Diagnosis of interatrial shunts
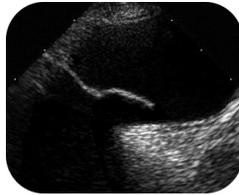# and the influence of patent foramen ovale
on oxygen desaturation in obstructive sleep apnea

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Cover picture: Transesophageal image of a patent foramen ovale.

Abstract

Patent foramen ovale (PFO) is found in 27% of the population and although mostly asymptomatic, PFO has been associated with e.g. cryptogenic stroke and, rarely, also with oxygen desaturation. PFO and atrial septal defects may nowadays be closed percutaneously without open heart surgery. Obstructive sleep apnea is a common condition, characterised by cessation of ventilation due to collapse of the upper airways and oxygen desaturation of varying degree.

The availability for percutaneous closure was studied in 66 consecutive patients with an indication for closure of an interatrial shunt and 58% of the patients were found to be available.

A descriptive study on 51 consecutive patients with atrial septal defect hypothesised that balloon sizing of the defect during percutaneous closure can be replaced by the size measured with pre-catheterisation transesophageal echocardiography. The results showed that the differences between measurements were too large for substituting pre-catheterisation size for balloon sizing.

The influence of PFO on the frequency of oxygen desaturations in proportion to the frequency of ventilation disturbances in obstructive sleep apnea was studied in a case control study. The presence of a PFO was assessed with contrast transesophageal echocardiography and ≥ 20 bubbles passing over to the left atrium was considered as a large PFO. The prevalence of large PFOs was 9 out of 15 (60%) cases with frequent desaturations, versus only 2 out of 15 controls (13%) (p=0.02) with infrequent desaturations, in proportion to the frequency of ventilation disturbances.

The effect of increasing numbers of contrast injections during transesophageal echocardiography, on the sensitivity for PFO detection, was studied. The sensitivity increased with increasing numbers of contrast injections and to safely rule out the presence of a PFO, up to five contrast injections were needed.

In conclusion, interatrial shunts can often be closed percutaneously and balloon sizing is an important part of the procedure. Nocturnal oxygen desaturation occurred proportionally more often in obstructive sleep apnea subjects with a PFO than in subjects without a PFO, indicating the importance of right-to-left shunting in obstructive sleep apnea subjects with a concomitant PFO. Furthermore, sensitivity for PFO detection increased with increasing numbers of contrast injections during transesophageal echocardiography.

Keywords: Patent foramen ovale, atrial septal defect, obstructive sleep apnea, contrast transesophageal echocardiography, percutaneous closure.

List of papers

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals.

I   Johansson M, Söderberg B, Eriksson P.
Availability of percutaneous closure for an adult population with interatrial shunts.
Cardiology 2003; 99: 85-89

II   Helgason H, Johansson M, Söderberg B, Eriksson P.
Sizing of Atrial Septal Defects in Adults.
Cardiology 2005; 104: 1–5

III   Johansson M. C., Eriksson P, Peker Y, Hedner J, Råstam L, Lindblad U. The influence of patent foramen ovale on oxygen desaturation in obstructive sleep apnea.
European Respiratory Journal 2007; 29: 149–155

IV   Johansson M. C. Helgason H, MD, Dellborg D, Eriksson P.
Sensitivity for detection of patent foramen ovale increased with increasing number of contrast injections. A descriptive study with contrast transesophageal echocardiography.
Journal of the American Society of Echocardiography October 2007, E-published ahead of print.

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Abbreviations

Abbreviation	Full text	Explanation
AHI	Apnea-Hypopnea Index	The number of apneas and hypopneas per hour of sleep
AI	Apnea Index	The number of apneas per hour of sleep. An apnea is a cessation of airflow for at least 10 seconds.
ASAN	Atrial Septal Aneurysm	Excessive bulging of the interatrial septum, of more than 10-15 mm.
ASD	Atrial Septal Defect	A congenital heart disease.
BMI	Body Mass Index	The bodyweight divided by the square of the height (kg/m²)
BSD	Balloon-Stretched Diameter	The diameter of a defect when a sizing balloon is inflated in the defect.
95% CI	95% confidence interval	With a probability of 95% the "true value" will be within the range of the 95%CI.
COPD	Chronic Obstructive Pulmonary Disease	A lung disease that makes it hard to breathe, because of partially blocked airflow in the lungs.
CPAP	Continuous Positive Airway Pressure	A treatment for obstructive sleep apnea. Positive air pressure is applied with a nasal (or facial) mask and act as a pneumatic splint, holding the upper airway open.
ECG	ElectroCardioGram	Recording of the electrical activity of the heart over time.

