Patent Foramen Ovale and Atrial Septal Defect: Diagnosis and Therapy

Laura Kleinebrecht1*, Amin Polzin1, Jan Balzer2, Tienush Rassaf3 and Tobias Zeus2

1Intern Division of Cardiology, Pulmonary Diseases, Vascular Medicine, University Hospital Düsseldorf, Moorenstr. 5, 40225 Düsseldorf, Germany
2Attending Division of Cardiology, Pulmonary Diseases, Vascular Medicine, University Hospital Düsseldorf, Moorenstr. 5, 40225 Düsseldorf, Germany
3Professor and Attending Division of Cardiology, Pulmonary Diseases, Vascular Medicine, University Hospital Düsseldorf, Moorenstr. 5, 40225 Düsseldorf, Germany

*Corresponding author: Dr. Laura Kleinebrecht, Intern Division of Cardiology, Pulmonary Diseases, Vascular Medicine University Hospital Düsseldorf, Moorenstr. 5, 40225 Düsseldorf, Germany; Tel: +49 (0)211 81-18800; Fax: +49 (0)211 81-18812; E-mail: Laura.Kleinebrecht@med.uni-duesseldorf.de

Epidemiology and Anatomy

Until recently there were no reliable data on the prevalence of congenital heart defects in Europe. The PAN Trial (prevalence of congenital heart defects in newborns) contributed to fill that gap. In Germany data on congenital heart defects in live-births were sampled in 260 facilities. In 2010 a survey referring to an acquisition period of one year (July 2006 until June 2007) was published. According to that 7,245 children (1.08 % of all live-births) were born with a congenital heart defect during this period of time. After ventricular septal defects (VSD), which are the most prevalent congenital heart defects (48.9%), atrial septal defects occurred in 17.0 % of all cases. Females were affected 1.5 to 2.5-times more often than males. In many cases spontaneous closure of the defect occurred during childhood [1].

The European Society of Cardiology defines five different types of atrial septal defects (ASD) (Figure 1):

I. The most common type of ASD is the ostium secundum atrial septal defect (80%). It is located within the area of the fossa ovalis and the adjacent septal myocardium.

II. The ostium primum atrial septal defect can be detected in 15 % of all patients with an ASD. It is found near the valve level and is often associated with a malformation of the atrioventricular valves. Synonymously, the terms atrioventricular septal defect (AVSD) or atrioventricular canal defect (AVCD) are used to describe this constellation.

One can define two types of sinus venosus atrial septal defect:

III. The superior sinus venosus atrial septal defect (5%) involves the inflow of the superior vena cava and is often associated with anomalous drainage of the pulmonary veins.

IV. The inferior sinus venosus atrial septal defect (<1%) can be found near the venous inflow of the inferior vena cava.

V. The unroofed sinus coronarius (<1%) corresponds with the inferodorsal left atrium [2].
A patent foramen ovale (PFO) can be observed in 27% of all individuals [3]. A PFO as such is no pathological finding. Potential complications are cryptogenic stroke (due to paradoxical embolism), migraine, decompression sickness or platypnea-orthodeoxia syndrome [3,4]. Rare clinical manifestations are renal infarctions or other forms of systemic embolization [5].

The patent foramen ovale resides from the embryonic circulation, when the window between septum primum and septum secundum allows physiological right-to-left-shunting in utero [6]. Post partum the foramen ovale is entirely sealed in two thirds of all individuals.

**Diagnosis and Therapy**

**ASD**

The guidelines of the European Society of Cardiology (ESC) precisely define diagnosis and therapy of atrial septal defects. An isolated ASD resolves in a left-to-right-shunt, since the pressure in the left atrium excels the one in the right atrium. Simultaneously, the compliance of the right ventricle exceeds the left one, which leads to volume overload of the right heart and thus to an increased pulmonary flow. Hence, the shunt volume depends on the pressure ratio, the compliance and the extent of the defect [2].

If an ASD is not diagnosed in utero or during childhood, it often remains undetected until adulthood - for most patients show first symptoms as grown-ups. The patient presents with reduced functional capacity, followed by dyspnoea and palpitations as manifestation of supraventricular arrhythmias [2].

