicians' preference. Finally, all trials had a modest statistical power with a relatively small population and low clinical event rates.

Even though PFO closure was at least equal in comparison to medical therapy, it did not change the guidelines or clinical practice.

Meta-analyses and review

Several meta-analyses were published discussing these trials mentioned above, including a total of 2303 patients.
Khan et al. suggest that PFO closure is beneficial when compared with medical therapy in the prevention of recurrent stroke. The effect-estimate HR was 0.67 (95%CI:0.44-1.00; *p*=0.05) in the intention-to-treat, 0.62 (95%CI:0.40-0.95; *p*=0.03) using per-protocol, and 0.61 (95%CI:0.40-0.95; *p*=0.03) using the as-treated cohort, all showing a beneficial effect for PFO closure. After pooling the results of the trials using the Amplatzer device, the results showed an even more positive effect for PFO closure (HR 0.54, 95%CI:0.29-1.01; *p*=0.05) [8].
Rengifo-Moreno et al. defined primary outcome as a recurrent stroke and/or TIA and found a significant risk reduction after PFO closure (pooled HR 0.59, 95%CI:0.36-0.97; *p*=0.04). The composite outcome of death, neurological events and peripheral embolism based on intention-to-treat analyses showed a possible benefit for closure (pooled HR 0.67, 95%CI:0.44-1.00; *p*=0.05). A substantial RLS at baseline tended to be associated with a decrease in vascular events after closure (pooled HR 0.35, 95%CI:0.12-1.03; *p*=0.06) [9].
There were also meta-analyses without a statistically significant difference between closure and medical therapy. Ntaios et al. and Kwong et al. showed no significant difference in recurrent stroke between closure and medical therapy (odds ratio (OR) 0.64, *p*=0.11 and OR 0.65, *p*=0.17, respectively). Furthermore, there was no difference in the occurrence of TIA or death between both treatment arms. Subgroup analyses showed a possible benefit on stroke rate for percutaneous closure using the Amplatzer PFO occluder (OR 0.46, *p*=0.04 and OR 0.47, *p*=0.06, respectively) [10-11]. And finally, a review by Li et al. showed no statistically significant difference in recurrent stroke or TIA between closure and medical therapy (relatively risk 0.73; 95%CI:0.45-1.17) [12].
The meta-analyses described above showed similar complications, mainly vascular complications and atrial fibrillation. The complications were significantly higher after closure.

Recent trials

Recently, two large randomised trials and one long-term follow-up study of the earlier described RESPECT trial were published [13-15]. A summary of these trials is shown in Table 1.
The Gore REDUCE trial ("GORE HELEX Septal Occluder/GORE CARDIOFORM Septal Occluder for Patent Foramen Ovale Closure in Stroke Patients") randomised 664 patients in a 2:1 ratio to percutaneous closure (Helex septal occluder/Cardioform septal

occluder, W.L. Gore and Associates) plus antiplatelet therapy or antiplatelet therapy alone. The co-primary endpoints were freedom from clinical evidence of ischaemic stroke and incidence of new brain infarction, which was a composite of clinical ischaemic stroke or silent brain infarction detected on imaging, both 24 months after randomisation. At least a moderate RLS was present in 81.3% and an ASA in 20.4%. During a median follow-up of 3.2 years, stroke occurred after closure and after medical therapy in 1.4% and 5.4%, respectively (HR 0.23; 95%CI:0.09-0.62; p=0.002). New brain infarctions were found in 5.7% and 11.3%, respectively (HR 0.51; 95%CI:0.29-0.91; p=0.04). A significant benefit for closure was found in patients having a substantial RLS (HR 0.18; 95%CI:0.06-0.58; p=0.001). Atrial fibrillation occurred significantly more often in the closure group (p<0.001). However, there was no significant difference in the overall serious adverse events (p=0.22) [13].

The CLOSE trial ("Patent Foramen Ovale Closure or Anticoagulants Versus Antiplatelet Therapy to Prevent Stroke Recurrence") assigned 663 patients who recently suffered a stroke in the presence of a high risk PFO (large RLS or ASA) in a 1:1:1 ratio to percutaneous PFO closure plus long-term antiplatelet therapy, antiplatelet therapy alone or OAC alone. At least a moderate RLS was present in 100% and an ASA in 32.8%. During a mean follow-up of 5.3 years, the primary endpoint (occurrence of stroke) was reached in 0% in the closure group, in 6.0% in the antiplatelet group (HR 0.03; 95%CI:0-0.26; p=<0.001), and 1.6% in the OAC group. This study was not powered to compare the outcome between antiplatelet therapy and OAC. Closure-related events occurred in 5.9%. There was no significant difference in serious adverse events between both treatment arms (p=0.56). Onset of atrial fibrillation occurred significantly more often after closure (p=0.02) [14].

The previously described RESPECT trial published data with an extended median follow-up of 5.9 years. The number of patients and the primary endpoint are described above. The two groups were not equal at the latest follow-up due to a high dropout rate (33.3%) in the medically treated group. Recurrent non-fatal stroke occurred in 3.6% (0.58 events per 100 patient-years) after closure and in 5.8% (1.07 events per 100 patient-years) receiving medical therapy (HR 0.55; 95%CI:0.31-0.999; p=0.046). Subgroup analysis showed a benefit for closure in presence of a substantial RLS (HR 0.26; 95%CI:0.10-0.71; p=0.005) or ASA (HR 0.20; 95%CI:0.06-0.70; p=0.005). Both serious adverse events and atrial fibrillation did not significantly differ between both groups [15].

In summary, the two recent trials and the extended follow-up study showed a significant benefit for percutaneous PFO closure when compared with medical therapy alone (especially antiplatelet therapy) in younger patients who suffer a cryptogenic stroke. This beneficial effect was greater in patients with a high-risk PFO (defined as a PFO with a at least a moderate RLS and/or ASA).

The difference between the earlier and recent trials could be explained by the fact that

recent trials were more uniform, had a long-term follow-up and a different endpoint compared with earlier trials. More importantly, recent trials included patients with at least a moderate RLS and/or an ASA, which are known as high risk PFO's, and showed an even greater effect of closure.

How to decide which PFO to close?

In the past, literature did not reach consensus in which symptomatic patient group the PFO should be closed. The latest ESC guidelines describe a class IIa level of evidence C for percutaneous PFO closure in young patients with a systemic paradoxical embolism [16]. The 2017 Dutch guideline acknowledges the potential benefit for percutaneous PFO closure in selected patients; class IIa level of evidence A [17].

Age and presence of atherosclerosis play an important role in whether PFO is a likely cause of cryptogenic stroke. Pezzini et al. showed that with lesser risk factors for atherosclerosis, the influence of PFO increases [18]. Kent et al. created a calculator to stratify the likelihood of PFO related to stroke [19]. The Risk of Paradoxical Embolism (RoPE) calculator uses important risk factors for atherosclerosis (hypertension, diabetes, history of stroke or TIA and smoking), the presence of a cortical infarct on imaging and age for identifying a PFO related stroke. The higher the RoPE score (between 0 and 10 points), the more likely a PFO is related to stroke. Using a multivariate model after inclusion of more than 3000 patients, younger age and the absence of risk factors mentioned above were found to be associated with the presence of a PFO related stroke. The optimal cut-off value to identify a stroke-related PFO was a RoPE score of at least 6. However, presence of a large shunt or ASA was not included despite the fact that previous studies have shown an association between cryptogenic stroke and these high-risk PFO's [20]. Using echocardiography, ASA is defined as more than 10 mm bulging of the atrial septum and the severity of a RLS is calculated on the maximum amount of bubbles in the left atrium, and graded as minimal, moderate or large. [21, 22]. In contrast to the CLOSURE-1 and PC trial, the earlier RESPECT trial found a significant benefit for closure in presence of a large RLS or ASA. The more recent studies (Gore REDUCE and RESPECT) found a large RLS or ASA as predictors for benefit of PFO closure. Moreover, the CLOSE trial only included patients with these PFO characteristics and showed an overall significant, positive effect for closure. The difference in significance between the earlier and recent trials could be explained by the limitations of the earlier trials.

Therefore, after exclusion of other possible causes, percutaneous PFO closure using a safe and effective device in combination with medical therapy should be recommended over medical therapy alone in young patients (≤ 55 years of age) who suffer a cryptogenic stroke confirmed by cerebral imaging. A RoPE score of at least 6 or a high-risk (at least

moderate RLS or ASA) PFO should be present. Adverse events of PFO closure should be taken into account. A recent study including more than 1800 percutaneous PFO closure procedures showed a complication rate of 4.9% in patients younger than 60 years of age (mainly vascular complications and paroxysmal atrial fibrillation). This rate is similar when compared with the recent trials [23].

In Fig. 1, we suggest an algorithm for the treatment of cryptogenic stroke in the presence of PFO.

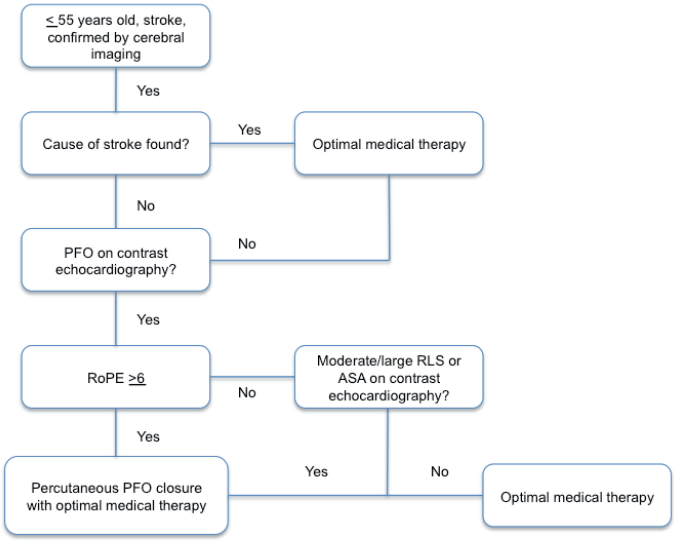

Figure 1. Algorithm for the treatment of cryptogenic stroke

ASA atrial septal aneurysm, *PFO* patent foramen ovale, *RLS* right-to-left shunt, *RoPE* risk of paradoxical embolism

Recommendation

At this moment, literature shows a significant beneficial effect of percutaneous PFO closure over medical therapy alone in selected patients who suffer a cryptogenic stroke. It is important to exclude other possible causes of stroke before considering percutaneous closure. The RoPE score, described earlier, could be a useful instrument in determining the possible association between stroke and the presence of a PFO, but the score might underestimate the risk. It has become clear that the presence of a significant RLS or an ASA are important discriminators to determine whether a stroke is related to a PFO. Based on the currently available literature, the current guidelines should be updated in favour of percutaneous PFO closure in young patients who suffer a cryptogenic stroke.

The RoPE score and the presence of a high-risk PFO should be important factors to guide the decision.

Conclusion

Percutaneous PFO closure should be the recommended treatment over medical therapy in young patients suffering cryptogenic stroke.

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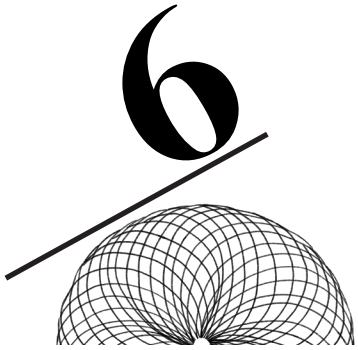

CASE REPORT: PERCUTANEOUS RECLOSURE OF A PATENT FORAMEN OVALE AFTER BIOABSORBABLE DEVICE IMPLANTATION

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EuroIntervention 2014;10(7):860

A 49-year-old woman with a history of cryptogenic stroke and per-cutaneous patent foramen ovale (PFO) closure using a bioabsorbable device with a diameter of 28 mm, was seen in our outpatient clinic for contrast transthoracic echocardiography (TTE) at three-year follow-up. Earlier contrast TTE had shown a small right-to-left shunt. Currently, her clinical investigation was unremarkable. The TTE showed a good device position, without thrombi on the device.
Colour Doppler showed no signs of shunting, but using contrast (Figure 1A) a severe right-to-left shunt was diagnosed during Valsalva. Under local anaesthesia and intracardiac echocardiographic guidance, the residual shunt was closed percutaneously using a 27-30 mm Occlutech® Figulla® device (Occlutech International AB, Helsingborg, Sweden) (Figure 1B and 1C). There were no complications and contrast TTE before discharge showed only small residual shunting with a good device position (Figure 1D). Residual shunting is common in patients who had received a bioabsorbable device for PFO closure [1]. Due to the increased risk of recurrent stroke in the presence of a large residual shunt, treatment might be necessary and can be provided by oral anticoagulation therapy, surgical or percutaneous closure [2]. Little is known about the safety and efficacy of these therapies in this specific situation. Successful implantation of a second device has been described in a small number of patients showing a good periprocedural result [3, 4].

We report a case of a successful second percutaneous device implantation, because of a severe residual shunt, after a previous percutaneous PFO closure with a bioabsorbable device.

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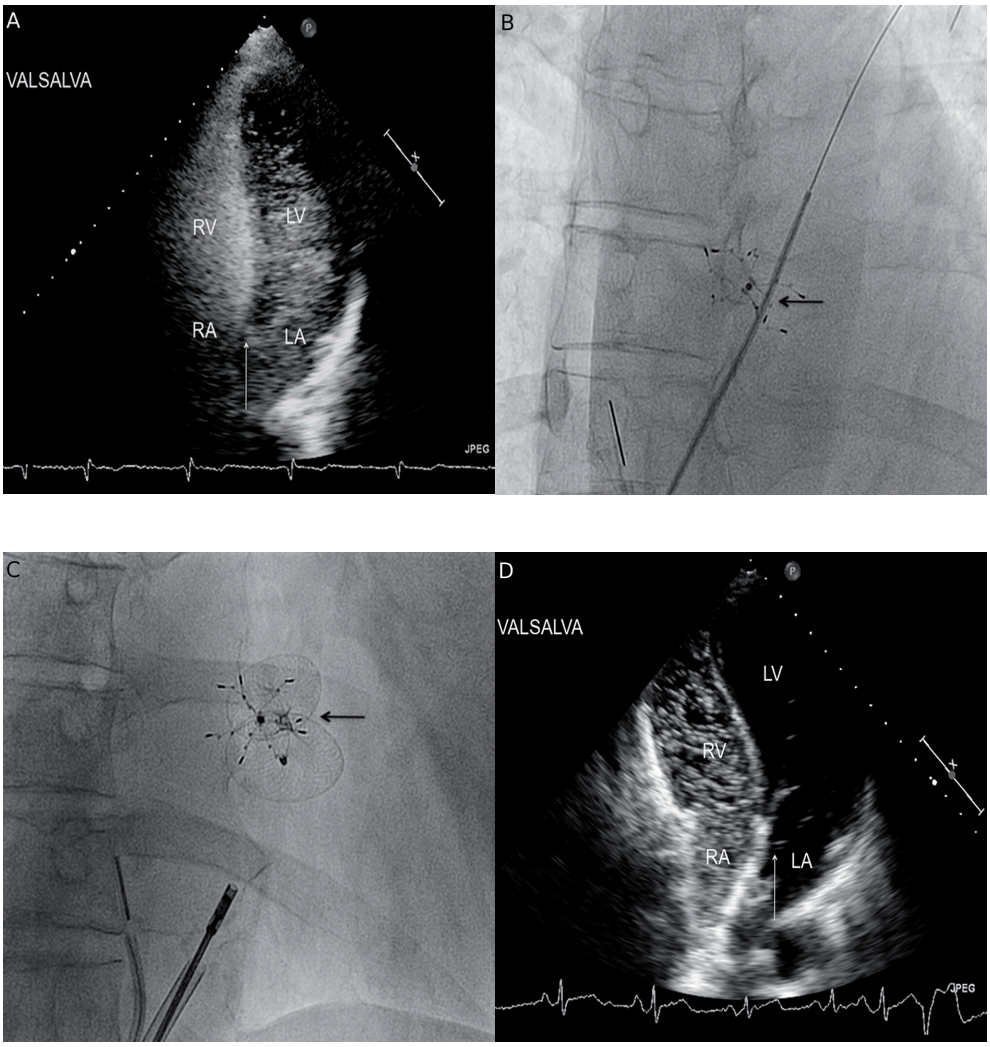
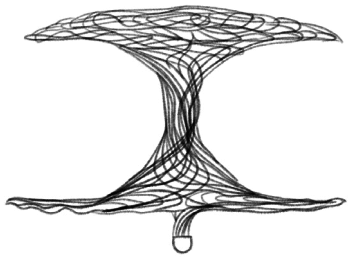


Figure 1. A) Contrast transthoracic echocardiogram (TTE) at three-year follow-up. During Valsalva a severe right-to-left shunt is visible (arrow). B) Fluoroscopic view of the bioabsorbable device (arrow) with the catheter passed through the residual opening. C) Fluoroscopic view of the bioabsorbable device and the Occlutech Figulla device (arrow). D) Contrast TTE 1 day after intervention. During Valsalva a small right-to-left shunt is visible (arrow).