Abbreviation	Full text	Explanation
ESS	Epworth Sleepiness Scale	A subjective measure of daytime sleepiness. An eight-item self-administered questionnaire rates the likelihood of dozing in eight daily situations.
HI	Hypopnea Index	The number of hypopneas per hour of sleep (≥40% reduction in ventilation).
ODI	Oxygen Desaturation Index	The number of episodes per hour of sleep with ≥4% decrease in saturation and lasting ≥10 s.
OSA	Obstructive Sleep Apnea	Intermittent cessation of respiration during sleep, due to collapse of the upper airways.
PFO	Patent Foramen Ovale	A congenital opening in the interatrial wall, present in 27% of the population.
PD	Proportional Desaturation	The number of desaturations in proportion to the number of respiratory events. (ODI/AHI)
Qp/Qs	Pulmonary blood flow/systemic blood flow	Quantification of shunting. Normal value=1 (no shunt)
TE	Transesophageal Echocardiography	Ultrasound the heart via a probe in the esophagus.
TIA	Transient Ischemic Attack	Brief neurological dysfunction due to temporary reduction in blood flow to a part of the brain.
VM	Valsalva Maneuver	The effort of exhaling towards a closed upper airway.

1. Background

Patent foramen ovale

Historical remarks

The first known description of an opening between the two atria was made by Galen in the second century. He was a Greek physician and philosopher who became famous as a physician who cared for wounded Roman gladiators so well that their mortality declined. Although the philosophical approach was important in ancient times, he also made dissections of animals and in describing the two atria of a foetal or newborn animal Galen wrote:

"So Nature made an opening (foramen ovale), common to both (atria), and attached to it in lid-fashion, a membrane. This membrane opens readily in the direction of the pulmonary vessel (left atrium); so that it may give passage to the blood stream flowing against it from the vena cava (right atrium) but may, on the other hand, prevent the return of the blood in the opposite direction…….All these operations of Nature are indeed wonderful, but more so still is the subsequent occlusion of the above-mentioned opening" [1].

Though written 1,800 years ago this is still a valid description of the function of a patent foramen ovale (PFO) and its closure after birth. The circulation of blood was however, still unknown for many years to come. According to the theory of Galen, the blood was produced in the liver, flow towards the periphery in both the veins and the arteries and was consumed in the tissues. Some blood was supposed to pass, through invisible pores in the interventricular septum, into the left ventricle, where it was enriched with the spirit of life, "pneuma".

The renaissance brought a novel approach, for example, when Leonardo da Vinci (1452-1519) began observing nature as it can be seen by the eye. He drew precise illustrations from dissections of animals and humans and added brief explanatory notes [2].
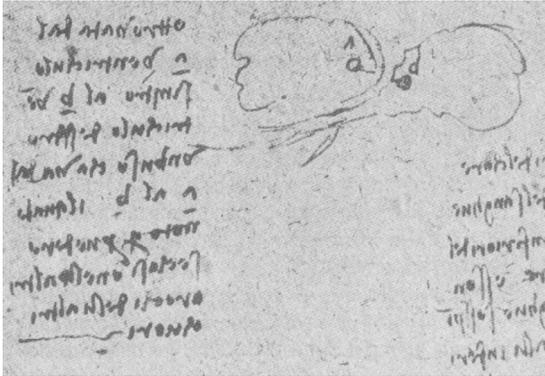

Figure 1 -1. A sketch by Leonardo da Vinci, of a perforating channel connecting the two atria with each other and the text:" I note it here to see whether this occurs in other auricles of other hearts":. Reprinted with permission, On the human body, Dover publications, N.Y. USA, 1983.

The existence of a pulmonary circulation was suggested by the Arab scientist Ibn al-Nafis in the 13th century and in Europe by Michael Servetus in the 16th century. Full evidence of the pulmonary and systemic circulation was not presented until the work of William Harvey in 1628 [3].