Clinical signs of right ventricular overload are late symptoms and represent an advanced stage of the disease. During physical examination one can determine a widely split second heart sound and a systolic murmur of the pulmonary valve due to hypercirculation. The standard diagnostic tools are transthoracic and transoesophageal echocardiography. Table 1 shows specific informations, which have to be obtained during echocardiographic ASD evaluation [2].

The therapeutic treatment depends on the anatomy. Whenever possible, an interventional procedure should be preferred. Indications for ASD closure are shown in Table 2 according to ESC guidelines [2].

**Table 1 Specific questions to echocardiography**

- Anatomy of the defect and the surrounding atrial septal myocard
- Analysis of further valvular or structural defects
- Quantification of shunting volume/haemodynamics
- Right atrial and right ventricular dimensions and function

**Table 2 Indications for closure of an ASD [2]**

- Signs of a depressed right heart function and/or right heart dilatation
- Pulmonary vascular resistance (PVR) of < 400 dyn * s * cm^-5
- After paradoxical embolization an ASD of any size should be closed
- ASD in patients with a PVR > 400 dyn * s * cm^-5 should only be closed, if the pulmonary arterial pressure is up to < 2/3 of the systemic arterial pressure or if the PVR accords to < 2/3 of the systemic vascular resistance (SVR)
- Eisenmenger’s syndrome is a contraindication for ASD closure

Correct sizing is crucial for successful interventional closure of secundum defects. Several preprocedural imaging modalities have been used and evaluated for sizing like cardiac computer tomography, transoesophageal echocardiography and intracardiac echocardiography to name the most common. With the help of these tools, the total length of the atrial septum, the minimum and the maximum diameter of the defect have to be obtained. Especially in oval shaped ASDs, diameters can differ significantly. The measurements should be complemented by intraprocedural balloon sizing. Therefore, specialized soft balloons are used with the stop-flow-technique. Here the balloon is inflated with a saline-contrast-mixture until no residual colour-doppler-flow is seen besides the balloon through the ASD. Overstretching of the septum should be avoided, leading to oversizing of the occluder or even septal tear. The waist of the chosen occluder should be equal or up to +2mm compared to the inflated balloon diameter. Sometimes in oval ASDs the diameter of the waist of the chosen occluder, after evaluation with the stop-flow-technique, could even be less than the maximum diameter. However for stability reasons the difference should not exceed -2mm.

Figure 1: Types of atrial septal defects (1= ostium secundum ASD, 2= ostium primum ASD, 3= superior sinus venosus ASD, 4= inferior sinus venosus ASD, 5= sinus coronarius)

Figure 2: Large ostium secundum ASD with considerably left-to-right-shunt
large ASDs the diameter of the discs of the occluder should not exceed the total length of the atrial septum.

**PFO**

In patients, who suffered from cryptogenic stroke or transient ischemic attack (TIA) and who are solely diagnosed with PFO (± atrial septal aneurysm), the ideal secondary prevention remains unclear.

The 2014 AHA/ASA (American Heart Association/American Stroke Association) guidelines recommend anti-platelet therapy for patients, who do not undergo anticoagulation for other reasons. In addition, anticoagulation should be applied, if there is a venous source of embolism. If anticoagulation is contraindicated in the latter situation, the guidelines advise an inferior vena cava filter. Interventional PFO-closure might be evaluated in the presence of a deep vein thrombosis [7].

However, many cardiologists rate interventional closure as a reasonable preventive therapy in the first place. Usually, antiplatelet therapy can be stopped six months after the procedure, which seems beneficial regarding bleeding complications with lifelong antiplatelet therapy.

Several non-randomized trials produced inconsistent results comparing PFO closure to pharmacotherapy.

In 2010 the CLOSURE I trial presented prospective, randomized data for the first time. It was a multicenter study, which included patients with a PFO, who had experienced ischemic stroke or TIA within the previous six months. They were treated with STARFlex® device closure, or using aspirin, warfarin or both. In a follow-up time of two years, the incidence of primary endpoints (TIA, ischemic stroke, death from any cause [30 days] or death from neurological cause [31 days to 2 years]) did not significantly differ in the groups in neither intention-to-treat nor per-protocol analyses [8].

Another two randomized trials, PC and RESPECT Trial, were published in 2013.