III

part III



PERCUTANEOUS ATRIAL SEPTUM DEFECT CLOSURE

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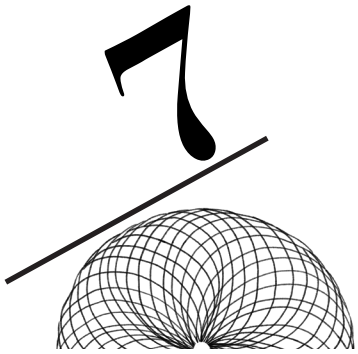

PERCUTANEOUS CLOSURE OF SECUNDUM TYPE ATRIAL SEPTAL DEFECTS: MORE THAN 5-YEARS FOLLOW-UP

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World J Cardiol 2015;7(3):150-156

Abstract

Aim: To investigate long-term efficacy of two different devices more than five years after percutaneous atrial septal defect (ASD) closure in adults.

Methods: All patients who underwent percutaneous closure of an ASD in the St. Antonius Hospital, Nieuwegein, The Netherlands, between February 1998 and December 2006 were included. Percutaneous closure took place under general anaesthesia and transesophageal echocardiographic monitoring. Transthoracic echocardiography (TTE) was performed 24 h post-procedure to visualize the device position and to look for residual shunting using color Doppler. All complications were registered. All patients were invited for an outpatient visit and contrast TTE more than 5-years after closure. Efficacy was based on the presence of a residual right-to-left shunt (RLS), graded as minimal, moderate or severe. The presence of a residual left-to-right shunt (LRS) was diagnosed using color Doppler, and was not graded. Descriptive statistics were used for patients' characteristics. Univariate analysis was used to identify predictors for residual shunting.

Results: In total, 104 patients (mean age 45.5 ± 17.1 years) underwent percutaneous ASD closure using an Amplatzer device (ASO) in 76 patients and a Cardioseal/Starflex device (CS/SF) in 28 patients. The mean follow-up was 6.4 ± 3.4 years. Device migration occurred in 4 patients of whom two cases occurred during the index hospitalization (1 ASO, 1 CS/SF). The other 2 cases of device migration occurred during the first 6 mo of follow-up (2 CS/SF). The recurrent thrombo-embolic event rate was similar in both groups: 0.4% per follow-up year. More than 12 mo post-ASD closure and latest follow-up, new-onset supraventricular tachyarrhythmia's occurred in 3.9% and 0% for the ASO and CS/SF group, respectively. The RLS rate at latest follow-up was 17.4% (minimal 10.9%, moderate 2.2%, severe 4.3%) and 45.5% (minimal 27.3%, moderate 18.2%, severe 0%) for the ASO- and CS/SF groups, respectively. There was no residual LRS in both groups.

Conclusion: Percutaneous ASD closure has good long-term safety and efficacy profiles. The residual RLS rate seems to be high more than 5 years after closure, especially in the CS/SF. Residual LRS was not observed.

Key words: Percutaneous intervention; Atrial septal defect; Closure device; Right-to-left interatrial shunt; Left-to-right interatrial shunt; Echocardiography

Core tip: Several atrial septal defect (ASD) closing devices have been proven safe and effective for percutaneous ASD closure. We evaluated long-term (*i.e.*, more than 5-year of follow-up) efficacy of two different devices used in adults. Percutaneous ASD closure seems to be relatively safe using the Amplatzer device. Though, the right-to-left shunt (RLS) rate is high, a residual left-to-right shunt was absent at latest follow up. The Cardioseal/Starflex device appears to be associated with a higher complication- and residual RLS rate. The importance of a residual RLS is unclear. Therefore, long-term follow up might be necessary.

Snijder RJ, Suttorp MJ, Ten Berg JM, Post MC. Percutaneous closure of secundum type atrial septal defects: More than 5-year follow-up. *World J Cardiol* 2015; 7(3): 150-156 Available from: URL: http://www.wjgnet.com/1949-8462/full/v7/i3/150.htm DOI: http://dx.doi.org/10.4330/wjc.v7.i3.150

Introduction

An atrial septal defect (ASD) is a common cardiac defect and accounts for one third of all congenital heart diseases detected in adults[1,2]. The diagnosis in adults is often made when complications of the shunt occur, such as pulmonary hypertension, heart failure, arrhythmias, or paradoxical embolism. Most of these complications might be prevented by closure.

Since the first description of the transcatheter closure device for an ASD in 1976 by King et al[3], percutaneous ASD closure has been practiced and described extensively. Other studies evaluated various ASD closure devices and showed good mid-term (up to 2 years) safety and efficacy profiles[4-7]. However, long-term (*i.e.*, more than 5-year after closure) safety and efficacy data on percutaneous closure devices has not been available yet. We report long-term efficacy and safety of two types of ASD closure devices.

Materials and methods

Population

All patients who underwent a percutaneous closure of an ASD in the St. Antonius Hospital, Nieuwegein, The Netherlands, between February 1998 and December 2006 were included in this study. All patients were invited for an outpatient visit and transthoracic echocardiography (TTE).

Closing procedure

As reported earlier, percutaneous closure took place under general anaesthesia and transesophageal echocardiographic (TEE) monitoring according to standard techniques[4]. TTE was performed 24 h post-procedure to visualize the device position and to look for residual shunting using color Doppler.

Follow-up and complications

Follow-up information was obtained at the outpatient clinic or by a telephone interview. All complications were documented, and divided into major and minor as described by Khairy et al[8]. Major complications included procedure related events such as haemorrhage requiring blood transfusion, occurrence of cardiac tamponade, need for procedure-related surgical intervention, massive fatal pulmonary emboli, occurrence of new thrombo-embolic events and death[8].

New-onset supraventricular tachycardia's were diagnosed by routine ECG when patients visited the outpatient clinic or when patients visited the emergency department because of symptoms.

Efficacy

The efficacy of the ASD closure was based on the presence of residual shunting using contrast TTE (cTTE) with Valsalva manoeuvre, and color Doppler. A residual right-to-left shunt (RLS) was present if microbubbles appeared in the left atrium. Opacification of the left ventricle and shunt grade were classified as minimal (maximum of 30 micro-bubbles in left ventricle), moderate (between 30 and 100 bubbles in left ventricle), and large (> 100 micro-bubbles in the left ventricle). This division was based on the maximum number of microbubbles counted in one still frame, as previously reported[9]. The presence of a left-to-right shunt (LRS) was based color Doppler imaging at the atrial septum. The LRS was not graded.

Statistical analysis

Descriptive statistics were used for patients' characteristics. Continuous variables with normal distribution are presented as mean ± SD or median with range if normal distribution was absent. Univariate analysis was used to identify predictors for residual shunting. All statistical analyses were performed using SPSS software (version 22.0 for Windows).

Results

Study population

Percutaneous ASD closure was performed in 104 consecutive patients (75% women; mean age, 45.5 ± 17.1 years). Baseline characteristics, risk factors, co-morbidity and indication for closure are summarized in Table 1.

Less than 12-mo follow-up: Safety and efficacy

Device implantation was initially uneventful in 102 patients (98.1%). In 76 patients (73.1%) an Amplatzer (ASO), and in 28 patients (26.9%) a Cardioseal/Starflex (CS/SF) was used for closure. In total, 4 major complications occurred within the first 6 mo. Two patients (1.9%, 1 ASO, 1 CS/SF) suffered from embolization of the device during the index hospitalization and two (1.9%, 2 CS/SF) within the first 6 mo after closure. All underwent surgical device extraction; the ASD was closed using a patch during the same operation. All patients recovered well. Procedural characteristics are shown in Table 2.
Between 6- and 12 mo, another two patients (1.9%, 2 CS/SF) underwent surgical extraction of the device and the ASD was closed with a patch during the same operation. One patient had a large residual shunt, which could not be closed with a second device. The other patient needed rhythm surgery, therefore, device extraction was performed.
Within the first 12-mo, recurrent thrombo-embolic events occurred in 1 patient (0.9%, 1 CS/SF). This 58-year-old patient suffered a transient ischemic attack (TIA). Because

of a history of supraventricular tachyarrhythmia's (SVT) the patient was already using oral anticoagulation. cTTE showed no residual RLS.
New-onset SVT's occurred in 6.6% of the ASO group and in 17.9% of the CS/SF group.

Table 1. Basline characteristics

Number	104
Age (years)	45.5±17.1
Female, n (%)	78 (75.0)
Weight (kg)	73.1±15.1
Risk factors and co-morbidities (%)	
Arterial hypertension	18.4
Hypercholesterolemia	3.9
Diabetes	1.9
Smoking	18.4
CAD	4.9
History of SVT	26.2
Antithrombotic treatment	
None	59 (56.7)
Aspirin	20 (19.2)
Dipyridamol	1 (1.0)
Oral antocoagulantia	21 (20.2)
Unknown	3 (2.9)
Indication for closure, n (%)	
RV volume overload	72 (69.2)
Cryptogenic TIA/stroke	21 (20.2)
Asymptomatic	11 (10.6)
RVSP + CVP (mmHg) *	34.6±10.5
ASD diameter (mm)#	18.3±6.3
Follow up (years)	6.4±3.4

Data are presented as mean ± SD.
*on transthoracic echocardiography
on transesophageal echocardiography
CAD, coronary artery disease; SVT, supraventricular arrhythmia; TIA, transient ischemic attack; RVSP, right ventricular systolic pressure; CVP, central venous pressure; ASD, atrial septal defect

Table 2. Procedural characteristics.

Devices, n (%)	
Amplatzer	76 (73.1)
Diameter, mm*	25 (12 – 38)
Cardioseal/Starflex	28 (26.9)
Diameter, mm*	33 (20 – 40)
General anaesthesia, n (%)	104 (100)
TEE guiding, n (%)	104 (100)
In-hospital complications, n (%)	
Device embolization	2 (1.9)
New-onset SVT	3 (2.9)
Allergic reaction	1 (1.0)
Fever	1 (1.0)
Groin hematoma	1 (1.0)
Tamponade	1 (1.0)
Shunt by TTE, n (%)**	
Color Doppler	9 (11.4)
Hospital stay, days*	2 (2-7)

*Data presented as median (range), ** data available in 79 patients
TEE, transesophageal echocardiography; SVT, supraventricular tachycardia; TTE, transthoracic echocardiography

More than 12-mo follow-up: Efficacy and complications

Contrast TTE was performed in 57 patients (54.8%, 46 ASO and 11 CF/SF). Median follow-up time for the ASO group was 6.6 years (5.0-11.1 years) and the CS/SF group 9.9 years (6.3-13.4 years). Though, cTTE could only be performed in 57 patients, follow-up information was available in a total of 81 patients.

Long-term follow-up data could not be retrieved (interview or cTTE) in 23 patients of which 6 were surgically closed, 4 died (no device related cause was suspected) and 13 were lost to follow-up.

Contrast TTE showed a RLS shunt in eight patients (17.4%) who received an ASO. Of these, five patients (10.9%) had a minimal, one patient (2.2%) a moderate and two patients (4.3%) a severe residual shunt. Five patients who received a CS/SF device (45.5%) had a residual RLS of which three patients (27.3%) had a minimal and two patients (18.2%) a moderate residual RLS. When minimal shunts were excluded, the

closure rate was 93.5% for ASO and 81.8% for the CS/SF device, respectively. There was no recurrent LRS at latest follow up. Our analyses showed no significant differences in the diameters of the ASD or the device used between the patients with or without a residual shunt. Secondly, no predictors for a right-to-left shunt at long-term follow-up could be found using univariate analysis.

Recurrent thrombo-embolic events after more than 12 mo of follow-up occurred in two patients (1.9%, 2 ASO). One 40-year-old patient suffered a cerebrovascular accident 2.5 years after ASD closure, while on aspirin because of coronary artery disease. Although there was no history of SVT or device thrombus, oral anticoagulation was initiated after this event. At long-term follow up, a minimal residual RLS was found. The other patient (48-year-old) was known with a history of multiple TIA's prior to closure and was therefore treated with Aspirin. Despite closure of the ASD and optimal medical treatment, the patient suffered from another TIA more than 5 years after ASD closure. At the long-term follow-up visit no residual shunt or thrombus formation on the device was found. This patient had no history of SVT. In total, 3 patients suffered a recurrent neurological event during a mean follow up of 6.4 years (0.5% per year follow up).

During long-term follow-up, new-onset SVT occurred in 3 patients (3.9%) who received an ASO and in none of the patients who received a CS/SF device.

Long-term residual shunt rate, recurrent thrombo-embolic event rate and new-onset SVT rate are presented in Table 3. Figure 1 shows the percentage of patients with residual right-to-left shunt at more than 5-year follow-up after percutaneous ASD closure.

A flow-chart showing the results of this study during follow-up is presented in Figure 2.

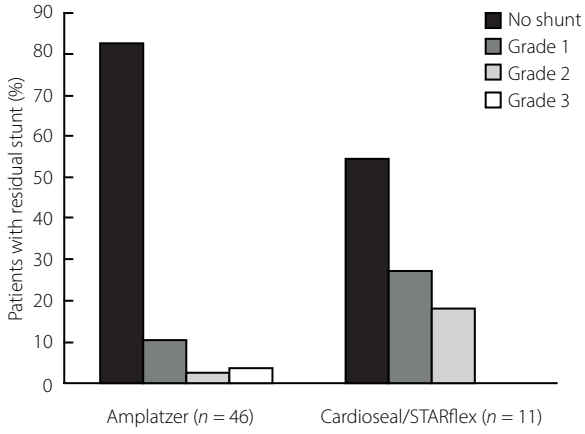

Figure 1. Percentage of patients with residual right-to-left shunt at more than 5-year follow-up after percutaneous atrial septal defect closure.

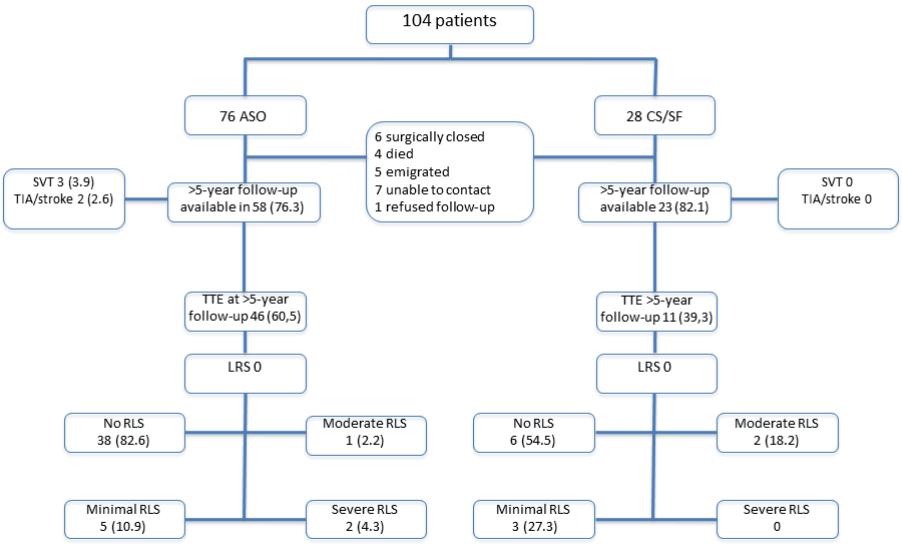

Figure 2. Flow-chart showing the results of this study during follow-up.
Data is presented as number of patients (%). ASO: Amplatzer; CS/SF: Cardioseal/Starflex; SVT: Supraventricular arrhythmia; TIA: Transient ischemic attack; TTE: Transthoracic echocardiography; LRS: Left-to-right shunt; RLS: Right-to-left shunt.

Table 3. Five years follow-up

	Amplatzer	Cardioseal/STARflex
5 years follow-up available, n (%)	58 (76.3)	23 (82.1)
New-onset SVT		
0 – 1 year	5 (6.6)	5 (17.9)
> 1 year	3 (3.9)	0
Reoccurrence TIA/stroke		
0 – 1 year	0	1 (3.6)
> 1 year	2 (2.6)	0
TTE > 5 years FU available, n	46	11
RLS:		
No shunt	38 (82.6)	6 (54.5)
Minimal	5 (10.9)	3 (27.3)
Moderate	1 (2.2)	2 (18.2)
Severe	2 (4.3)	0
LRS	0	0
Follow up (years)	6.6 (5.0 – 11.1)	9.9 (6.3 – 13.4)

SVT, supraventricular arrhythmia; TIA, transient ischaemic attack; TTE, transthoracic echocardiography; FU, follow-up; RLS, right-to-left shunt; LRS, left-to-right shunt.

Discussion

Percutaneous ASD closure has relatively good long-term safety- and efficacy profiles, especially using the ASO device. A high residual RLS was present in CS/SF. Residual LRS was not observed in either the ASO- or the CS/SF group.