The role of PFO as a pathway for venous emboli to enter the arteries, and cause systemic embolisation was first suggested by Cohnheim in 1877. He described a 35-year-old woman, deceased from a cerebral thrombus. Autopsy showed venous thrombosis of the lower extremity and a very large PFO through which he could pass three fingers [4]. He also referred to another autopsy case with the pulmonary embolism, were both the femoral vein and artery were filled with thrombus. Inspection of the heart showed thrombus in the right atrium and a PFO.

Ultrasound cardiography (UCG) or nowadays, echocardiography (echo), was first performed in 1953 in Lund, Sweden, by Inge Edler [5] and has become widely used as a diagnostic tool. It was combined with contrast injection by Gramiak in 1969 [6] and the usefulness of contrast echo to diagnose interatrial shunts was described in 1975 [7]. This technique was the basis for two studies in 1988 that showed an association between PFO and stroke of unknown cause in patients younger than 40-55 years [8, 9]. Since then, over 1600 published articles on "patent foramen ovale" have been registered in the Pubmed.

Foetal circulation

The open foramen ovale is a vital part of the foetal circulation. The blood of the foetus receives oxygen and nutrition in the placenta. It flows through the umbilical vein, through the liver or the ductus venous into the inferior vena cava and into the right atrium. Due to the Eustachian valve and the geometry of the right atrium this flow is directed towards the foramen ovale and into the left atrium. The blood enters the left ventricle and is pumped into the aorta. Thence it is distributed, almost entirely, to the head and upper extremities, thus supplying the growing brain with oxygen and nutrition.

Figure 1-2.

The blood is returned from the brain into the upper vena cava and the right atrium. This flow is directed towards the right ventricle and pumped into the pulmonary artery. Since the lungs of the foetus are filled with fluid they are almost impervious and the greater part of the blood flows through the ductus arteriosus into the aorta. Some of it supplies the abdomen and lower body but the chief portion is conveyed back to the placenta.

After birth there are huge changes in the circulation that are mainly triggered by the child's gasping and crying. When the lungs are filled with air the pulmonary arterioles relax and the pulmonary blood flow increases enormously. Well-oxygenated blood flows through the pulmonary veins into the left atrium. The left atrial pressure rises to a higher level than the right atrial pressure and a thin membrane on the left side of the atrial septum is pressed towards the rims of the foramen ovale that will act as a flap valve. The membrane adheres to the rim during the first five years of life in about 2/3 of all children. For unknown reasons, in the remaining third of all children, the membrane does not coalesce with the rim around the whole of the circumference, i.e., a PFO is present.
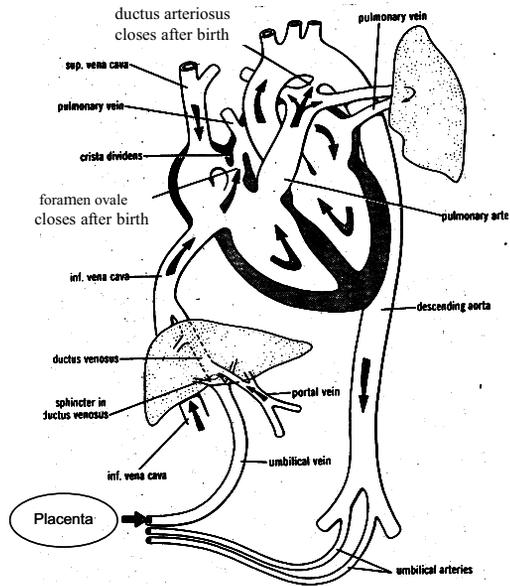
Definition of PFO and ASD

The interatrial wall contains an oval opening, the foramen ovale that is covered by a thin membrane. In most subjects, this membrane is firmly attached to the rims of the foramen ovale. When the attachment is absent in a part of the circumference a PFO exists, which is regarded as a normal variant, present in 27% of the population. When there is a defect within the membrane, an atrial septal defect (ASD) is present, defined as an ASD secundum or simply an ASD confined to the ovale fossa [10]. This is a congenital heart defect and much rarer.

Function and significance of PFO

A PFO acts as a flap valve in the interatrial septum, preventing left to right flow. As the left atrial pressure is normally slightly higher than the right atrial pressure, the valve is mostly closed. Transient reversal of the pressure opens the flap, forming a tunnel, and forces the blood directly from the right to the left atrium thus bypassing the lungs. Venous blood has low oxygen content and may carry compounds that are normally filtered or metabolised in the lungs. The lungs are not only the place for gas exchange; it also serves a filter with a significant thrombolytic capacity. Such pressure reversals normally occur during end diastole-early systole and are augmented by the normal inspiration [11, 12]. The pressure reversal is further increased during augmented intra thoracic pressure swings; for example, during coughing, defecation and lifting.