In PC trial patients with ischemic stroke/TIA or extracranial thromboembolism participated. Amplatzer® PFO occluder was used during procedures. Oral anticoagulation or anti-platelet therapy was applied per discretion of the particular physician. The follow-up was the longest of all three trials with a mean time period of 4.1 years in the closure group (4.0 in the medical group). The incidence of adverse events was low (6 nonfatal strokes in 414 patients). The absolute number of strokes in the closure group was lower than in the medical-therapy group, but with few events it did not meet significance [9].

RESPECT trial enrolled patients, who sustained a cryptogenic stroke within the precedent 270 days. Amplatzer® device was used, too. The medical-therapy group was treated with warfarin or - in most cases (74.8%) - with anti-platelet drugs. Notably, the dropout rate was much higher in the medical-therapy group (17.2% to 9.2% in the device group). Follow-up ended with occurrence of the 25th primary end point (all of them nonfatal strokes) with a median of 2.1 years of follow-up. Intention-to-treat analysis showed no significant advantage of interventional closure. In the interventionally treated group, three patients suffered from a stroke prior to device implantation. Consequently, in per-protocol and as-treated analyses device closure in fact was superior to medical therapy [10].

Thus, subgroup analyses in RESPECT trial strongly suggested a beneficial effect, but a clear advantage of the procedure could not be shown.

These data provoked several reviews and meta-analyses. However, results from the meta-analyses remain inconsistent as well. One the one hand meta-analyses of the three randomized trials supported the conclusion, that there is no significant benefit of PFO closure compared to medical therapy in patients with a cryptogenic stroke [11-15]. It was even associated with a higher rate of adverse events like atrial fibrillation [12]. Other meta-analyses showed a significant advantage of the interventional procedure [16-21]. The effect became more apparent in sub-group analyses e.g. of patients from RESPECT and PC Trial only [16-18,20,21]. A recently published meta-analysis that included 14 prospective studies again did not determine a benefit of device closure compared to medical therapy [22].

We would like to discuss the following aspects, which could help to define, why the three randomized trials produced inconsistent information and did not show clear beneficial effects of PFO closure:

- The occluder used in CLOSURE I trial is inferior to other devices regarding occlusion rates in a long-term perspective [23]. The device was associated with an increase of atrial fibrillation. This effect was not observed in sub-analyses of RESPECT and PC trial, assuming this complication was occluder-related. Otherwise, device closure showed to be as safe as medical therapy (i.e. bleeding complications) [16]. In accordance to that a lately published meta-analysis showed that the effectiveness of the procedure is device related, making PFO closure with Amplatzer® device superior to medical therapy [24].

- In consequence of divergent inclusion criterias of the trials (TIA in or excluded), the groups pooled in meta-analyses are quite heterogeneous.

- In the medical group, the specific treatment for each patient depended on the individual physician’s preference making the groups difficult to compare [16,17].

- As the procedure was often performed off-label, the trials did likely not target the representative population [16].

- The total number of neurological events was notably low with considerably statistical relevance for each incident [16].

- Data suggest, that the benefit of device closure becomes clearer after about five years, meaning the follow-up period of time of two years was generally too short (CLOSURE I, RESPECT) [16].

- The low number of studies and patients enrolled dampens the statistical power [16].

Enliven Archive | www.enlivenarchive.org
Based on these thoughts more randomized trials are needed to further investigate the issue. As not all ischemic insults profit from device closure [16] future studies should pay major attention on identifying high-risk-groups. For instance, some data show, that patients with spontaneous shifting of contrast agent from right to left atrium via PFO might profit from an early interventional closure [25].

At the moment the perfect strategy of treating cryptogenic strokes remains unclear and an individualized decision.

3D Echocardiography

The exact identification of the size and the anatomy of the defect plays a crucial role in diagnosing an atrial septal defect. Based on the echocardiographical findings, an interventional or surgical therapy is planned. By using real-time 3D echocardiography during a transoesophageal examination, the defect can be overviewed in its full extent - which is the obvious difference to 2D echocardiography [26]. Regarding tissue bridges or multiply fenestrated defects, 3D echocardiography outperforms the 2D technique. (Figure 3) Current data show significant advantages in depicting the calibre of the defect and the anatomy of the interatrial septum [27].