Complications

Device embolization and dislocation is a well-known complication after percutaneous ASD closure[10,11]. The CS/SF is related to a relatively high embolization rate compared to the ASO[12]. In literature, embolization of the CS/SF has been described between 1.4% and 2.5% and for the ASO between 0.1% and 2.4%[7,10,13,14]. In all studies, embolization occurred during the procedure or the index hospitalization. Kefer et al[15] and Masura et al[16], described 112 and 151 patients with a mean follow-up of 5 and 6.5 years, respectively, and showed no device embolization using the ASO device.
In our study 4 major complications (3.8%) occurred within the first six months after closure. Device migration occurred in 10.7% of the patients with a CS/SF device and in 1.3% using an ASO device. All devices were surgically extracted and the ASD was closed with a patch. Compared to the literature our CS/SF subgroup had a higher complication rate, while the ASO subgroup was similar. Hence, the CS/SF devices are no longer available for ASD closure. However, long-term follow-up of patients who received a CS/SF device is recommended.
Because device embolization occurred more often in patients with a Cardioseal/Startflex device, we analysed potential reasons/risk factors only for this device. Post et al[5] showed that the initial ASD and the device diameter were significantly higher in the patients in whom the device was embolized. However, due to the small sample size of this study it is difficult to make any conclusions.

Recurrent thrombo-embolic events

Kefer et al[15] described a recurrent stroke rate of 0% after percutaneous ASD closure with similar devices and follow-up time as in our study. Masura et al[16] described no thrombo-embolisms during the entire follow-up period. One patient (0.6% per follow-up year) with an ASO device in the study of Spies et al[7] suffered a thrombo-embolic event, which could not be related to a residual shunt or device related thrombus formation.
In our study, the recurrent thrombo-embolic event rate during long-term follow-up was 0.4% per follow-up year for both devices, which is similar when compared to the literature. As described above, all patients were treated with anti-platelet therapy or oral anticoagulation and a minimal residual RLS was found in only one patient.

Arrhythmias

arrhythmias early after ASO or other devices implantation are common and extensively described[10,17,18]. Masura et al[16] also mentioned SVT's at early follow-up, but none during long-term follow-up. Chessa et al[10] noted that arrhythmias are the second most common complication in their study (2.6%) early after the procedure using both the ASO and the CS/SF. Tomar et al[19] described peri-procedural arrhythmias but none were seen during long-term follow-up (median 56 mo). At 2-year follow-up, Spies et al[18] found an annual incidence of new-onset atrial fibrillation of 4.1%. Butera et al[13] described 274 patients (153 ASO, 121 CS/SF) and showed no arrhythmias at follow-up (respectively 16- and 24-mo).

In our study, 3.9% of the patients with an ASO device had new-onset SVT without any abnormalities during cTTE at long-term follow up.

Residual shunting

Residual LRS rates for the ASO has previously been described in several studies and ranged between 0%-12.5% at long-term follow up[13-16,19,20]. Kefer et al[15] described a residual LRS rate of 4%. However, only 2 patients (1.8%) with a residual LRS had received an ASO. At 3-year follow-up, Masura et al[16] showed no residual shunt using color-Doppler. Butera et al[20] described 165 patients with a residual LRS rate of 2% in patients suffering multiple ASD's. At 24-mo follow-up, a non-significant difference between the ASO and CS/SF was found (respectively 0% *vs* 4.4%). In a study by Nugent et al[14], 72 patients received a CS/SF device with a total residual LRS of 12.5% between 12- and 24-mo of follow-up.

Our study showed no residual LRS for both devices at more than 5-year of follow-up. However, the prevalence of a RLS is relatively high. Earlier, Luermans et al[12] described a residual RLS rate of 14% 3.4 years after closure in 29 patients who received a CS/SF device.

In our study, the RLS rate for the ASO was 17.4% and 45.5% for the CS/SF device more than five years after closure. When excluding the minimal shunts, the ASO had a RLS rate of 6.5% and the CS/SF of 18.2%. The importance of this relatively high rate of RLS is unclear, as the reason for closure was mainly related to the presence of a LRS. Therefore, the fact that we did not notice residual LRS is an important observation. Moreover, to assess the clinical importance of the presence of a RLS, long-term follow-up might be necessary.

The difference in RLS rate after percutaneous ASD closure might be due to the different closing mechanisms; the ASO has a "stent-like" mechanism and consists of Nitinol metal with rounded disks with a polyester fabric sewn inside the meshed disks. The CS/SF device has a "double patch" mechanism and the fabric is directly exposed to blood[13,21]. The latter might delay the endothelialisation of the devices, which is important for complete closure of the ASD. Why endothelialisation happens in some patients better than others is unclear.

Limitations

Firstly, it is a single-centre design with a small sample-size. Secondly, we used cTTE at follow-up for residual shunt classification while the gold standard is contrast TEE. Though, we did not use contrast TEE, literature describes mostly studies where only color Doppler is used for the assessment of residual shunts. Thirdly, an independent core lab did not review the TTE's. Fourthly, the long-term follow up data was available in about 80% of patients; this might lead to an under- or overestimation.

Percutaneous closure of a secundum-type atrial septal defect seems to be safe using the ASO. Though, the RLS rate is relatively high, a residual LRS is absent more than 5-year after closure. The CS/SF appears to be associated with a relatively high complication- and residual RLS rate. Because of the unclear importance of a RLS after percutaneous ASD closure, long-term follow-up might be necessary.

Comments

background

An atrial septal defect (ASD) is a common cardiac defect and accounts for one third of all congenital heart diseases detected in adults. The diagnosis in adults is often made when complications of the shunt occur, such as pulmonary hypertension, heart failure, arrhythmias, or paradoxical embolism. Most of these complications might be prevented by closure.

Research frontiers

Since the first description of transcatheter device closure of an ASD in 1976, percutaneous closure of an ASD has been practiced and described extensively. Other studies showed the efficacy and safety of percutaneous closure of ASD's with different devices, mainly during mid-term follow up. Little is known about follow-up more than 5 years after percutaneous ASD closure in adults. We report the efficacy of ASD device closure at more than 5 years follow-up (long-term follow-up).

Innovations and breakthroughs

Previous studies showed that a percutaneous closed ASD using a Cardioseal/Startflex (CS/SF) is associated with a high residual right-to-left shunt (RLS) at mid-term follow-up. This study confirmed that a high residual RLS is still present during long-term follow-up. However, no left-to-right shunt (LRS) was present. Percutaneous closure using a Amplatzer device (ASO) has proven to be efficient at mid-term follow-up. During long-term follow-up no LRS was found. However, a relatively high RLS was present. The importance of RLS at follow-up is unclear. The safety for both devices is similar when compared to literature.

Applications

During long-term follow-up, percutaneous closure of ASD's seems to be safe using different devices, especially using the ASO device. A high residual RLS is present in CS/SF, however there was no residual LRS observed using both the ASO- and the CS/SF device.

Terminology

An ASD is an opening in the septum between the right- and left atrium. It is a congenital heart disease and therefore present at birth. An ASD can cause symptoms due to heart failure, arrhythmia's, paradoxical embolism and pulmonary hypertension. Percutaneous closure of an ASD is a relatively simple procedure where a Nitinol device is placed in the opening between the right- and left atrium. Tansthoracic ultrasound of the heart is used to check whether there is a residual opening in the atrial septum.

Peer-review

The paper by Dr. Snijder et al reports the experience in percutaneous closure of atrial septal defects in 104 patients using two devices. Interestingly, in a long-term follow-up a residual left-to-right shunt is absent, although the rate of a residual right-to-left shunt is relatively high.

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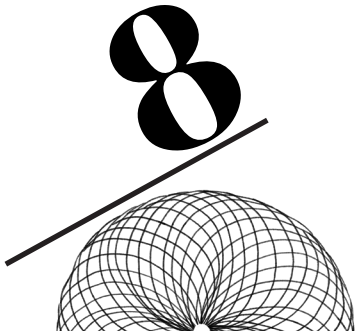

PERCUTANEOUS ATRIAL SEPTAL DEFECT CLOSURE USING THE OCCLUTECH FIGULLA DEVICE IN ADULTS, MORE THAN 800 PATIENT- YEARS OF FOLLOW UP

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Abstract

Purpose: The Occlutech Figulla occluder has been proven safe and effective at mid-term follow-up after percutaneous atrial septal defect (ASD) closure. We describe the safety and efficacy at long-term follow-up in adults.

Methods: All consecutive adult patients that underwent ASD closure between 2008 and 2015 were included. All complications were registered. Residual left-to-right shunt (LRS) was diagnosed using color-Doppler transthoracic echocardiography (TTE). Right-to-left shunting was diagnosed using contrast TTE. Successful closure was defined as no LRS at follow-up.

Results: In total, 166 patients (mean age 56.7±16.1 years, 62% female) underwent percutaneous ASD closure using the Occlutech Flex I (70%) or Flex II (30%) device (diameter 24mm, range 10-40mm) under general anesthesia and transoesophageal echocardiographic guidance. Long-term follow-up data were available in 144 patients (87%) with a mean follow-up of 5.9±2.6 years, a total of 814 patient-years. During hospitalization, device embolization occurred in three patients (1.8%) with successful extraction in all. During long-term follow-up, 15 patients (9.8%) suffered new onset atrial fibrillation and stroke occurred in 2.1%. There was no residual LRS at 12-months follow-up. No device embolization occurred during long-term follow-up.

Conclusion: Percutaneous ASD closure using the Occlutech device appears to be safe at long-term follow-up with a high successful closure rate at one year.

Introduction

Atrial septal defects (ASD) are a common cardiac congenital finding with complications due to the left-to-right shunt (LRS). Percutaneous closure of an ASD is considered to be the first choice and has been proven safe and effective using different devices [1, 2]. Worldwide, there is a lot of good experience with the Amplatzer Septal Occluder. The Occlutech Figulla Septal ASD Occluder (OFSO) was developed to improve feasibility of implantation and lower the rate of possible complications such as device thrombosis with an absent left atrial hub. In the past decade, three generations of the OFSO device were developed. All generations have proven to be safe and effective with a low complication rate during short- and mid-term follow-up [3-6]. However, little is known about the long-term complications of this extensive used device. We describe the safety and efficacy of percutaneous ASD closure in adults using the OFSO after more than 5 years of follow-up.

Methods

Population

All consecutive adult patients, ≥18 years of age, that underwent percutaneous ASD closure with the Occlutech Figulla ASD Flex I or Flex II device (Occlutech®) in the St. Antonius Hospital, Nieuwegein, the Netherlands, between 2008 and 2015 were included. The local ethics committee approved the study (registration number R&D/Z16.054).

Closing procedure

Percutaneous closure was performed under general anaesthesia using transesophageal echocardiography (TEE) and balloon sizing as reported earlier [6]. Depending on the size and morphology of the ASD, device size was chosen by the interventional cardiologist. The initial success rate was defined as successful implantation.

Follow-up

All complications were registered. All patients were discharged on antiplatelet therapy: clopidogrel (75 mg) for 4 weeks and aspirin (80-100 mg) for at least 6 months. If a patient was under anticoagulation therapy, only clopidogrel was associated for 4 weeks. Routine follow-up after closure was scheduled at 1, 6, 12 and 24 months using color-Doppler echocardiography to determine the presence of a residual LRS. Bubble contrast, at rest and after Valsalva, was used to identify a right-to-left shunt (RLS). The size of the RLS was classified by the number of bubbles in the left ventricle on a still frame and graded as minimal (<30 bubbles), moderate (30-100 bubbles), and

large (>100 bubbles) [7]. Successful closure was defined as no residual LRS shunt using color-Doppler. Firstly, the electronic patient file was studied whether the patient had recent follow-up (within 6 months). If not, the patient was asked to participate an interview by phone. A questionnaire was created together with the interventional and congenital cardiologists with standard follow-up questions. Besides complaints that were mentioned by the patient, questions were asked about: cerebral ischemic events (TIA's or stroke), presence of supraventricular tachycardia's and hospital admissions. If a patient was admitted to another hospital, this hospital was contacted to retrieve the necessary information. When it was unable to get in contact with the patient, the general practitioner was contacted. The questions were standardized to create complete and uniform data.

Statistical analysis

Descriptive statistics were used for patients' characteristics. Continuous variables with normal distribution are presented as mean ± standard deviation. All statistical analyses were performed using SPSS software (version 24.0 for Windows).

Results

Patient characteristics

In total, 166 adult patients (62% women; mean age 56.7±16.1 years) underwent percutaneous ASD closure using the Occlutech Figulla device between 2008 and 2015. During that study period no other closure device had been used. The Occlutech Figulla Flex I was implanted in 116 patients (69.9%) and the Occlutech Figulla Flex II in 50 patients (30.1%). There were no differences in baseline characteristics between patients who received the different devices. Patient characteristics of the whole group are summarized in table 1.

In-Hospital

Device implantation (mean diameter 24mm, range 10-40mm) was initially successful in all patients. However, device embolization occurred in three patients (1.8%) within 24 hours after implantation. After a failed attempt to retrieve the devices percutaneously, they were extracted surgically followed by closure of the ASD. Balloon sizing (using the Amplatzer sizing balloon II, 34 mm (Abbott)) was performed in almost all of the patients. However, another sizing balloon (NuMED PTS-X 40mm/5cm-sizing balloon (NuMED inc.)) had been used, in 2 out of the 3 device embolizations, leading to an inappropriate sizing due to inadequate calibration. In the other patient, a deficient aortic rim was present.

One patient (0.6%) suffered a significant amount of pericardial effusion (PE) a few hours

after closure and needed percutaneous drainage. The next day, a second TTE showed no PE. The drain was retrieved and the TTE repeated a couple of hours thereafter. Again the TTE showed no PE. The patient was discharged, and after one and four weeks, no recurrent PE was found by TTE.

Table 1. Baseline characteristics

Number of patients	166
Age (years)	56.7 ± 16.1
Female, n (%)	103 (62.0)
BMI (kg/m^2)	25.6 ± 4.5
Systolic blood pressure (mmHg)	129.3 ± 17.0
Diastolic blood pressure (mmHg)	79.2 ± 9.3
Risk factors and co-morbidities, n (%)	
Smoking	23 (13.9)
Diabetes	11 (6.6)
Arterial hypertension	50 (30.1)
Hypercholesterolemia	39 (23.5)
CAD	10 (6.0)
History of AF or AFl	19 (11.4)
Indication for closure, n (%)	
RV volume overload	104 (62.7%)
Cryptogenic stroke/TIA	47 (28.3%)
Other	15 (9.0%)
Echocardiography	
RVSP (mmHg)	25.4 ± 7.8
Peak TRV (m/sec)	2.5 ± 0.4
Peak TRV (2.9 – 3.4 m/sec), n (%)	24 (14.5)
Peak TRV (>3.4 m/sec), n (%)	4 (2.4)
Mean follow-up (years)	5.9±2.6

Data are presented as mean ± SD or number (percentage)
BMI, Body Mass Index; CAD, coronary artery disease; AF, atrial fibrillation; AFl, atrial flutter; RV, right ventricle; TIA, transient ischemic attack; RVSP, right ventricular systolic pressure

Follow-up

At 6 months follow-up, device thrombosis occurred in one patient (0.6%) who was noncompliant for oral anticoagulation therapy prescribed for recurrent idiopathic deep

venous thrombosis. The device was extracted surgically followed by closure of the ASD. All patients in whom a complication occurred recovered well. There were no significant differences in complications between both devices. In hospital complications are shown in table 2.
In total, new-onset AF occurred in 9.8% of the patients during the overall follow-up. Recurrent thrombo-embolic events occurred in seven patients (3 stroke 2.1%, 4 TIA 2.8%) during the total follow-up of almost 6 years. Details of these patients are summarized in table 3.
Six patients died during follow-up. Three patients died 15 months, two 18 months and one 33 months after closure, respectively. One patient died due to the complications of liver cirrhosis. This patient had no evidence of pulmonary hypertension on TTE prior to closure. Another patient died because of systemic inflammatory response syndrome due to orbital cellulitis. He had a slightly elevated right ventricular systolic pressure (RVSP 40 mmHg) prior to closure. A third patient died after a tuberculosis infection. Before closure, this patient an elevated RVSP (46 mmHg), which decreased after closure to 34 mmHg. A 70-years old male, with a history of arterial hypertension and coronary artery disease, died due to sever systolic heart failure after myocardial infarction. There was no thrombus on the device and no elevated RVSP or secondary signs of pulmonary hypertension prior to closure. The cause of dead of the other two patients is unknown. No device related cause was suspected after interviewing the families and general practitioners. One of these patients had a RVSP of 43 mmHg without secondary signs of pulmonary hypertension and the other patient had normal pressures and no signs of pulmonary hypertension either. However, no autopsy was performed. Therefore, a device related cause could not be excluded.

TTE was performed in 71 patients (49.3%) at 12 months follow-up. Follow-up information was available in 144 patients at long-term follow-up (mean 5.9±2.6 years); data (interview or TTE) could not be retrieved in 22 patients. There was no recurrent LRS at latest follow up. There were no significant differences between both devices at long-term follow-up. Long-term follow-up data are presented in table 4.