A PFO is present in about a quarter of the adult population [13]. This high prevalence means that the presence of a PFO is normally of no or only limited clinical significance. However, recent research has found an increased prevalence of PFO in conditions such as cryptogenic stroke [9], decompressions illness [14], and migraine [15]. Not all PFOs have the same size: about half of them have a potential opening diameter of at least 4 mm and the association with pathological conditions has been stronger for this group [16]. Presence of a PFO is a risk factor for stroke and death in pulmonary embolism [17]. It can cause oxygen desaturation in conditions such as platypnoea-orthodeoxia and obstructive pulmonary disease [18] and leads to an increased risk of pulmonary oedema after ascent to high altitudes [19]. Thus, current knowledge indicates that, in some conditions, the concomitant presence of a PFO creates or worsens a patophysiological process and can lead to disease.

Diagnosis of PFO

In the days before contrast ultrasound, a PFO could only occasionally be diagnosed during a person's lifetime. A catheter could be passed through the opening or a dye dilution curve could suggest a right to left shunt [20].

Nowadays, bubble contrast injections, during ultrasound imaging are commonly used. Imaging modalities such as transcranial Doppler [21], transthoracic [22] or transesophageal imaging (TE) have been described as comparable [23], even though, since the study by Siostrzonek and co-workers, contrast transesophageal echocardiography is considered to be the method of choice for PFO detection [24]. The high resolution of the interatrial septum makes transesophageal echocardiography very valuable when percutaneous closure of PFO is a treatment option. Transcranial Doppler has high sensitivity, for detection of a right-to-left shunt but gives no reliable information on the location of the shunt. There are occasional descriptions of PFO detection with contrast computed tomography or contrast magnetic resonance imaging [25, 26].

Autopsy

A probe is passed through the interatrial septum to discover a PFO. The diameter of the largest probe that ca be passed through is defined as the PFO diameter. The autopsy study from Hagen and co-workers found a PFO prevalence of 27% in normal hearts, which declined with increasing age. During the first decade of life the prevalence was 34%, in the 4th to 8th decade 25% and in the 9th and 10th decade only 20%. The diameter varied between 1 and 19 mm. Fifty-two percent of the PFOs had a diameter >4 mm, 26% >6 mm and only 2% >10 mm [13]. There was a tendency for the PFO diameter to increase with age. In the first decade the mean diameter was 3.4 mm and in the 10th decade 5.8 mm. The most common explanation offered, is that small PFOs seal with time. The true reasons are, however, unknown. An alternative explanation could be that the presence of a PFO actually increases mortality in certain circumstances, such as pulmonary embolism were a concomitant PFO has been found to be an independent risk factor for adverse outcome [17]. The increase in PFO size with age could also be due to dilatation of the left atrium secondary to commonly occurring cardiovascular disease [27].

Contrast transesophageal echocardiography

The contrast effect

When small gas bubbles in a solution are hit by ultrasound they create a strong echo, as gas has much lower density than liquids. A simple method to create microscopic bubbles is to agitate the solution, mixed with 5-10% air, by repeated and forceful injections from one syringe to another through a three-way stopcock [28] and then immediately inject it into a peripheral vein. A volume of only 2 ml can completely opacify the right heart and when the solution passes through the lung capillaries the bubbles are cleared.

Definition of PFO in contrast echocardiography

A PFO is commonly defined as the appearance of microbubbles in the left atrium within three heart beats from when the contrast filled the right atrium in the absence of a tissue defect [9, 29]. There is however some debate on the exact requirements for a positive PFO study [30]. Surprisingly, the three beat rule originates from only a single case study by Shub and co-workers [31]. In a patient without PFO but with intrapulmonary shunting, echo contrast was seen in the left atrium, four beats and later after contrast filling of the right atrium.