The interventional closure of an ostium secundum atrial septal defect can be a procedure of less than 30 minutes or a complex intervention of more than one hour – depending on the anatomy of the defect. Most centres use transoesophageal echocardiography as per procedural imaging. Particularly with complex anatomies, 3D imaging is beneficial - resulting in decreased length of procedural time and thus reduced dosage of radiation [28]. These data match our own experiences in daily clinical practice with rising relevance of 3D imaging (Figure 4).

Furthermore, 3D echocardiography has a major role during preparation of a PFO closure, as rare variations like a small ASD next to a PFO can reliably be detected. Information from 2D echocardiography is sufficient for interventional closure of an isolated PFO.

Since 2014 real-time-fusion of echocardiography and fluoroscopy is an additional tool to facilitate procedures in structural heart disease (Echonavigator release II, Philips, Eindhoven). Using this tool, the interventionalist is able to control the echocardiographic views himself and gets an exact overlay (Figure 5).

Antiplatelet Medication Following Interventional PFO/ASD Closure

The PFO/ASD closure devices represent intracardial foreign material. This is known to induce platelet activation, which may lead to thrombus formation on the device. The incidence of thrombus formation on the device has been described to range from 0-10%[29]. Neoendothelialisation was described to be completed within three to six months [30,31]. Therefore, especially during this period, antiplatelet medication after PFO/ASD closure is crucial. Currently, multiple regiments regarding duration and substances after interventional PFO/ASD closure are applied. The ESC guidelines recommend antiplatelet medication with “aspirin minimum” for at least six months [2]. The CLOSURE I trial administered dual antiplatelet therapy (DAPT) with aspirin and clopidogrel for six months after interventional PFO/ASD closure, followed by aspirin medication for at least eighteen months [8]. Likewise, the PC trial also applied DAPT early after procedure. However, the duration of DAPT varied. Aspirin was administered for five to six months, duration of clopidogrel medication was recommended from one to six months [9]. DAPT for one month, followed by aspirin alone for five months has been prescribed in the RESPECT trial [10]. However, no randomized controlled data regarding the optimal antithrombotic regiment exists at all.
Krumsdorf et al. investigated the incidence of thrombus formation on PFO/ASD closure devices in a real-world registry of 1000 patients. Transoesophageal echocardiography was performed four weeks and six months after intervention to assess potential thrombus formation on the occluder. They reported an incidence of thrombus formation of 1.2% (ASD-occluder) and 2.5% (PFO-occluder). Three regimes of anticoagulation had been used [aspirin alone, dual antiplatelet therapy (DAPT) with aspirin plus clopidogrel and warfarin alone]. There were no significant differences between the groups regarding thrombus formation. Interestingly, in 91% of patients who experienced thrombus formation on the occluder, protamine was administered immediately after procedure to antagonize heparin effects. Thus, protamine administration was stopped. Subsequently, only one thrombus formation occurred in the following 183 patients. Additionally, the incidence of thrombus formation differed significantly between the applied occluders (CardioSEAL® device: 7.1%; STARFlex® device: 5.7%; PFO-STAR® device: 6.6%; ASDOS® device: 3.6%; Helex® device: 0.8%; Amplatzer® device: 0.0%) [23].

Braun et al. reported device adherent thrombus formation in 8 of 276 (2.9%) investigated patients undergoing transcatheter PFO closure. They empirically changed the postinterventional anticoagulation regime from aspirin alone to DAPT with aspirin and clopidogrel during the study. Afterwards, no further thrombus formation was detected. However, the used occluder device (PFO-Star® device) was refined simultaneously. The nitinol arms were translocated to the inner side, thus preventing nitinol material exposure to the left atrium [32].

Looking at this limited dataset it seems reasonable to apply DAPT for three months and aspirin alone for three months thereafter. Six months after closure antiplatelet therapy may be stopped until there is other indication.

Conclusion

Today, ASD and PFO closure are standardized and safe interventions in dedicated catheterization laboratories. As indications for ASD closure are well defined, indication for PFO closure remains source of debate and individualized solutions have to be sought. Perinterventional 3D echocardiography has improved safety and efficacy. Data on postinterventional antiplatelet therapy are rare. However, three months of dual antiplatelet therapy seems reasonable.

The authors declare, not to have any financial relation to a company that provides a product issued in this article (or a company that provides a rival product).

Reference