Table 2. Peri-procedural characteristics

General anaesthesia, n (%)	166 (100)
TEE guiding, n (%)	166 (100)
ASD diameter on TEE, mm⁺	15.6±6.1
ASD balloon sizing, mm⁺	20.9±6.7
Device	
Occlutech Flex I, n (%)	116 (69.9)
Occlutech Flex II, n (%)	50 (30.1)
Device diameter, mm*	24 (10 – 40)
In hospital complication	
Device embolization	3 (1.8%)
Pericardial effusion	1 (0.6%)
New-onset AF	3 (1.8%)
Groin hematoma	13 (7.8%)
TTE shunt, n (%)	
Color-Doppler	23 (14.1%)

* data presented as median (range)
⁺ data presented as mean ± standard deviation
TEE, transesophageal echocardiogram; ASD, atrial septal defect; AF, atrial fibrillation; TTE, transthoracic echocardiogram

Table 3. Thrombo-embolic events during follow-up

Patient, n	Age, years	Sex	Stroke/TIA	History of Stroke/TIA	Time after closure	AF history	RLS	Device thrombus
1	46	Male	Stroke	Stroke	<12 months	No	Minimal	No
2	74	Female	Stroke	No	<12 months	No	No	No
3	26	Female	TIA	Stroke	<12 months	No	Moderate	No
4	71	Female	Stroke	TIA	>12 months	No	No	No
5	79	Female	TIA	No	>12 months	No	No	No
6	46	Female	TIA	TIA	>12 months	No	No	No
7	58	Female	TIA	TIA	>12 months	No	No	No

TIA, Transient Ischemic Attack; AF, atrial fibrillation; RLS, Right-to-left shunt

Table 4. Efficacy and safety during follow-up

	<12 months follow-up	≥12 months follow-up
Number, n	166	144
Complications, n (%)		
TIA	1 (0.6%)	3 (2.1%)
Stroke	2 (1.2%)	1 (0.7%)
AF	9 (5.4%)	6 (4.4%)
Death	0 (0%)	6 (4.4%)
TTE available, n	163 (98.2%)	71 (49.3%)
LRS, n (%)	0 (0%)	0 (0%)
RLS, n (%)		
No shunt	113 (69.3%)	49 (69.0%)
Minimal	30 (18.5%)	16 (22.5%)
Moderate	15 (9.2%)	5 (7.1%)
Severe	5 (3.0%)	1 (1.4%)

TIA, transient ischemic attack; AF, atrial fibrillation; TTE, transthoracic echocardiography; RLS, right-to-left shunt

Discussion

Percutaneous ASD closure using the Occlutech device is safe and effective during a long-term follow-up of more than 800 patient-years.

Complications

In current literature, an overall initial successful device implantation using the Occlutech device had been described between 94% and 99% of the procedures [2-4, 8, 9]. Complications that are described are related to the invasive procedure itself, such as groin hematoma and pericardial effusion. Other complications are related to the specific procedure using a device. Firstly, a device embolization is described between 0% and 2.6% for which percutaneous- or surgical retrieval was necessary [2-4, 6, 9-13]. Haas et al. described 1291 patients that underwent successful percutaneous ASD closure with the Occlutech device. A device embolization occurred in 20 patients (1.6%) during hospitalization. There were another five embolizations during a mean follow-up of 2.7 years. Predictors for embolization are the absence of balloon sizing and the use of larger devices [9]. Kim et al. studied both the Occlutech and Amplatzer device in ASD closure and found an embolization in one patient (1.0%) using the Amplatzer device and none in the Occlutech group [14]. More recently, Kenny et al. described a randomized controlled

multi-center trial comparing the Occlutech and Amplatzer device in 176 patients (both children and adults). They found a more successful device placement (99% vs. 90%) and early efficacy (94% vs. 90%), and less in-hospital major complications (5.6% versus 9.8%) using the Occlutech versus Amplatzer device [12]. Secondly, atrioventricular block occurs between 0% and 3.4%, mostly caused by oversizing the device [2, 3, 6, 8-9]. This complication often resolved after extraction of the device. An atrioventricular block occurred in seven patients (0.5%) during hospitalization in the study by Haas et al. of which five needed a smaller device. Thirdly and less common is device thrombosis, this occurred between 0% and 1% [3-5, 7, 8]. There was no device thrombosis in the study by Haas et al. Fourthly, pericardial effusion after percutaneous ASD is found in about 1.9%. The etiology of the pericardial effusion is unclear, but predictors are older age and higher body surface area at closure [13].
In our study, implantation was successful in 98%. Embolization occurred in 1.8%, which is similar when compared to the other studies. All three devices were extracted surgically and the ASD had been closed without complications. There was one patient, non-compliant for coumadin, who suffered a device thrombosis (0.6%). One patient suffered pericardial effusion without evidence of device perforation. As mentioned above, there were no significant differences in complications between second and third generation devices. As earlier mentioned, Haas et al. described a large patient group of both children and adults. The median age was 26 years, range 0.3 to 83 years), which is significantly lower than our population. Furthermore, the first generation Occlutech Septal Occluder (OSO) was used in 42% of patients. In our study, only second and third generations devices were used. Though, our results are similar to those described by Haas et al., cautiousness is necessary when comparing both studies.

Cerebrovascular events

In literature, cerebrovascular events after closure are rare and occur between 0% and 2.3% [3-5, 8-11]. None of the patients described in four studies with a total number of 501 patients suffered a TIA or stroke after closure [3-5, 8]. The study by Haas et al. described four patients (0.3%) who suffered a TIA or minor stroke [9]. Takaya et al. and Wang et al. described a stroke rate after closure between 1.2% and 2.2%, which is higher when compared to other studies. Though it is unclear what causes this higher cerebrovascular event rate, the age of the patients in both studies is significantly higher when compared to the other studies and might be the reason for this difference [10, 11].
In our study, a stroke rate of 2.1% was found during long-term follow-up without a device related cause. One patient had a minimal RLS at follow-up; however, the clinical relevance of this small RLS is unclear. Patient characteristics as age and the presence of cardiovascular risk factors together with the longer follow-up duration could be the explanation. As described above, the age and cerebrovascular rate in the study by Takaya et al. and Wang et al. was high as well. A higher age is a predictor for cerebrovascular

events after closure and in the overall population as well [15]. The cerebrovasculair event rates were similar between both devices.

Arrhythmias

New-onset AF or atrial flutter is a known complication after percutaneous ASD closure and varies in studies between 0% and 4.7%. Supraventricular tachycardia's (SVT) occurred in 4.7% in the study by Haas et al. [9]. There was no new onset of SVT's reported during follow-up in the study by Pedra et al. and Roymanee et al. In 1% of the patients from the study of Aytemir et al. a SVT was diagnosed [4, 5, 8].
In our study, new onset AF occurred in 5.4% during the first year and in 4.4% at long-term follow-up, which is slightly higher when compared to literature. A possible explanation is the higher age of our patients when compared to the other studies. There were new-onset SVT's in 11.7% in the study by Wang et al., which is much higher than other studies [11]. This study also included patients with a higher age. Literature showed a higher incidence of AF in older patients and this might be the explanation [16]. There were no significant differences between both devices used. In most studies, new-onset SVT's were diagnosed according to symptoms or co-incidental finding on ECG during regular outpatient visits. Therefore, it is difficult to know the exact incidence of new-onset SVT's after closure.

Residual shunting

Successful closure using the Occlutech device varies between 90% and 100% at different follow-up times [2, 3, 8, 9]. In our study, successful closure was achieved in all patients that underwent TTE at 12-months follow-up. Though, TTE was only performed in 49% of patients so the success rate might be overestimated. Secondly, the LRS rate could be higher if TEE had been used instead of TTE. However, a small residual LRS found by TEE would probably have no clinical importance.

Limitations

Our study was an observational, single center study describing the Occlutech device without comparison to other devices. Further, TTE was used at follow-up making it possible to underestimate the residual LRS rate. However, it is unclear whether such a small LRS would be of clinical importance. There are no data about residual LRS at long-term follow-up but TTE at discharge or one-year follow-up showed no LRS making it unlikely that it would be found at long-term follow-up. We used telephone interviews for obtaining long-term data. This might be insufficient, and data about TTE are therefore not available.

Conclusion

Percutaneous ASD closure using the Occlutech device has a high successful closure rate at 12 months and appears to be safe at long-term follow-up with a low complication rate. However, more follow-up data is needed to make a reliable conclusion.

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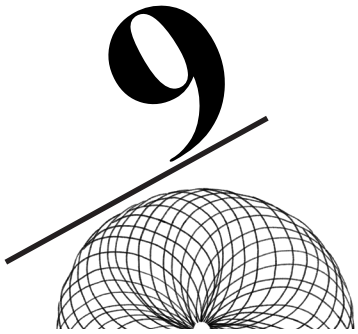

CASE REPORT: IMAGING OF AN UNUSUAL CASE OF A COMPLETELY UNROOFED CORONARY SINUS WITHOUT PERSISTENT LEFT SUPERIOR VENA CAVA

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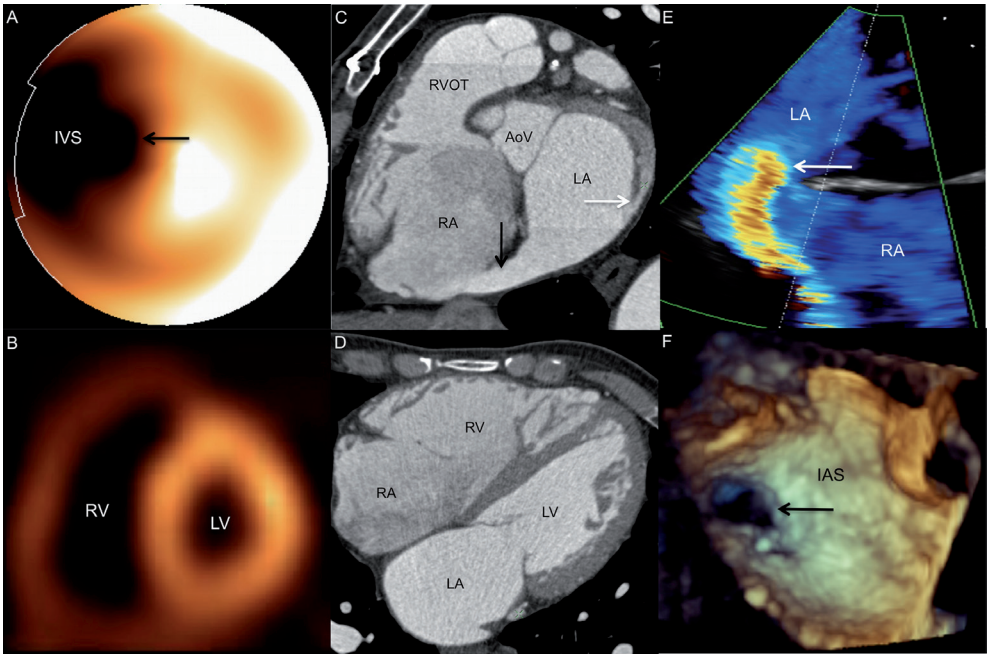
Eur Heart J Cardiovasc Imaging 2013;13(3):297

A 66-year-old male with a history of surgically closed secundum type atrial septal defect (ASD) during childhood and a percutaneous coronary intervention, suffered of recurrent stable angina. Clinical investigation and 12-lead ECG were unremarkable. He was referred for hybrid myocardial perfusion SPECT (SPECT) and 64-slice CT coronary angiography (CCTA). SPECT showed normal perfusion of the left ventricle (LV) and an enlarged right ventricle (RV). Gated images showed a decreased LV ejection fraction of 50% due to septal wall motion abnormalities suggestive for RV overload. Prospectively ECG-triggered CCTA revealed minor coronary atherosclerosis and a patent stent. Severe dilatation of the RV (388ml mid-diastolic) was confirmed. By coincidence, an inferior sinus venosus defect with unroofed coronary sinus with right-sided superior vena cava was observed (situs solitus, atrio-ventricular and ventriculo-arterial concordance). Mid- and great cardiac veins were inserted into the roof of the left atrium and a clear left-to-right shunt was visualized by CCTA. Three-dimensional transesophageal echocardiography showed the circular ASD (14mm) near the inferior vena cava. Right heart catheterization confirmed the left-to-right shunt (Qp:Qs 2.1) and pulmonary arterial hypertension (PaHT) (mean PAP 29 mmHg and PVR 106 dynes/sec/cm-5). Invasive coronary angiography confirmed the absence of recurrent significant CAD.

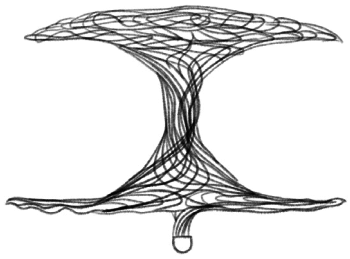
The patient was discussed in our grown-up-congenital-heart-disease team, and he underwent surgical closure of the defect, which is the treatment of choice in patients without Eisenmenger syndrome. Currently, four months after surgery he is free from anginal complaints.



Panel A. Quantitative gated SPECT showing bulls eye of left ventricle (LV) motion with a septal wall motion abnormality (black arrow).
Panel B. Myocardial perfusion SPECT, attenuation corrected, showing an enlarged right ventricle (RV) and normal perfusion of the LV.
Panel C. Computed tomography coronary angiography showing an interatrial connection with left-to-right shunt (black arrow) and insertion of the great cardiac vein in the left atrium (LA) (white arrow).
Panel D. Computed tomography coronary angiography showing an enlarged RV, 388ml mid-diastolic.
Panel E. Transesophageal color-doppler echocardiography showing severe interatrial left-to-right shunting (white arrow).
Panel F. Three-dimensional transesophageal echocardiography view from LA towards the interatrial septum showing an atrial septal defect (black arrow).
IVS indicates interventricular septum, RVOT, right ventricular outflow tract; AoV, aortic valve; RA, right atrium; LA, left atrium, LV, left ventricle; RV, right ventricle; and IAS, interatrial septum.

IV

part IV



IMAGING DURING PERCUTANEOUS PATENT FORAMEN OVALE AND ATRIAL SEPTAL DEFECT CLOSURE

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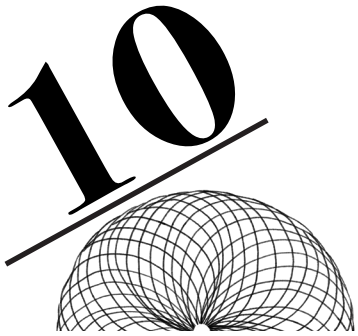

MICRO-TRANSESOPHAGEAL ECHOCARDIOGRAPHIC GUIDANCE DURING PERCUTANEOUS INTER-ATRIAL SEPTAL CLOSURE WITHOUT GENERAL ANAESTHESIA

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Abstract

Objective: Study the safety and efficacy of micro-transesophageal echocardiography (micro-TEE) and TEE during percutaneous atrial septal defect (ASD) and patent foramen ovale (PFO) closure.

Background: TEE has proven to be safe during ASD- and PFO closure under general anaesthesia. Micro-TEE makes it possible to perform these procedures under local anaesthesia. We are the first to describe the safety and efficacy of micro-TEE for percutaneous closure.

Methods: All consecutive patients who underwent ASD- and PFO-closure between 2013 and 2018 were included. The peri-procedural complications were registered. Residual shunts were diagnosed using transthoracic contrast echocardiography (TTCE). All data were compared between the use of TEE or micro-TEE within the ASD and PFO group separately.

Results: In total, 82 patients underwent ASD closure, 46 patients (49.1±15.0 years) with TEE and 36 patients (47.8±12.1 years) using micro-TEE guidance. Median device diameter was respectively 26mm (range 10-40mm) and 27mm (range 10-35mm). PFO closure was performed in 120 patients, 55 patients (48.6±9.2 years, median device diameter 25mm, range 23-35mm) with TEE and 65 patients (mean age 51.0±11.8 years, median device diameter 27mm, range 23-35mm) using micro-TEE.

There were no major peri-procedural complications, especially no device embolizations within all groups. Six months after closure, there was no significant difference in left-to-right shunt after ASD closure and no significant difference in right-to-left shunt after PFO closure using TEE or micro-TEE.

Conclusion: Micro-TEE guidance without general anaesthesia during percutaneous ASD- and PFO closure is as safe as TEE, without a significant difference in residual shunt rate after closure.

Keywords: Atrial septal defect, patent foramen ovale, percutaneous closure, micro probe, transesophageal echocardiography

Introduction

Transesophageal echocardiography (TEE) has proven to be safe and important during the guidance of transcatheter interventions for structural heart disease, such as closure of an atrial septal defect (ASD) or patent foramen ovale (PFO) [1-4]. One of the downsides of TEE is the relatively large probe that causes inconvenience for the patient, making general anaesthesia necessary. Another downside is the potential complications, such as local trauma to the oropharynx, esophagus or stomach. Microprobe TEE (micro-TEE) has proven to be safe and effective during transcatheter cardiac interventions in neonates and infants since 2009 [5-7]. More recently, micro-TEE is safely used in adults as well [8, 9]. Using a significant smaller probe makes general anaesthesia not necessary, which might result in fewer complications. The use of micro-TEE during ASD and PFO closure has not been reported earlier. We describe the safety and efficacy of micro-TEE in comparison to TEE for guidance of these procedures.

Methods

Population

All consecutive patients that underwent percutaneous ASD- or PFO closure with micro-TEE guidance between January 2016 and November 2018 in the St. Antonius Hospital, Nieuwegein, The Netherlands, were included. These patients were compared to all consecutive patients that underwent percutaneous closure with TEE guidance between March 2013 and December 2015. All patients underwent TEE previous to the procedure during an outpatient clinic visit. The local ethical commission approved the study.