Provocative maneuvers and contrast injections

As a PFO is functionally closed, most of the time, due to a higher left atrial than right atrial pressure, a provocation such as the Valsalva maneuver (VM) has been used in order to invert the interatrial pressure gradient and thus open the PFO. The VM is named after the Italian physicist Antonio Maria Valsalva, who described in the 17th century that an expiration effort against a closed mouth and pinched nose can be used to inflate air into the middle ear [32]. The VM can also be made against a closed glottis, as occurring during bowel movement, heavy lifting or briefly during coughing and sneezing. During the strain, the intrathoracic pressure increases and the venous inflow to the heart is reduced. The interatrial pressure gradient then seems to equalise or sometimes be inverted [33]. Upon release of the strain, blood surges from the inferior vena cava into the right heart and makes the right atrial pressure higher than the left atrial pressure during 2-3 heart beats [34].

The effect of the VM can be recognised during transesophageal echocardiography (TE) because the atria shrink, the septum undulates, and upon release of the strain the septum bulges over towards the left atrium. When the region in the right atrium adjacent to atrial septum is filled with contrast at this very moment, contrast will pass over to the left atrium and the PFO will be visualised. Lynch and co-workers showed the VM to increase the frequency of PFO-positive contrast studies from 5 to 18% in a group of healthy volunteers [35]. The timing of contrast injection and VM varies between published studies. Contrast has been injected during the VM [9, 36], before the start [37], at the start [38], or after the end of the VM [39]. Other provocations than the VM has also been recommended for PFO detection. Coughing has been argued to be more effective than VM by Dubourg in 1984 [12] and by Stoddard in 1993 [39]. In 2001, Kerr found bed tilt to be at least as good as VM for PFO detection and advocated his method as it is easier to standardize and less dependent on patient co-operation than VM [40].

The number of contrast injections given, is often not specified [41]. As Agmon pointed out in an a retrospective analysis in 2001, different diligence

in cases versus controls may also affect the number of PFOs found [42]. Contrast is usually injected in an antecubital vein but femoral vein injection has been found to be more effective for PFO detection during transthoracic imaging (Gin 1993) [43], during transesophageal and transcranial Doppler imaging (Hamann 1998) [44]. The authors have argued that femoral vein delivery is more efficient as the blood flow from the inferior vena cava is directed towards the foramen ovale, while cava superior flow is directed towards the tricuspid valve. This explanation was challenged by Saura and co-workers in 2006 who brought an alternative hypothesis to the fore [45]. Femoral injections are made through a larger catheter and closer to the heart than antecubital injections, so the contrast will be less diluted and the right atrium more densely filled.

PFO size

A large PFO can be defined, as by Stone and co-workers, as at least 20 bubbles passing over to the left atrium. Such large PFOs entailed a risk of new stroke or transient ischemic attack (TIA) of 31% vs. 0% among those with only 3-19 bubbles passing over (p=0.03) [29]. A large PFO, associated with increased risk, can also be defined as a visible opening diameter of at least 4 mm; (Schuchlenz and co-workers) [46]. The potential maximal opening diameter can however, not be reliably determined from TE as the diameter is underestimated compared to invasive balloon sizing in a various degree [47]. Schuchlenz also found the number of visible bubbles in the left atrium to be correlated with the balloon size diameter of the PFO only during femoral injections and not during antecubital injections.

Stroke and PFO

Stroke in general

Stroke is a sudden loss of brain function caused by a blockage of blood flow to the brain. It is a leading cause of morbidity and disability with approximately 30,000 new cases each year in Sweden [48]. Stroke can be divided into ischemic stroke (85%) and haemorrhagic (15%). Ischemic stroke is caused by large vessel atherosclerotic disease (carotid artery stenosis) in about 10% and by intracerebral small vessel disease (lacunar infarction) in 25% of the cases. About 20% are caused by cardiac embolism (e.g. atrial fibrillation, recent myocardial infarction, low ejection fraction and mitral stenosis). A few percent are due to rare causes, such as dissection or arteritis. However, about 40% of all ischemic strokes are cryptogenic, i.e. no cause can be found despite thorough examination [49]. The risk of stroke can be predicted by several factors, age being one of them. The risk of stroke doubles every 10 years after the age of 55 and 80% of the cases are over 65 years of age. There are also important modifiable risk factors which are

similar to those for cardiac disease and established cardiac disease, such as atrial fibrillation, myocardial infarction and congestive heart failure entail a significantly increased risk.