Probes

TEE guidance was performed using the X7-2t TEE-probe (Philips Healthcare) with a shaft diameter of 10mm and head of 16 x 12 x 40mm. The imaging frequency ranges between 2- to 7MHz.

The micro-TEE probe used was a S8-3t (Philips Healthcare) with a shaft diameter of 5.2mm and head diameter of 7.5 x 5.5 x 18.5mm. The centre frequency is 6MHz on a bandwidth of 3.2- to 7.4MHz. Nijenhuis et al. described other specifications previously [8]. Both image modalities are presented in Figure 1 and Figure 2.

Sedation protocol

All patients received 2- to 6 sprays of Xylocaine (Lidocaine 100mg/ml) sprayed onto the oropharynx. When patients were anxious or restless during the procedures, Diazepam 2.5-10mg was administered intravenously. When light or moderate sedation was

necessary, Fentanyl (0,5–1mg/kg) or Midazolam (0,025–0,05mg/kg) was used and Propofol (0,5–0,75mg/kg i.v.) for general anaesthesia.

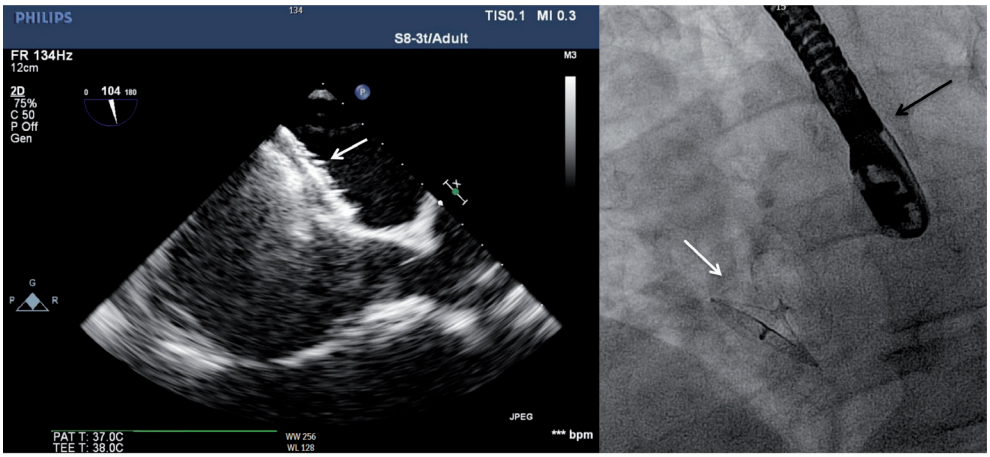

Figure 1. The Occlutech ASD device (white arrow) using the transesophageal echocardiography (TEE) probe (left side) and fluoroscopy (right side). The black arrow indicates the TEE probe during fluoroscopy.

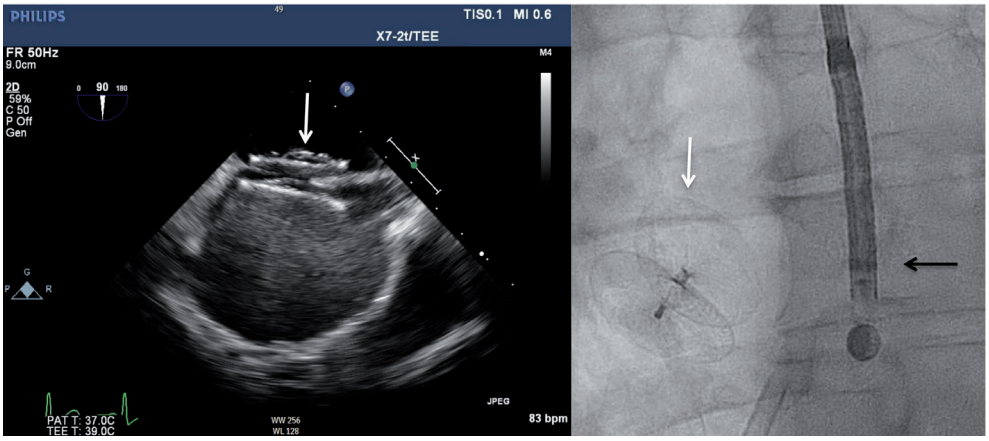

Figure 2. The Occlutech ASD device (white arrow) using the micro-transesophageal echocardiography (micro-TEE) probe (left side) and fluoroscopy (right side). The black arrow indicates the micro-TEE probe during fluoroscopy.

Procedure

Percutaneous closure with TEE guidance was performed under general anaesthesia and local anaesthesia was given in procedures were the micro-TEE was used. The interventional cardiologist chose the size of the device using balloon sizing and/or (micro-) TEE guidance. In all patients, the Occlutech Figulla Flex II device was used.

The procedures are described in detail earlier [10, 11].

Follow-up

All complications were registered. At 6-months follow-up a contrast TTE (TTCE) with color-Doppler was performed to determine the presence of a left-to-right shunt (LRS) in case of an ASD or for detecting a right-to-left shunt (RLS) after PFO closure using contrast. Successful ASD and PFO closure were defined as no residual LRS using color-Doppler and no- or a minimal RLS, respectively. The RLS was graded as none, minimal, moderate or severe [12].

Statistical analysis

Descriptive statistics were used for patients' characteristics. Continuous variables with normal distribution are presented as mean ± standard deviation. All statistical analyses were performed using SPSS software (version 24.0 for Windows).

Results

Patient characteristics

Between March 2013 and December 2015 percutaneous ASD closure was performed in 46 patients (mean age 49.1±15.0 years, 52.5% female) and PFO closure in 55 patients (mean age 48.6±9.2 years, 49.1% female) under TEE guidance.
Between January 2016 and November 2018, ASD closure was performed in 36 patients (mean age 47.8±12.1 years, 52.8% female) and PFO closure in 65 patients (mean age 51.0±11.8 years, 38.5% female) using micro-TEE guiding.
Within the ASD group, an atrial septal aneurysm (ASA) was present in 23.9% and 36.1% of the patients in both groups, respectively. Within both PFO groups, 40% of patients suffered an ASA.
Baseline characteristics and indication for closure are summarized in table 1.

Procedural outcome and in-hospital complications

All procedures using TEE guidance were performed under general anaesthesia, whereas all micro-TEE guidance were performed under local anaesthesia. Device implantation was successful in all patients and no procedural complications occurred in all groups.
Within the ASD closure group, the median diameter of the device used was 26mm (range 10-40mm) in the TEE-group and 27mm (range 10-35mm) in the micro-TEE group. PFO closure was performed using a device with a median diameter of 25mm (range 23-35mm) within the TEE group and 27mm (23-35mm) in the micro-TEE group.
After ASD closure, there was one patient (2.2%) with pericardial effusion without the

need for intervention in the TEE group. New-onset supraventricular tachycardia (SVT) occurred in one patient (2.8%) in the micro-TEE group.
In-hospital, there was one patient (1.8%) after PFO closure pericardial effusion without the need for intervention in the TEE-group and one patient (3.1%) with new-onset SVT in the micro-TEE group.
Peri-procedural complications are summarized in table 2.

Table 1. Baseline characteristics

	ASD			PFO		
	TEE	**Micro-TEE**	**P-value**	**TEE**	**Micro-TEE**	**P-value**
Number	46	36		55	65	
Age (years) *	49.1 ± 15.0	47.8± 12.1	0.682	48.6 ± 9.2	51.0 ± 11.8	0.227
Female, n (%)	53 (52.5%)	19 (52.8%)	0.735	27 (49.1%)	25 (38.5%)	0.242
BMI (kg/m^2) *	27.2 ± 5.9	26.9 ± 4.9	0.733	24.9 ± 3.1	25.5 ± 4.3	0.520
Risk factors and co-morbidities, n (%)						
Smoking	7 (15.2%)	3 (13.9%)	0.866	11 (20%)	6 (9.2%)	0.092
Diabetes	4 (8.7%)	2 (5.6%)	0.588	2 (3.6%)	4 (6.2%)	0.528
Arterial hypertension	13 (28.3%)	6 (16.7%)	0.222	14 (45.5%)	9 (13.8%)	0.107
Hypercholesterolemia	10 (21.7%)	5 (13.9%)	0.358	20 (36.4%)	10 (15.4%)	0.010
CAD	0 (0.0%)	1 (2.8%)	0.255	0 (0%)	2 (3.1%)	0.190
History of SVT	7 (15.2%)	1 (2.8%)	0.060	1 (1.8%)	2 (3.1%)	0.660
Positive family history	9 (19.6%)	6 (16.7%)	0.736	15 (27.3%)	12 (18.5%)	0.249
TEE characteristics, n (%)						
RLS after Valsalva	-	-		55 (100%)	65 (100%)	
Floppy/ASA	11 (23.9%)	13 (36.1%)	0.328	22 (40.0%)	26 (40.0%)	1.000
LRS	46 (100%)	36 (100%)		-	-	
ASD diameter (mm) ‡	15 (11-34)	15 (9-27)		-	-	

* Data are presented as mean ± SD or number (percentage)
‡ Data are presented as median (range)
ASD, atrial septal defect; PFO, patent foramen ovale; TEE, transesophageal echocardiography; BMI, Body Mass Index, CAD, coronary artery disease; SVT, supraventricular arrhythmia; RLS, right-to-left shunt; ASA, atrial septal aneurysm; LRS, left-to-right shunt

Follow-up

Six months follow-up data were available in 72 patients (88%) after ASD closure (46 TEE, 26 micro-TEE) and in 99 patients (83%) after PFO closure (54 TEE, 45 micro-TEE). A TTE was available in 71 (87%) and 96 patients (80%) six months after ASD and PFO closure, respectively.

ASD closure was effective in 100% (no LRS) in the TEE group and in 92% in the micro-TEE group. PFO closure was effective (no- or minimal RLS) in 51 patients (94%) in the TEE group and in 36 patients (86%) in the micro-TEE group. These differences were not statistically significant.
During follow-up, a stroke occurred in one patient after ASD closure in the TEE group. It concerned a 46-years old man with a history of two transient ischemic attacks (TIA's) and a stroke with a recurrent stroke three weeks after closure; a thrombus on the device could not be diagnosed. The patient was still on dual platelet therapy and had a minimal RLS at 6-months follow-up and no RLS at 12-months follow-up.

Table 2. In-hospital follow-up data after percutaneous ASD- and PFO closure using TEE and micro-TEE

	ASD		**PFO**	
	TEE	**Micro-TEE**	**TEE**	**Micro-TEE**
Number, n	46	36	55	65
Device diameter (mm) *	26 (10-40)	27 (10-35)	25 (23-35)	27 (23-35)
Complications, n (%)				
SVT	0 (0%)	1 (2.8%)	0 (0%)	2 (3.1%)
Device embolism	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Bleeding no transfusion	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Pericardial effusion	1 (2.2%)	0 (0%)	1 (1.8%)	0 (0%)
TTE, n	46 (100%)	36 (100%)	55 (100%)	65 (100%)
RLS, n (%)				
No shunt	-	-	20 (36.4%)	53 (81.5%)
Minimal	-	-	26 (47.3%)	8 (12.3%)
Moderate	-	-	4 (7.3%)	2 (3.1%)
Severe	-	-	5 (9.1%)	2 (3.1%)
LRS, n (%)	11 (24%)	3 (8.3%)	-	-

* Data are presented as median (range)
ASD, atrial septal defect; PFO, patent foramen ovale; TEE, transesophageal echocardiography; SVT, supraventricular tachycardia; TTE, transthoracic echocardiography; RLS, right-to-left shunt; LRS, left-to-right shunt

Discussion

Micro-TEE guidance during inter-atrial septal defect closure under local anaesthesia is safe, but shows a non-significant difference in efficacy during six months follow-up when compared to standard TEE and general anaesthesia.

Procedural complications

In literature, TEE guiding during percutaneous cardiac interventions has proven to be safe and effective [1-4]. Also, several studies have shown that micro-TEE is safe in infants and adults during percutaneous cardiac interventions [5-9]. None of these studies show peri-procedural complications related to the use of TEE or micro-TEE. Complications that could occur using (micro-) TEE are trauma to the oropharynx, esophagus or stomach. The advantage of local anaesthesia is spontaneous respiration, with a reduced risk for patients with cardiac and pulmonary comorbidities. There is also less need for nursing and monitoring with lower costs compared to general anaesthesia. However, local anaesthesia has disadvantages as well; a higher risk of anxiety, stress and discomfort during the procedure. Ehret et al. compared general and local anaesthesia in a systematic review and meta-analysis in patients undergoing transcatheter aortic valve implantation [13]. They found that both types of anaesthesia are equally safe. There was no difference in in-hospital and 30-day mortality and other complications. In our study, there were no TEE- or micro-TEE related complications as well. Furthermore, there were no complications due to general- or local anaesthesia. The hospitalization duration was equal in both groups. Importantly, in none of the sub-groups a device-embolization occurred.

Image quality

The difference in image quality was earlier published by Nijenhuis et al. They studied the difference in image quality between TEE, micro-TEE and intracardiac echocardiography (ICE) during left atrial appendage closure and MitraClip implantation. Image quality was comparable between micro-TEE and ICE, and the accuracy of micro-TEE is comparable to TEE. An important difference between TEE and micro-TEE is that micro-TEE has no three-dimensional view possibilities, which could help in sizing the defect and positioning the device [8]. Klettas et al. compared micro-TEE and TEE as well during different types of interventions (transfemoral aortic valve implantation, transfemoral mitral valve implantation, ASD- and PFO closure). They found that micro-TEE provides good anatomical image quality of relevant structures during these interventions [9].

Residual shunts

A residual LRS after ASD closure varies between 0% and 10% during a follow-up period between 6 months and 5 years [14-17]. In our study, a residual LRS was present in 24% in the TEE group and in 8.3% in the micro-TEE group immediately after ASD closure. During 6-months follow-up, the LRS resolves completely in the TEE group (0%) but was unchanged in the micro-TEE group (8.0%) using color-Doppler echocardiography. The difference between these groups was not significant (p=0.063). Unfortunately, the percentages of patients who underwent a TTE at 6-months follow-up differed significantly between both groups (100% versus 69%). The difference between

in-hospital and 6-months follow-up is unclear. It is possible that a better device position thanks to better image quality may cause an optimize device endothelialisation.
After PFO closure, the residual RLS rate ranges from 3% to 39% during a follow period between 6 months and 2 years [18-21]. The large difference between the studies can be explained by the difference in population size, but more important, by the difference in definition and method used for the diagnosis of RLS. In our study, a moderate- to severe RLS was present in 5.6% in the TEE group and in 14.3% in the micro-TEE group (p=0.197) at 6-months follow-up. Our population was relatively small, which could explain why the difference was not significant. The residual shunt rate of the micro-TEE group increased during 6-months follow-up when compared to in-hospital. It is possible that the patients that were lost to follow-up had no- or minimal RLS at follow-up creating a false high RLS rate.
It is unclear why this difference occurred. In literature, defect size, presence of an ASA, type and size of the device size, and experience of the operator influence the chance of a residual shunt after percutaneous ASD- and PFO closure [22, 23]. Firstly, balloon sizing for measuring the defect size was used in all patients in the ASD group making under- and oversizing unlikely. As balloon sizing was not used in percutaneous PFO closure, choosing the device size was based on imaging during the procedure. In both the ASD- and PFO-group, there was no difference in defect size in the subgroups. Secondly, the defect anatomy was determined by TEE previous to the procedure in all patients. The presence of an ASA was equal in all groups making this an unlikely cause. Thirdly, there was no significant difference in device size between all groups. Fourthly, there was no difference in device choice as all defects were closed using the same device. Finally, the operators were both very experienced and performed all procedures. There were no differences between operators.
As the predictors mentioned above did not show any difference between both groups, the only difference was the image modality. Because device position and device size (during PFO closure) were chosen using TEE and micro-TEE, the cause of the differences could be the image quality between these modalities. It is possible that the difference in image quality might cause undersizing or incorrect positioning of the device. However, previous studies did not find a difference in image quality during cardiac procedures [8, 9]. More studies are needed to show if there is an actual difference. Further, there was an important difference in available follow-up data making it more difficult to compare.

Arrythmia's and cerebrovascular events

A common complication after percutaneous ASD- and PFO closure is new-onset SVT's. New-onset SVT's can occur in up to 3.5% of the patients after ASD closure [16, 17, 24] and can rise up to 6.6% after PFO closure as described in large trials [24-26].
Arrythmia's after ASD- or PFO closure can occur due to oversizing of the device causing stress on the atrial cells of the inter-atrial septum. Therefore, the larger the device, the

more chance on the development of new-onset SVT's [27].
In our study, there was no significant difference in new-onset SVT's in both the ASD- and PFO-groups, in-hospital and at 6-months follow-up.
After ASD- and PFO closure, a recurrent cerebrovascular event has been described in respectively 0% to 0.3% and 0% to 5% [11, 15-18, 24, 28]. In our study, there was a recurrent stroke in one patient who underwent ASD closure (TEE group). After PFO closure, there were no recurrent cerebral ischemic events in both groups during 6-months follow-up. Though, the complication rate is low, our follow-up time is relatively short.

Costs
Besides improving the comfort of the patient, local anaesthesia makes general anaesthesia (including anaesthesiology backup) unnecessary during this procedure and therefore reduces costs.
Ahmad et al. did a cost analysis of patients receiving a transcatheter aortic valve replacement with general anaesthesia versus conscious sedation [29]. Though, hospitalization was shorter in the conscious sedation group, the total costs were not significantly different. Further, studies describing the costs of different surgical interventions under local versus general anaesthesia found significant reduction in cost when performing the intervention under local anaesthesia [30, 31].
In our cohort, we studied local- versus general anaesthesia instead of conscious sedation, making it difficult to compare the study of Ahmad et al. As the other studies did compare local- versus general anaesthesia we can conclude that using local anaesthesia can lower the costs of the procedure.

Limitations

Firstly, it was a single center, non-randomized study. Secondly, our study had a relatively small population making it more difficult to compare both image modalities. We used (contrast) TTE at follow-up for detecting a residual shunt while TEE is the gold standard. Finally, because 15% of the micro-TEE patients were lost to follow-up, it is possible that the event rate and residual shunting rate might differ significantly.

Conclusion

Using the micro-TEE during percutaneous ASD- and PFO closure is safe when compared to standard TEE, but it seems to be associated with a non-significant increase in shunt rate. However, it is less invasive without the need for general anaesthesia and no peri-procedural complications.

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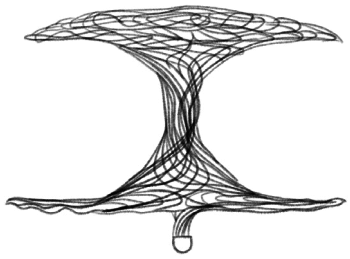
V

part V



GENERAL DISCUSSION

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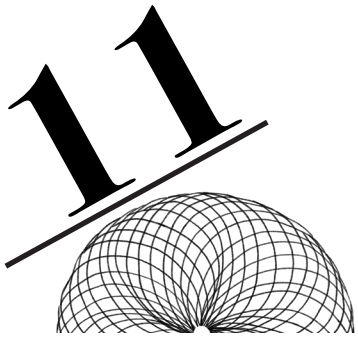

GENERAL DISCUSSION

Patent foramen ovale closure versus medical treatment

For years it was unclear whether patients suffering a cryptogenic stroke or transient ischemic attack (TIA) in the presence of a patent foramen ovale (PFO) should be treated with medical therapy alone or undergo percutaneous PFO closure as well. In 2012 and 2013, three large, prospective randomized trials were published studying the difference between medical therapy and percutaneous PFO closure in patients suffering cryptogenic stroke or TIA. Unfortunately, these trials did not show the benefit of PFO closure over medical therapy alone.

The first trial published was the CLOSURE-1 trial. They compared the Starflex device with medical therapy and found no significant difference in composite of stroke/TIA during 2-year follow-up, death from any cause during the first 30 days, and death from neurologic cause between 31 days and 2 years (respectively 5.5% and 6.8%) [1]. Secondly, the PC trial compared the Amplatzer device with medical therapy during a 4-year follow-up. The primary endpoint (composite of death, non-fatal stroke, TIA or peripheral embolism) occurred after closure and after medical therapy in 3.4% and 5.2%, which was not significant [2]. Thirdly, the RESPECT trial showed no significant difference between the Amplatzer device and medical therapy (respectively 1.8% and 3.3%) in composite of recurrent fatal and non-fatal ischaemic stroke, death from any cause within 30 days after implantation or 45 days after randomisation [3].

After the publication of these trials, there was even more discussion about PFO closure. However, these trials had some shortcomings. Firstly, the CLOSURE-1 trial used the Starflex device, which proved to be ineffective and less safe and is even off market. Though, the RESPECT trial used stroke as a primary endpoint, the CLOSURE-1 trial and PC trial used stroke and TIA. Further, inclusion criteria were disputable; the CLOSURE-1 trial included patients without proven ischemia on imaging and the PC trial patients with peripheral embolism. There was also a difference in long-term medical therapy, based on physicians' preference.

A few years later, two randomized trials and one long-term follow-up study of the earlier described RESPRECT trial were published and did show the benefit of PFO closure over medical therapy alone.

The Gore REDUCE trial randomized patients in a 2:1 ratio to percutaneous closure using the Helex Septal Occluder/Cardioform Septal Occluder and medical therapy versus medical therapy alone. They found significant more strokes in the medical therapy group during a median follow-up of 3.2 years [4].

During 5.3 years of follow-up, there were significant more strokes in the CLOSE trial as well. All devices that were approved by the interventional cardiology committee were accepted in this trial [5].

The previously described RESPECT trial published data with an extended median follow-up of 5.9 years. While there was no benefit of closure over medical during the

short-time follow-up, there were significant more strokes in the medical group during long-term follow-up [6].
In summary, the two trials and the extended follow-up study showed a significant benefit for percutaneous PFO closure when compared to medical therapy alone (especially antiplatelet therapy) in younger patients who suffer a cryptogenic stroke. This beneficial effect was greater in patients with a PFO with at least a moderate RLS and/or an atrial septal aneurysm (ASA) that are known to be a high-risk PFO [7]. A summary of these trials is shown in table 1.

Table 1. Study characteristics of CLOSURE 1- PC-, RESPECT-, Gore REDUCE- and CLOSE trial.

	CLOSURE 1	PC	RESPECT	Gore REDUCE	CLOSE
Patients (n)	909	414	980	664	663
Mean age (years)	45.9±9.5	44.5±10.1	45.9±9.9	45.2±9.4	43.3±10.4
Male (%)	51.8	49.8	54.7	60.1	58.9
Moderate or large RLS (%)	52.9	65.6	75.2	81.3	100.0
ASA (%)	36.6	23.7	35.6	20.4*	32.8
Treatment					
Type of medical therapy	Aspirin, OAC or both	Antiplatelet, OAC or both	Antiplatelet or OAC	Antiplatelet	Antiplatelet or OAC
Oral anticoagulation (%)	34.0	31.0	25.0	0.0	28.2
Type of closure device	STARFlex	Amplatzer PFO	Amplatzer PFO	Helex septal occluder/Cardioform septal occluder	Any ICC approved device
Follow-up					
Mean follow-up time (months)	44.0	49.0	31.0	38.4	63.6
Effective closure (%)	86.1	95.9	93.5	75.6	93.0
Drop-out medical therapy (%)	0.87	15.2	17.2	14.8	5.1
Drop-out closure device (%)	10.1	3.9	9.2	8.8	8.8
Adverse events medical therapy					
Major bleeding (%)	1.1	1.4	1.9	2.7	2.1
Atrial fibrillation (%)	0.7	1.0	1.5	0.4	0.9
Adverse events closure device					
Major procedural complication (%)	3.2	1.5	0.6	2.5	5.9
Non procedural major bleeding (%)	2.6	0.5	1.6	0.9	0.8
Atrial fibrillation (%)	5.7	2.9	3.0	6.6	4.6

Endpoints medical therapy					
Stroke (%)	3.1	2.4	3.3	5.4	6.0
TIA (%)	4.1	3.3	-	-	-
Death (%)	0.0	0.0	1.2	0.0	0.0
Endpoints closure device					
Stroke (%)	2.9	0.5	1.8	1.4	0.0
TIA (%)	3.1	2.5	-	-	-
Death (%)	0.0	1.0	0.6	0.5	0
Conclusion	No significant benefit for closure	No significant benefit for closure	No significant benefit for closure	Significant benefit for closure	Significant benefit for closure

RLS, right-to-left-shunt; ASA, atrial septal aneurysm; OAC, oral anticoagulation; ICC, Interventional Cardiology Committee. * = ASA was only measured in closure device group.

Safety and efficacy of PFO closure

Percutaneous PFO closure has proven to be safe using different devices, including the Occlutech Figulla device [8, 9].

Complications

The complication rate after percutaneous PFO closure varies between 0% and 15% [8, 10, 11]. There is a wide range in complication rate within several studies, which is probably due to the difference in population size. The larger randomized trials and the study with the extended follow-up reported a major peri-procedural event rate that rises up to 5.9% [4-6]. Our long-term follow-up study of the Occlutech PFO device showed no major peri-procedural events, proving that implantation of the Occlutech device is safe [12].

In literature, PFO closure using the bioabsorbable BioSTAR device has a complication rate that varies between 0% and 1.7% [13-15]. In these studies, with a total of 89 patients, only one malposition occurred (1.1%) for which retraction and replacement was needed. In our long-term follow-up study, no major complications occurred either using the BioSTAR device [16].

In summary, when looking to the Occlutech and the BioSTAR device, both these devices appear to be safe with a low peri-procedural complication rate.

Recurrent thrombo-embolic events

After percutaneous PFO closure, the recurrent thrombo-embolic event rate is different in the studies and varies between 0.0% and 5.0% [4-6, 8, 11, 17]. The larger trials described earlier had a longer follow-up time and found a recurrent strokes rate after closure in 0.0% to 3.6% and TIA in 3.4% [4-6]. The medical therapy group in these studies had a much higher stroke rate (5.4% to 6.0%). In our study using the Occlutech device, recurrent stroke occurred in 9 patients (3.9%) after more than 1300 patient-years of follow-up [12]. This is comparable to the results of the large trials. Furthermore, none of the patients with a recurrent stroke or TIA had a moderate or severe RLS at follow-up showing that the Occlutech device seems to be very effective.

In the study by Aytemir et al. both the Occlutech (57%) and the BioSTAR (9.5%) device were used. In total, 221 patients underwent closure and a recurrent stroke or TIA occurred in 0.5% and 1.3% during a median follow-up of 30 months [17].

Ussia et al. and Karagianni et al. both studied the BioSTAR device as well and found a recurrent stroke in respectively 0.0% and 3.0% of the patients during a follow-up time of 8 and 36 months, respectively [14, 18].

During 24-months follow-up, we found no recurrent strokes, a recurrent TIA occurred in 3.6%, both comparable to literature [16].

In summary, the recurrent thrombo-embolic rate at long-term follow-up is low for both

the Occlutech and the BioSTAR device.

Residual right-to-left shunt

An atrial septal defect (ASD) is an ovale-shaped defect, whilst a PFO is a slit-like opening, making it more challenging for a device to fully close a PFO. For adequate endothelialization, it is important that the closure device approximate the septa completely. Devices that are not self-centering push against the edge of the PFO, making it even wider. Larger PFO's and anatomical differences such as a long-tunnel PFO (≥10mm tunnel length), ASA, floppy inter-atrial septum, presence of a prominent Eustachian valve or Chiari's network can create technical difficulties during implantation and may prevent effective closure. Another predictor for a residual RLS seems to be the use of larger devices (>30mm) [23-26].

In literature, the residual shunt rate after PFO closure ranges from 8% to 21% [23-25]. The difficulty about interpreting the results is not only the difference in population sizes, devices used or follow-up time, but also the imaging technique used to diagnose RLS. The best way to detect an RLS is by contrast TEE, however, most studies use contrast TTE. Further, the way the Valsalva maneuver is performed can variate and some studies did not even perform a bubble contrast TTE but only used color-Doppler for RLS detection, for example in the study by Aytemir et al [8]. Valsalva is normally performed by letting the patient stop breathing, closing their mouth and nose, and strain. Because this technique is mostly dependent on the patient's effort, it can fail. Takaya et al. found that when Valsalva is performed with forced abdominal compression the sensitivity of detecting a PFO by contrast TTE increased from 85% to 99% [27].

The definition of a residual RLS differed between studies. An RLS is graded as minimal, moderate or severe depending on the amount of bubbles present in the left atrium on a still frame. Some studies only report severe RLS in their follow-up as others also mentioned moderate or minimal RLS. The clinical relevance of a minimal RLS at follow-up seems to be not relevant.

For example, Saguner et al. found a residual RLS in 39% including patients with a minimal- and moderate RLS [11], while Krizanic et al. found only a 3.7% residual RLS rate but excluded all patients with a minimal RLS [10]. A larger and more recent study by Hildick-Smith et al. described 100 patients who received an Occlutech device and found a residual RLS (moderate or severe) in 20.7% [25]. This shows the wide variation between studies. After 12-months follow-up, we found an RLS in 32.1% (minimal 26.2%, moderate 4.3% and severe 1.6%) using the Occlutech device.

Looking at the Amplatzer PFO Occluder, a variation in RLS is found as well. Where Shah et al. only found an overall residual RLS in 8.4% at 11-months follow-up, Cheli et al. described a residual RLS in 29% [26, 28]. Though Shah et al. reported a low residual RLS rate in 880 patients; they only repeated contrast TTE during follow-up in patient who had a residual RLS during a previous contrast TTE. It is possible that a Valsalva

maneuver was performed incorrectly during a previous contrast TTE and therefore missing an RLS. As mentioned above, it is possible that difference in devices (design) or RLS detection techniques could be the cause for the variation in RLS rate after closure. The residual shunt rate at 6-months follow-up using the bioabsorbable device varies between 4% and 45% [13, 15, 18, 29, 30]. Mullen et al. and Karagianni et al. found a residual RLS in respectively 4% and 13% (moderate and severe) at 6-months follow-up [13, 18]. At 12-months follow-up, Karagianni et al. found a residual RLS in only 3%. Though, Morgen et al. found no residual shunt during follow-up, they only used color-Doppler. Furthermore, their study population consisted of children, whereas in our study only adults were included [29]. Van den Branden et al. found a mild- to moderate RLS in 23.7% during 6-months follow-up [31].
Although, the device has been of market for a while due to a relatively high residual RLS rate and a high percentage of new-onset supraventricular tachycardias (SVT) (17% at 6-months follow-up), we reported the 24-months follow-up data because many patients were treated with this device making it important to study the long-term effects. We found that this device has still a high residual RLS rate of 30.1% (21.8% minimal, 9.1% moderate and 0.0% severe) at 24-months follow-up [16].
In summary, the Occlutech device in effective at 12-months follow-up with a relatively low moderate- to large shunt rate. However, the BioSTAR device proved to be a less effective device during long-term follow up with a higher residual shunt rate and a high percentage of SVT's.

Arrhythmias

An SVT has been reported frequently after percutaneous PFO closure. The exact reason remains unclear, but several hypotheses have been theorized. The device itself is a foreign body that causes a local inflammatory response, which can cause an arrhythmia. Further, the device can cause an electrical disturbance in the septum causing new reentry circuits. It is also seen more frequent in older patients and in patients treated with the STARFlex device [32]. Oversizing of the device creates stress on the atrial cells, which can lead to arrhythmias as well [33].
In literature, the incidence of SVTs after PFO closure rises up to 6.6% [4-6, 11, 17, 25]. In the smaller observational studies, SVT was found in 0.0% to 1.3% [11, 17, 25]. All studies used the Occlutech device. The earlier described larger trials found SVTs in a wider range from 0.6% to 6.6%. We found SVT in 6.6% of patients after closure with the Occlutech device during long-term follow-up, only 2.6% occurred more than 2 years after closure [12]. In our study, the new-onset SVT rate using the BioSTAR device was 11.3% within the first month and 1.6% between 1- and 6-months [16].
The true incidence of SVTs after PFO closure remains unknown. Mostly, a SVT is diagnosed when a patient presents with symptoms at the hospital or when a SVT is found by coincidence during physical examination or on ECG during a regular check-

up. Rarely, 24- or 48-hour Holter registration is performed. Even then, a SVT is easily missed, as it is only a short moment in time that is registered. Further, it is possible that patient already had asymptomatic, paroxysmal SVTs before closure.
In summary, new-onset SVT after percutaneous PFO closure is a common complication, but its true incidence remains unclear.

Migraine and patent foramen ovale

Migraine is a common cause of headache with a huge impact on the quality of life and therefore acknowledged to be one of the most important disabling diseases [34]. Although, migraine is a multifactorial disease on which environmental factors and genetics play a role, the reason that these attacks occur remain unclear. One of the potential mediators of these attacks was thought to be a PFO. However, the association between migraine and a PFO was unclear due to conflicting results in literature [35-39]. The positive studies included patients that suffered a cryptogenic stroke or TIA; thus, symptomatic high-risk PFO's. Furthermore, there are studies of patients with migraine that show a higher prevalence of an RLS using transcranial Doppler [40, 41]. The negative studies excluded all these patients with a high-risk PFO and therefore lack to find the association between migraine and PFO. In literature, an important factor that is associated with a cryptogenic stroke or TIA is a PFO in combination with an ASA [42]. Because patients with migraine with aura (MA) have a higher risk for stroke, a PFO might be the clue [43-46]. A larger prospective trial was published confirming the association between PFO closure and MA. The PRIMA trial compared percutaneous PFO closure and pharmacological treatment in 107 patients and showed a lower frequency of MA days in the percutaneous closure group [47]. There were previous, smaller studies that showed a decrease in migraine attacks after PFO closure as well [48-52]. On the opposite, the MIST trial compared PFO closure with a sham procedure in patients with migraine and found no difference in migraine attacks [53]. Data were analyzed between 3- and 6-months after closure, which could mean that device-endothelialization was not yet complete and could therefore not show the benefit of closure. Further, the Starflex device was used, which has proven to be ineffective and less safe. The primary endpoint of this trial was cessation of migraine, which might be not realistic as other studies use reduction in migraine frequency.
More recently, Ben-Assa et al. included 110 patients with migraine (77% MA) and had a significant improvement of their migraine burden after PFO closure. Presence of an aura was associated with complete resolution of migraine symptoms (p=0.006). Absence of an RLS after closure was associated with improvement of more than 50% in migraine burden (p=0.017) [54]. He et al. included 450 patients in their retrospective study and divided the patients in two groups; with- and without ASA. The group with

ASA had significant more MA, ischemic lesions in the brain and a larger PFO size. After closure there was a reduction in migraine burden in both groups, but without significant difference between the groups [45].
In our large observational study, we found a strong association between MA and the presence of a PFO with ASA [55]. There was no association between MA and PFO without ASA and neither between PFO with ASA and migraine without aura. This finding helps us understand the discrepancy between all the previous studies. Though, many older studies tried to find an association between migraine and PFO, none studied the anatomy of the inter-atrial septum as well. Therefore, the difference in anatomy (the presence or absence of an ASA) could have influenced all the results. An ASA is found in 1%-2.5% of the general population in large autopsy and population-based studies [56, 57]. This also explains why some of the studies found a reduction in migraine attacks (especially in MA) and some did not after PFO closure. The more recent studies that looked to the anatomy of the inter-atrial septum as well did find this association.
More studies are needed to study the association between the anatomy of the inter-atrial septum and migraine. We might assume that PFO closure in patients with MA and an ASA could show the best results in the reduction in migraine-burden. Just like the difference in results of the large PFO closure trials in cryptogenic stroke [1-6]: patient selection is everything.