The long-term risk factors for stroke have been described in several studies, among them the Multifactor Primary Prevention Study carried out in Göteborg, Sweden [50]. The hazard ratios of stroke, by individual baseline factors, among 7 457 middle aged men, during 0-15 years and 22-28 years of follow-up are shown in Table 1-1.

Table 1-1. The hazard ratios of stroke with confidence intervals by individual baseline factors during 0-15 years and 22-28 years of follow-up, adapted from Harmsen and co-workers [50].

Baseline Factor Present	Age-Adjusted Hazard Ratio (95% Cl)	
Time period	0-15 y	22-28 y
SBP quintile 5 vs. quintile 1	3.11 (2.14-4.54)	1.59 (1.26-2.01)
HypMed	2.28 (1.59-3.28)	2.22 (1.60-3.09)
Previous TIA	2.39 (1.31-4.37)	0.85 (0.35-2.05)
Atrial fibrillation	10.33 (5.49-19.4)	0.00 (0.00-6.29)
Stroke in either parent	1.39 (1.09-1.79)	1.18 (0.96-1.46)
History of diabetes	3.81 (2.39-6.08)	1.58 (0.71-3.54)
Coronary events in parent	1.21 (0.92-1.60)	1.01 (0.80-1.29)
Smoking	1.34 (1.08-1.71)	1.06 (0.88-1.28)
History of chest pain	1.83 (1.39-2.42)	1.16 (0.88-1.53)
Psychological stress	1.48 (1.10-1.99)	1.26 (0.98-1.63)
BMI quintile 5 vs. 1 quintile	1.11 (0.84-1.46)	1.60 (1.25-2.06)
Low physical activity	1.15 (0.83-1.60)	1.46 (1.10-1.93)
S-Chol quintile 5 vs. 1 quintile	1.09 (0.75-1.60)	1.17 (0.92-1.49)
Social class low, quintile 5 vs. 1 quintile	1.21 (0.93-1.57)	1.13 (0.79-1.16)

SBP, systolic blood pressure. HypMed, hypertension medicine at baseline. BMI, body mass index. S-Chol, serum cholesterol.

During the very late follow-up, in the period 22-28 years after the baseline exam, the significant risk factors after adjustment for age were: hypertension medication, high systolic blood pressure, high BMI and physical inactivity [50]. Thus, despite that treatment of hypertension reduces the risk by about 40% [51]; hypertension is still a risk factor, even when treated. This is intriguing and supports the hypothesis that the blood pressure in treated cases is not low enough. In fact, in Swedish primary care, optimum blood pressure control is achieved in only 3 out of 10 of treated patients [52]. Even though, the study does not include women it is interesting because of the very long follow-up period of subjects that were free from stroke at baseline. A study from Scotland identified high blood pressure, smoking, high cardiothoracic ratio, pre-existing coronary heart disease and diabetes to be risk factors for stroke mortality during 20 years of follow-up, without finding significant differences between men and women [53]. In fact, according to recent guidelines for stroke prevention, the three risk factors hypertension, physical inactivity, and obesity are considered to be the basic cause in a majority of all cases of stroke [51].

PFO as a risk factor for stroke

In 1988 two studies found an association between cryptogenic stroke and PFO. Lechat and co-workers found a PFO in 40% of cryptogenic stroke patients under the age of 55 compared to only 10% in controls without stroke [8]. Webster and co-workers found a PFO in 50% of cryptogenic stroke under the age of 40 as compared to only 15% in healthy control subjects [9]. Subsequent studies have confirmed this association in groups defined in the same way i.e. the combination of a cryptogenic stroke and a young or middle aged subject. This is not, however, a typical stroke case. Only 3% of all strokes occur under the age of 55 years [54].

Recent research has added information on special anatomical features of the right atrium, which combined with a PFO, involves an additional risk of stroke. Such a feature is a flaccid and undulating motion of the thin-walled portion of the interatrial septum. When it undulates from side to side or bulges into one of the atria more than 10-15 mm, it is defined as an atrial septal aneurysm (ASAN) [55]. Among patients with ASAN, about 80% have a concomitant PFO and these PFOs are larger than in patients without ASAN [56]. Another feature associated with PFO and maybe with stroke is a prominent Eustachian valve. It is a remnant of the foetal circulation that directs the flow from the inferior vena cava towards the oval fossa [57]. In addition, functional features are important. The association with stroke has been stronger for cases with right to left shunting also during resting respiration as compared to those with shunting only during the Valsalva maneuver [9]. Common activities during daily life, such as physical exercise,

lifting, coughing, defecation and sexual intercourse are Valsalva like maneuvers and may have a role as trigger events [58]. The combination with concomitant coagulation disorders or factors predisposing to venous thrombosis, such as surgery and long-distance travel, has also been discussed [58]. An increased prevalence of venous thrombus has been reported in cases with cryptogenic stroke and PFO. In the pelvis study, magnetic resonance imaging showed a pelvic thrombus in 20% of cases versus 4% in strokes of known cause [59]. However, in the majority of cryptogenic stroke cases with a PFO, there was no evidence of venous thrombosis. Instead, the general theory is that small thrombi or debris often exist in the venous blood, even without a manifest venous thrombosis.

In clinical practice, the diagnosis of paradoxical emboli is presumptive and based on the combination of a stroke without obvious cause and a PFO, making the PFO guilty by association. However, in rare cases, "the guilty PFO can be found red-handed" as shown in Figure 1-3 [60].
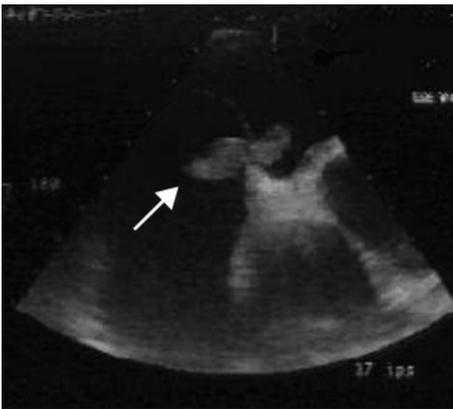

Figure 1-3. Transesophageal image of a thrombus trapped in a PFO. This image is from an 80- year-old woman with pulmonary embolism. It shows a large thrombus stuck in the PFO. It later disappeared and a thrombus was found in a renal artery. Reprinted with permission, European Journal of Echocardiography 2007

PFO and stroke recurrence

Mas and co-workers studied a group of 581 subjects, below 55 years of age, with cryptogenic stroke [61]. At baseline 48% had a PFO or an ASAN. A small group of 9% had both a PFO and an ASAN. Their hazard ratio for recurrent stroke was 4.17 and significantly higher than in those without any septal abnormality. The estimated risk of recurrent stroke in this group, after four years of follow-up, was 15% as compared to 2% in the group with PFO alone and 4% amongst those with no septal abnormality. Moreover, the group with septal abnormality at baseline had a lower prevalence of cardiovascular risk factors than the group without a septal abnormality. Those with a septal abnormality were younger (40 vs. 45), had lower prevalence of hypertension

(9 vs. 21%), hypercholesterolaemia (12 vs. 23%), high BMI (19 vs. 29%), and a lower prevalence of excessive alcohol consumption (14 vs. 21%), underlining the importance of septal abnormality as a risk factor for stroke recurrence.
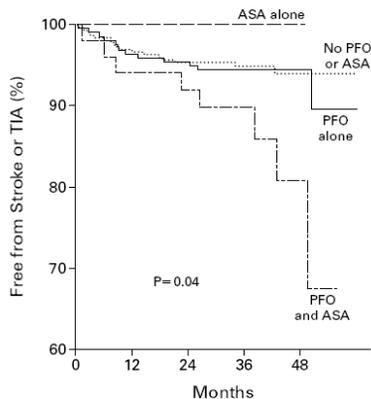
Figure 1-4.

Probability that the patient will remain free from stroke and transient ischemic attack (TIA) according to presence or absence of PFO and (ASA) atrial septal aneurysm

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The risk of stroke recurrence amongst subjects with cryptogenic stroke and PFO is also dependent of the number of cerebrovascular events. Those who have suffered more than one event run a higher risk of stroke recurrence (3.6% vs. 1.8% per year) [62]. A study by Homma and co-workers on PFO in cryptogenic stroke subjects was designed to study the effect of warfarin or aspirin in a randomised, double-blind study, with 2 years of follow-up. It included patients of a wider age range, 18-85 years. At baseline, the PFO group had fewer cardiovascular risk factors. The endpoint was stroke or death and there was no significant difference according to presence of PFO-ASAN. Warfarin-treated subjects showed a trend towards a better prognosis than those with antiplatelet treatment (odds ratio 0.47; 95%CI: 0.22-1.04) [63].