The pathophysiology of MA remains unclear and is mostly hypothesis based. As we described in our manuscript, we think that the micro-thrombi hypothesis is very plausible in some cases [44]. Micro-thrombi that originate in the venous circulation cross the PFO into the systemic- and cerebral circulation and might trigger a migraine attack. The aura is thought to be caused by cortical spreading depression, but if micro-thrombi are the substrate is unknown [58]. There are studies that show that the frequency of migraine attacks declines after atrial fibrillation ablation and that new diagnosed migraine occurred in patients with subtherapeutic INR. Also, some cases showed the benefit of warfarin on migraine [59-61]. We also found a protective effect of coumadin in patients with MA. These studies support the micro-thrombi hypothesis, but do not prove it. Unfortunately, there are no studies that truly prove this hypothesis, however, there are also no studies that prove otherwise. The etiology of migraine is multifactorial. In summary, a PFO with ASA is strongly associated with MA and closure of a PFO in these selected patients might be helpful. More studies are necessary to support this theory.

Atrial septal defect closure: safety and efficacy

The first percutaneous closure of an atrial septal defect (ASD) was described by Kings

and Mills in 1976 [51]. Between then and now, there has been a lot of development in closure devices and safety and efficacy has been reported extensively [9, 17, 63-68]. There has been good experience with the Amplatzer- and the Occlutech device, however other devices appear to be less safe and effective.

Complications

One of the major complications is embolization of the device [69, 70]. The incidence of embolization varies between devices and rises up from 2.5% for the Occlutech and Amplatzer device to almost 11% for the Cardioseal/Starflex device [53, 55, 56, 71-81]. Haas et al. described a large population with an in-hospital embolization rate of 1.6% using the Occlutech device [71]. They found that absence of balloon sizing and the use of larger devices are predictors for embolization.

There were a few studies that compared the Occlutech- and the Amplatzer device and found a slightly lower embolization rate (respectively 0.0% versus 1.0%) and a lower in-hospital complication rate (respectively 5.6% versus 9.8%) in favor of the Occlutech device [74, 76].

In our study, embolization occurred in 1.8% using the Occlutech device, which is comparable to literature. All devices could be extracted and the ASDs were successfully closed surgically [82].

Kefer et al. and Masura et al. included a total of 263 patients that underwent percutaneous ASD closure using the Amplatzer device and none of these patients experienced embolization; in-hospital and after more than 5-years follow-up [78, 79].

Embolization occurred in 1.3% in our study using the Amplatzer device that is comparable to literature [77]. Extraction of the device and closure of the ASD was performed surgically without complications.

The Cardioseal/Starflex device is no longer available for ASD closure due to a high complication rate (device embolization and device fracture). Though, Butera et al. found a non-significant difference in embolization rate between the Cardioseal/Starflex device and the Amplatzer device (respectively 2.5% and 0.7%), our embolization rate was 10.7% using the Cardioseal/Starflex device [77, 80-83]. One of the difference between both studies is the lager diameter of the ASD closed and used device, which is known to be associated with embolization.

Other complications like atrioventricular (AV) block, device thrombosis and pericardial effusion are rare using the Occlutech- or Amplatzer device (respectively 3.4%, 1% and 1.9% in literature) [9, 64, 66, 68, 71].

An AV-block mostly occurs due to oversizing of the device and resolves after device extraction [64, 66, 68, 71]. There were no AV-blocks in our studies using the Occlutech-, Amplatzer- or Cardioseal/Starflex device [77, 82]. There was one patient with device thrombosis in our study using the Occlutech device, however, this patient was non-compliant using coumadin for atrial fibrillation [82]. The etiology of pericardial effusion

remains unclear. A higher age and body surface area at closure appear to be predictors [75]. Pericardial effusion occurred in 0.6% using the Occlutech device and in 1.0% using the Amplatzer device. None of the patients with Cardioseal/Starflex device had pericardial effusion [77, 82].

Recurrent thrombo-embolic events

A recurrent thrombo-embolic event after percutaneous ASD closure is not common and occurs between 0.0% and 2.3% in literature [17, 66, 67]. Though, many studies report a recurrent stroke or TIA in only 0.0% to 0.3% of patients, two studies found a rate of 1.2% and 2.2% [17, 66-79]. We also had a relatively high cerebrovascular event rate after closure using the Occlutech device (2.1%), the Amplatzer device (2.6%) and the Cardioseal/Starflex device (3.6%) [77, 82].

A possible explanation is the higher age in these studies, as it is known that higher age is a predictor for cerebrovascular events after closure and in the overall population [84]. It is possible that the increase of atherosclerosis and (asymptomatic) atrial fibrillation with higher age could be the explanation for this finding. Also, we had a longer follow-up than other studies.

Arrhythmias

Arrhythmias are common after ASD closure and described extensively. The incidence of arrhythmias in patients with untreated ASDs is estimated to be 10% in patients under the age of 40 years and rises above 20% with increase of age, pulmonary arterial pressure and arterial hypertension. Atrial remodeling occurs due to longstanding haemodynamic overload caused by the LRS. The changes in the atrial tissue predispose to atrial fibrillation. Although ASD closure reduces the prevalence of atrial arrhythmias at long-term follow-up, evidence shows that these patients still have a higher risk than the general population [85-87].

Risk factors for arrhythmias after closure are oversizing of the device, which causes stress on the atrial cells and the inflammatory response to the foreign body [32, 33].

The incidence of arrhythmias after ASD closure varies between 0% and 11.7% independent of which device was used [17, 67-69, 71, 73, 79, 80, 88].

We found atrial fibrillation in 4.4% of the patients after closure with the Occlutech device at long-term follow-up [82]. The onset of arrhythmias after closure using the Amplatzer and the Cardioseal/STARTflex device was respectively 3.9% and 0% at one-year follow-up [77].

There are multiple possible reasons for this big difference. Firstly, there was a difference in age between the studies. Wang et al. included patients with a higher age and their arrhythmia rate was 11.7% [73]. Literature shows a higher incidence of atrial fibrillation in older patients, which could be the explanation [89]. Another explanation could be the way an arrhythmia was diagnosed. Mostly, studies diagnosed arrhythmias when

patients present themselves with symptoms or by coincidence on the outpatient clinic during routine physical examination or ECG. Therefore, it is hard to report the exact incidence. Further, the difference in design of the device might influence the prevalence.

Residual shunting

Regardless of which device was used, a residual LRS has been described in 0-12.5% of the patients after closure at long-term follow-up [64, 66, 68, 71, 78-80, 90-92]. We found no residual LRS using the Occlutech, Amplatzer and Cardioseal/STARflex device during long-term follow-up [77, 82]. Most studies used transthoracic color Doppler to diagnose a LRS, however, the LRS rate would be probably higher when using TEE, as this study is more sensitive to detect a LRS.
A residual RLS is often found during follow-up, but the clinical importance of an RLS after ASD closure is unclear because indication for closure was mainly related to the LRS, such as RV enlargement.

Image guiding during percutaneous PFO- and ASD closure

Choosing the most adequate image modality is important for transcatheter cardiac interventions. Many have been developed, some evolved and some are no longer in use. Besides the best image quality, other factors such as complication rate, comfort for the patient and costs play a role as well.

Complications

TEE has proven to be safe and effective during percutaneous PFO- and ASD closure [93-95]. However, the chance of complications and the need for general anesthesia makes TEE guidance less attractive. The complication rate varies between 0.1% and 1.4% and mainly concerns odynophagia [96]. More severe, gastro-intestinal complications such as esophagus perforation are rare [97]. Micro-TEE has proven to be safe and effective as well in both children and adults [98-102]. No peri-procedural complications occurred in these TEE- and micro-TEE studies.
The difference between TEE and micro-TEE is important, but between general- and local anesthesia as well. However, the rate of complication between general- and local anesthesia in patients undergoing transcatheter aortic valve implantation were similar [103].
There was no difference between TEE and micro-TEE in our study as well, nor was there between general- and local anesthesia [104].

Residual shunts

The goal of percutaneous PFO- and ASD closure is to close the connection between the

left- and right atrium. Unfortunately, sometimes a residual shunt remains after closure as described above.

TTE, TEE and intra-cardiac echocardiography (ICE) have been described during closure. All modalities have their advantages and disadvantages that could influence the chance on a residual shunt after closure. TTE allows using multiple planes, but its view on the inferior rim is limited after device deployment, which makes it difficult to check for residual shunts. The patient's habitus influences the acoustic window making it case dependent if TTE can be used [105]. A randomized trial studying TEE and TTE in ASD closure showed that TTE is as safe and effective (similar residual shunt rate) as TEE in selected cases [106]. TEE provides real-time images of the inter-atrial septum, especially when using three-dimensional (3D) TEE [105]. A dedicated echo cardiographer is needed to gain optimal images. Micro-TEE provides detailed images of the inter-atrial septum as well but without 3D possibility. ICE can be performed by the operator but needs additional expertise to use and is non-reusable [105]. It has a higher complication rate and a less wide view when compared to (micro-) TEE, which can influence device position [101]. Koenig et al. showed that there was no significant difference in residual shunt rate after the use of ICE and TEE in ASD closure [107]. Because there is no evidence that one modality has a lower residual shunt than the other, it is important to look at complications, costs and patient comfort.

We found no significant difference in residual shunts between the TEE- and micro-TEE group [104]. Although a non-significant increase in shunt rate in the micro-TEE group was seen, it is unclear why this difference occurred. Defect size, presence of an ASA, type and size of the device size, and experience of the operator all influence the chance of a residual shunt after percutaneous ASD- and PFO closure, but none differ significantly in our study [19-108]. Therefore, the only difference was the image modality. Unfortunately, our groups were relatively small with a high lost to follow-up rate in the micro-TEE group making it difficult to take firm conclusion.

Costs

In more invasive procedures, the hospitalization duration will be longer, and total costs higher. Besides minimize the complication rate and improving patient comfort, reducing costs play a role as well. A less invasive imaging technique makes general anesthesia unnecessary, with lower respiratory complications and hospitalization duration; decrease the costs. In literature, several surgical studies show a significant reduction in costs when local anesthesia was used [109, 110]. Other studies failed to show a significant reduction in costs comparing conscious sedation and general anesthesia [111]. Therefore, to reduce costs of the procedure, local anesthesia can make a difference.

Limitations

There were several limitations to our studies. Our studies were not randomized and single center, which decrease their value. Due to the relatively small population size of our- and some of the reported studies, it is difficult to compare these to each other. Also, different in- and exclusion criteria and different devices were used making it even harder to compare studies. There was a relatively high lost to follow-up rate is some of our studies making it hard to interpret these results. It was unclear if the lost to follow-up created over- or underestimation of complications and residual shunts. Almost all patients were referred for closure, creating a selection bias. As no sham procedure was used in our migraine study, it is unclear what contribution placebo has on the symptoms of these patients.

Conclusions and recommendation for the future

After a rough start, percutaneous PFO closure has finally proven to be the treatment of choice in young patients suffering a cryptogenic stroke in the presence of a PFO. It is safe and effective using different devices.
In the future, devices will keep improving, consisting of less material and have an even higher closure rate. Also, the selection process in choosing the right patient for closure will improve. More studies with larger populations and a wider range of age (not only young patients) will have to follow. Only then, we can find out which patients really benefit of percutaneous closure.
There seems to be an association between a right-to-left shunt and migraine with aura. Especially in the presence of a large shunt size and an atrial septum aneurysm. Closure of a PFO in these patients might improve symptoms. However, more studies are needed to prove this. Not only larger studies with longer follow-time are needed, also sham procedures to rule out a possible placebo effect have to be performed in these studies.
Percutaneous ASD closure is safe and effective. Though many devices have been used, the Occlutech device and the Amplatzer device have demonstrated to be effective with a high closure- and low complication rate. In the future, new devices will be developed consisting of less material, but keep up their high closure rate.
Just like TEE, micro-TEE has proven to be safe and effective in percutaneous PFO- and ASD closure. Though it seems that more patients had a residual shunt after closure when micro-TEE was used. Larger studies are needed to truly show that micro-TEE is as effective as TEE. Furthermore, more image modalities will be developed to improve image quality and patient comfort, while the complication rate and costs reduce even further.

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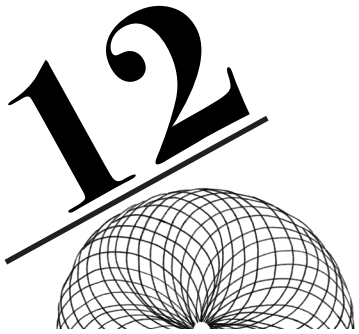

SUMMARY
SAMENVATTING
DANKWOORD
LIST OF PUBLICATIONS
CURRICULUM VITAE

Summary

This thesis reports the efficacy and safety of different devices in percutaneous patent foramen ovale- (PFO) and atrial septal defect (ASD) closure during long-term follow-up.
A PFO is a tunnel-like opening between the left- and right atrium. During Valsalva-like maneuvers, such as coughing, a right-to-left shunt (RLS) can occur, creating the possibility for a peripheral embolus to access the systemic circulation resulting in a stroke. Percutaneous PFO closure has proven to be safe and effective for several devices during long-term follow-up, whereas other devices have been taken off market because they proved to be ineffective and less safe.
Migraine is a common neurological disease with an immense disability burden. Patients with migraine with aura (MA) are known to have a higher risk for strokes. This seems to be related to the presence of a PFO, especially in combination with an atrial septal aneurysm (ASA).
An ASD is congenital defect of the atrial septum. A left-to-right shunt (LRS) is present in these patients due to the higher left atrial pressure compared to the right atrial pressure. An LRS causes right ventricle pressure- and/or volume overload. Percutaneous ASD closure is safe and effective in these patients using different devices.
Image guiding during these procedures is essential. Transesophageal echocardiography (TEE) is the gold standard for these procedures, but has some important downsides such as general anesthesia, inconvenience of the patient and possible complications. Micro-TEE has proven to be safe and effective during these procedures as well, but less downsides. An important downside however is that micro-TEE does not have three-dimensional view possibilities.
The aims of this thesis were to study the safety and efficacy for different devices in percutaneous ASD- and PFO closure during long-term follow-up. Further, comparing TEE and micro-TEE guiding during these procedures. Also, to study the association between migraine, presence of a PFO and septal anatomy.

Part one of this thesis consist **chapter 1**, which offer an introduction of the anatomy, pathophysiology and treatment/percutaneous closure of an ASD and PFO, including different image modalities during the closure procedures. Further, migraine and the relation to PFO is described.

Part two of this thesis consists of the efficacy and safety of percutaneous PFO closure. It further focusses on the association between migraine and atrial septal anatomy.
In **chapter two**, the efficacy of the bioabsorbable BioSTAR device at two-year follow-up is been evaluated. All 62 patients who underwent percutaneous PFO closure using the BioSTAR device in the St. Antonius Hospital between 2007 and 2009 were included.

Ninety-seven percent of the patients were referred by a neurologist because they suffered a cryptogenic stroke or transient ischemic attack (TIA). During two-years follow-up no major adverse cardiac events or strokes occurred. However, there was a moderate- or severe residual right-to-left shunt (RLS) present in 28.3% of the patients one day after closure. After two-years follow-up a moderate- or severe RLS was present in still 9.1% of the patients, which is much higher when compared to other devices. In conclusion, the bioabsorbable BioSTAR device is insufficient for percutaneous PFO closure.

Chapter 3 evaluates the safety and efficacy of the Occlutech PFO closure device during long-term follow-up. All consecutive patients that underwent percutaneous PFO closure between 2008 and 2015 in the St. Antonius Hospital were included. In total, 250 patients underwent closure and were included. Main indication for closure was stroke or TIA (89.6%). There were no major peri-procedural complications. Minor complications occurred in 7.2%. During a mean follow-up of 5.9±1.8 years, a cerebrovascular event occurred in 7.4%, a total cerebrovascular event rate of 0.02% per patient-year of follow-up. There was a residual moderate- or severe RLS in 5.9% at one-year follow-up. In conclusion, the Occlutech PFO Occluder is safe at long-term follow-up with a low annual cerebrovascular event rate and has a high closure rate at one-year follow-up.

In **chapter 4** we studied the association between migraine and atrial septum anatomy. All patients who underwent agitated saline transesophageal echocardiography (TEE) in the St. Antonius Hospital, Nieuwegein, the Netherlands and University Hospital Gasthuisberg, Leuven, Belgium were included. All patients received headache questionnaires, which were evaluated by two neurologists. Indication for TEE was evaluation of cardio-embolic source (45.1%), atrial thrombi pre-pulmonary vein isolation (20.2%), valve abnormalities (18.9%) and other (15.8%). A total of 889 patients were included. A PFO was present in 23.2%, an isolated atrial septal aneurysm (ASA) in 2.7% and a PFO with ASA in 6.9%. The occurrence of migraine was 18.9%, migraine with aura (MA) was 8.1% and migraine without aura (MA-) was 10.8%. In univariate analysis, the presence of a PFO with ASA was associated with MA (odds ratio 3.73, 95% confidents interval 1.86-7.44, P<0.001). A PFO without ASA was not associated with MA or MA-. Further, younger age and female sex were associated with MA as well. Thus, PFO with ASA is significantly associated with MA only.

In **chapter 5** we evaluate the literature in a point of view about percutaneous PFO closure and gives our perspective on how to decide which patients are suitable for percutaneous PFO closure.

Chapter 6 describes a case about a reclosure of a PFO after bioabsorbable device implantation.

Part three of the thesis concerns the efficacy and safety of percutaneous ASD closure for different devices.

In **chapter 7** we describe the efficacy and safety of two different devices more than five years after percutaneous ASD closure. All patients that underwent percutaneous ASD closure in the St. Antonius Hospital between 1998 and 2006 were included. The Amplatzer device (ASO) was implanted in 76 patients and the Cardioseal/Starflex (CS/SF) device in 28 patients. Major peri-procedural events occurred 1.9%. Two devices embolized during hospitalization (1 ASO, 1 CS/SF). There were two more embolizations during the first 6-months after closure, both with the CS/SF device. There was no difference in recurrent strokes or TIA's between both devices (0.4% per follow-up year). During a mean follow-up of 6.4±3.4 years, a supraventricular tachycardia (SVT) occurred in 3.9% in the ASO group and in 0% in the CS/SF group respectively. There was no residual left-to-right shunt (LRS) present in both groups. A moderate- or severe RLS was present in 6.5% in the ASO group and in 18.2% in the CS/SF group. Percutaneous ASD closure using the ASO and CS/SF device is safe during long-term follow-up, however, a relatively high RLS rate is present, especially in the CS/SF group. There was no residual LRS.

Chapter 8 reports on the efficacy and safety of the Occlutech Figulla ASD device during long-term follow-up. A total of 166 patients underwent percutaneous ASD closure using the Occlutech device between 2008 and 2015. The Occlutech Flex I was implanted in 70% and the Flex II in 30%. Indication for closure was right ventricle volume overload (62.7%), cryptogenic stroke or TIA (28.3%) and other (9.0%). Device embolization occurred in 1.8% during hospitalization. All devices were extracted successfully. During a mean follow-up of 5.9±2.6 years an SVT occurred in 9.8% and a stroke in 2.1%. There was no LRS at 12-months follow-up. In conclusion, percutaneous ASD closure using the Occlutech device is safe during long-term follow-up with a high successful closure rate after 12-months follow-up.

Chapter 9 provides a case of an unusual type of ASD, an unroofed coronary sinus.

Part five of this thesis consists of image modalities during percutaneous ASD- and PFO closure.

In **chapter 10** we compare the efficacy and safety of micro-TEE with local anesthesia to TEE with general anesthesia. All patients that underwent percutaneous ASD- and PFO closure with micro-TEE guidance between 2016 and 2018 in the St. Antonius Hospital were included and were compared to all patients that underwent ASD- and PFO closure with TEE guidance between 2013 and 2015. In total, 36 patients underwent ASD

closure with micro-TEE guidance and 46 patients with TEE guidance. PFO closure was performed using micro-TEE guidance in 65 patients and TEE guidance in 55 patients. There were no peri-procedural complications in all groups. There was no significant difference in residual LRS after ASD closure using micro-TEE and TEE. There was also no significant difference in residual RLS after PFO closure using micro-TEE and TEE. Therefore, micro-TEE guidance during percutaneous ASD- and PFO closure is safe without a significant difference in residual shunt rate.

Part six consists of **chapter 11**, the general discussion, gives an overview of the literature about the treatment of an ASD- and PFO. A short overview of the relationship between migraine and PFO is described. The limitations of these studies are discussed and recommendation for future research is given.

Samenvatting

In dit proefschrift wordt de effectiviteit en veiligheid van verschillende devices beschreven voor percutane atrium septum defect (ASD) en patent foramen ovale (PFO) sluiting gedurende een lange follow-up duur.
Een PFO is een tunnel-achtige opening tussen het linker- en het rechter atrium. Tijdens Valsalva-achtige manoevers zoals hoesten, ontstaat een rechts-links shunt (RLS) waardoor er mogelijk een perifere embolie in de systemische circulatie kan komen, resulterend in een cerebrovasculair accident (CVA). Percutane PFO-sluiting is bewezen veilig en effectief voor verschillende devices tijdens lange follow-up duur, andere devices zijn juist van de markt gehaald.
Migraine is een veel voorkomende neurologische aandoening die erg invaliderend kan zijn. Patiënten met migraine met aura (MA) hebben een hoger risico op het krijgen van een CVA. Dit lijkt gerelateerd aan een PFO, vooral in combinatie met een atriaal septum aneurysma (ASA).
Een ASD is een congenitaal defect van het atriale septum. Een links-rechts shunt (LRS) is in deze patiënten aanwezig door de hogere druk in het linker atrium in vergelijking met het rechter atrium. Een LRS zorgt voor rechter ventrikel druk- en volume overbelasting. Percutane sluiting van een ASD is veilig en effectief voor verschillende devices.
Beeldvorming tijdens deze procedures is essentieel. Transoesofageale echocardiografie (TEE) is de goud standaard voor deze procedures, maar heeft belangrijke keerzijdes zoals gehele anesthesie, ongemak voor de patiënt en mogelijke complicaties. Micro-TEE is bewezen veilig en effectief voor deze procedures, maar dan zonder de genoemde keerzijdes. Een belangrijk minpunt voor de micro-TEE is de afwezigheid van drie-dimensionele beeldvorming.
Het doel van dit proefschrift betreft het onderzoek naar de veiligheid en de effectiviteit van verschillende devices voor percutane ASD- en PFO-sluiting gedurende een lange follow-up tijd. Verder het vergelijken van TEE en micro-TEE tijdens deze procedures en het bestuderen van de associatie tussen migraine, de aanwezigheid van een PFO en atrium septum anatomie.

Deel 1 van dit proefschrift omvat **hoofdstuk 1**, de inleiding, geeft een overzicht geeft over de anatomie en de pathofysiologie. Verder geeft het een overzicht over de behandeling/ percutane sluiting van een ASD en PFO, inclusief verschillende beeldvorming technieken gedurende de procedures. Verder wordt migraine en de relatie tot PFO besproken.
In **deel 2** van dit proefschrift wordt de effectiviteit en veiligheid van PFO-sluitingen onderzocht. Verder wordt de relatie tussen migraine en de anatomie van het atriale septum onderzocht.

In **hoofdstuk 2** evalueren we de effectiviteit van het bioabsorbeerbare BioSTAR device na

een follow-up van 2 jaar. Alle 62 patiënten die een percutane PFO-sluiting ondergingen met het BioSTAR device in het St. Antonius Ziekenhuis tussen 2007 en 2009 werden geïncludeerd. Van alle patiënten werd 97% verwezen door een neuroloog in verband met een cryptogeen CVA of transient ischemic attack (TIA). Gedurende twee jaar follow-up ontstonden geen majeure cardiale complicaties of CVA's. Er was echter wel één dag na sluiting een matig- of ernstige residuale rechts-links shunt (RLS) aanwezig in 28.3% van de patiënten. Na twee jaar follow-up was er nog een matig- of ernstige RLS aanwezig in 9.1% van de patiënten wat meer is dan bij andere devices. Concluderend is het bioabsorbeerbare BioSTAR device insufficiënt voor percutane PFO-sluiting.

Hoofdstuk 3 evalueert de veiligheid en effectiviteit van het Occlutech PFO device met een lange follow-up tijd. Alle opeenvolgende patiënten die een percutane PFO-sluiting ondergingen tussen 2008 en 2015 in het St. Antonius Ziekenhuis werden geïncludeerd. In totaal ondergingen 250 patiënten percutane PFO-sluiting. Allen werden geïncludeerd. De voornaamste reden van sluiting was een CVA of TIA (89.6%). Er waren geen majeure per-procedurele complicaties. Kleine complicaties ontstonden in 7.2%. Gedurende een mean follow-up van 5.9+1.8 jaar ontwikkelden 7.4% een cerebrovasculair event met een cerebrovasculair event rate van 0.02% per patiëntjaar follow-up. Er was een matig- of ernstige RLS aanwezig in 5.9% na 1 jaar follow-up. Concluderend, de Occlutech PFO Occluder is veilig gedurende een lange follow-up tijd en heeft een hoog sluitingspercentage na 1 jaar follow-up.

In **hoofdstuk 4** bestuderen we de associatie tussen migraine en de anatomie van het atriale septum. Alle patiënten die een transoesofageaal echocardiogram met bubbel contrast ondergingen in het St. Antonius Ziekenhuis, Nieuwegein, Nederland en Universitair Ziekenhuis Gasthuisberg, Leuven, België werden geïncludeerd. Alle patiënten ontvingen een hoofdpijn vragenlijst die door twee neurologen werden geanalyseerd. De indicatie voor de TEE was evaluatie van een cardiale emboliebron (45.1%), atriaal trombus pre-pulmonale vene isolatie (20.2%), klepafwijkingen (18.9%) en overig (15.8%). In totaal werden 889 patiënten geïncludeerd. Een PFO was aanwezig in 23.2%, een geïsoleerd atriaal septum aneurysma (ASA) in 2.7% en een PFO met een ASA in 6.9%. Migraine was aanwezig in 18.9%, migraine met aura (MA) in 8.1% en migraine zonder aura (MA-) in 10.8%. Univariate analyse toonde een associatie tussen een PFO met ASA en MA (odds ratio 3.73, 95% confidents interval 1.86-7.44, P<0.001). Een PFO zonder ASA was niet geassocieerd met MA of MA-. Verder werd een associatie gevonden tussen het vrouwelijk geslacht en jonge leeftijd met MA. Samengevat, een PFO met ASA is significant geassocieerd met alleen MA.

In **hoofdstuk 5** evalueren we de literatuur in een point of view over percutane PFO-sluiting en geeft ons perspectief over welke patiënten geschikt zijn voor percutane PFO-sluiting.

Hoofdstuk 6 beschrijft een casus over een hersluiting van een PFO na implantatie van een bioabsorbeerbaar device.

Deel drie van dit proefschrift omvat de effectiviteit en veiligheid van percutane ASD-sluiting voor verschillende devices.

In **hoofdstuk 7** beschrijven we de effectiviteit en veiligheid van twee verschillende devices voor percutane ASD-sluiting na meer dan 5 jaar follow-up. Alle patiënten die een percutane ASD-sluiting ondergingen in het St. Antonius Ziekenhuis tussen 1998 en 2006 werden geïncludeerd. Het Amplatzer device (ASO) werd in 76 patiënten geïmplanteerd en het Cardioseal/Starflex device (CS/SF) in 28 patiënten. Majeure per-procedurele complicaties ontstonden in 1.9%. Device embolisatie gebeurde in twee patiënten tijdens opname (1 ASO, 1 CS/SF). Device embolisatie gebeurde nog tweemaal gedurende 6 maanden follow-up, beiden met een CS/SF device. Er was geen verschil in het aantal recidiverende CVA's of TIA's tussen de twee devices (0.4% per follow-up jaar). Gedurende een mean follow-up van 6.4+3.4 jaar, een supraventriculaire tachycardie (SVT) ontstond in 3.9% in de ASO groep en in 0% in de CS/SF groep respectievelijk. Er was geen residuale LRS in beide groepen. Een residuale matig- of ernstige RLS was aanwezig in 6.5% in de ASO groep en in 18.2% in de CS/SF groep. Percutane ASD-sluiting middels het ASO- en CS/SF device is veilig gedurende een lange follow-up tijd, maar een relatief hoog percentage RLS is aanwezig, vooral in de CS/SF groep. Er was geen residuale LRS.

Hoofdstuk 8 rapporteert de effectiviteit en veiligheid van het Occlutech Figulla ASD device gedurende een lange follow-up tijd. In totaal ondergingen 166 patiënten percutane ASD-sluiting middels het Occlutech device tussen 2008 en 2015. De Occlutech Flex I werd in 70% geïmplanteerd en de Occlutech Flex II in 30%. Indicatie voor sluiting was rechter ventrikel volume overbelasting (62.7%), een cryptogeen CVA of TIA (28.3%) en overig (9.0%). Device embolisatie gebeurde in 1.8% tijdens opname. Alle devices werden succesvol geëxtraheerd. Gedurende een mean follow-up van 5.9+2.6 jaar, een SVT ontstond in 9.8% en een CVA in 2.1%. Er was geen LRS aanwezig na 12 maanden follow-up. Concluderend, percutane ASD-sluiting middels het Occlutech device is veilig gedurende een lange follow-up tijd en heeft een hoog succesvol sluitingspercentage na 12 maanden follow-up.

Hoofdstuk 9 toont een casus van een zeldzaam type ASD, een sinus coronarius zonder dak/bovenkant.

Deel 5 van dit proefschrift bevat verschillende beeldvorming technieken voor percutane ASD- en PFO-sluitingen.

In **hoofdstuk 10** vergelijken we de effectiviteit en veiligheid van micro-TEE met lokale anesthesie en TEE met gehele anesthesie. Alle patiënten die een percutane ASD- of PFO-sluiting ondergingen met behulp van micro-TEE in het St. Antonius Ziekenhuis tussen 2016 en 2018 werden geïncludeerd en werden vergelen met alle patiënten die een percutane ASD- of PFO-sluiting ondergingen met behulp van TEE tussen 2013 en 2015. In totaal ondergingen 36 patiënten ASD-sluiting met micro-TEE en 46 patiënten met TEE. PFO-sluitingen werden verricht met behulp van micro-TEE in 65 patiënten en TEE in 55 patiënten. Er waren geen per-procedurele complicaties in alle groepen. Er was geen significant verschil in residuale LRS na ASD-sluiting voor zowel de micro-TEE- als de TEE-groep. Er was ook geen significant verschil in residuale RLS na PFO-sluiting voor zowel de micro-TEE- als de TEE-groep. Derhalve concluderen wij dat micro-TEE tijdens percutane ASD- en PFO-sluitingen veilig is zonder een significant verschil in residuale shunts.

Deel zes van dit proefschrift bevat **hoofdstuk 11**, de algemene discussie, geeft een overzicht van de literatuur over de behandeling van ASD's en PFO's. Een kort overzicht wordt gegeven over de relatie tussen migraine en PFO. De beperkingen van onze studies worden genoemd en er worden suggesties gedaan voor toekomstig onderzoek.

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Curriculum Vitae

Roel Jaap Robbert Snijder is geboren op 19 juli 1987 in Utrecht. Hij behaalde het Atheneum op het Montessori Lyceum Herman Jordan in Zeist in 2005. In datzelfde jaar startte hij met de studie Geneeskunde aan de Universiteit van Maastricht. De interesse in wetenschappelijk onderzoek ontstond na zijn derde jaar toen hij voor drie maanden naar Belém, Brazilië ging om deel te nemen aan een onderzoeksproject op de afdeling Chirurgie van Universidade Do Estado do Pará. Het project ging over reperfusieschade in ratten na verschillende ischemietijden. Vervolgens heeft hij dat jaar onderzoek gedaan naar de combinatie van ergometrie, coronaire calciumscore en CT-angiografie in de voorspelling van majeure cardiale events. Dit onderzoek vond plaats op de afdeling Cardiologie van het Maastricht Universitair Medisch Centrum onder begeleiding van Prof. dr. Hofstra.
Na één jaar arts-assistent niet in opleiding op de afdeling Cardiologie van het St. Antonius Ziekenhuis in Nieuwegein, startte op 1 januari 2014 de opleiding tot cardioloog (opleider Dr. ten Berg). Naast zijn opleiding tot cardioloog begon hij simultaan met zijn promotietraject wat resulteerde in dit proefschrift. Tijdens zijn hartkatheterisatiestage in het laatste jaar werd zijn interesse gewekt voor de interventie cardiologie en kon na het afronden van zijn opleiding op 31 december 2018 starten met zijn fellowship interventiecardiologie in het Catharina Ziekenhuis in Eindhoven.
Op 5 mei 2018 trouwde hij met Laura Renes en kregen een zoon in 2019 genaamd Bram.