Stroke recurrence after transcatheter closure of PFO

The outcome after percutaneous closure has been studied in several non-randomised studies and a summary was published in The Lancet in July 2006 [64]. The mean frequency of major complications after closure was 2.3% and included device embolisation, cardiac tamponade and need for surgery. The annual recurrence rate for stroke or transient ischemic attack was 1.3% which was significantly lower than the event rate of 5.2% for medically treated patients. Post-procedural shunt has been found to be a risk factor for stroke recurrence with a relative risk of 4.2 [65]. Closure seems more effective in cases with both PFO and ASAN. These subjects had a high recurrence rate during medical treatment (5.3-11.7%), but closure eliminated this excessive

risk (0.6-4.9%). Another known risk factor for recurrence is multiple events and closure appears to eliminate also this risk. The recurrence rate during medical treatment was 33% after four years, as compared to 7% after closure [66]. The recurrence rate may also be affected by concomitant atherosclerosis. In a paper from 2007, an annual recurrence rate of only 0.16% was reported after closure in patients without atherosclerosis on extracranial Doppler sonography and coronary angiography [67]. Prospective, randomised studies are underway, but enrollment has been slow and no study has yet been completed [68].

PFO and other conditions

PFO and myocardial infarction

Some patients with acute myocardial infarction show no signs of coronary artery disease on coronary angiography [69]. The reasons for these infarctions are still unknown, but veno-arterial embolisation through a PFO has been described [70, 71].

PFO and pulmonary embolism

Major pulmonary embolism increases the pulmonary resistance, leads to right ventricular pressure overload and reduced filling of the left ventricle. In the presence of a PFO the result will be a right-to-left interatrial shunt and a pathway for thrombus embolisation. The significance of a concomitant PFO in the setting of major pulmonary embolism was shown by Konstantides and co-workers in 1998 [17]. Of 139 consecutive patients, 35% had a PFO on contrast echo. The presence/absence of a PFO was associated with an in hospital risk of, ischemic stroke (13% vs. 2%), peripheral arterial embolisation (15% vs. 0%), and death (33% vs. 14%). PFO was an independent predictor of death with an odds ratio of 11.3.

PFO and decompression illness

During a dive, nitrogen is absorbed in the body because of the high ambient pressure under water. Pressure increases with one atmosphere for every 10 metres of descent in seawater [72]. When the pressure declines during ascent, the dissolved gas should be transported via the blood to the lungs. If the reduction in pressure is too fast for the gas transporting capacity, supersaturation in the tissues results, and bubbles may be formed in the tissue and bloodstream. To avoid supersaturation with nitrogen, divers stop intermittently during ascent. However, bubbles in venous blood are quite common after the ascent from a dive. Venous gas bubbles can be expected in 50% of subjects after an ascent from a prolonged stay at a depth of only 11 feet (3.4 metres) of seawater [73]. These bubbles follow the blood flow into larger and larger veins and are eventually cleared in the lungs and exhaled. Bubbles that for one reason or another, reach the arteries of the systemic

circulation follow the blood flow into smaller vessels and may eventually be squeezed into a small vessel and block the blood flow. Divers frequently perform Valsalva-like maneuvers to equalise the pressure in the middle ear. This is a maneuver that provokes right-to-left shunting when a PFO is present. In fact, venous bubbles and a concomitant PFO seem to be more or less a prerequisite for arterial bubbles. Venous bubbles occurred in 11 of 40 divers after a sport dive while arterial bubbles occurred in seven of those 11 divers. A PFO was found in five of the seven divers with arterial bubbles. [74].

The classic form of decompression illness, "the bends", involves joint pain, and is presumed to be caused by bubble formation near the joint. Together with mild symptoms such as rashes it is included in the concept of minor decompression illness.

When an event is more severe with stroke-like features it is defined as a major decompression illness. The incidence of major decompression illness is 1.5-2.5 per ten thousand dives, while the incidence of minor decompression illness is about ten times higher. Signs and symptoms of minor decompression illness after a dive were found in approx 2/1000 dives among 2000 Swedish diving instructors who answered a retrospective questionnaire [75]. Torti and co-workers correlated the prevalence of PFO in 230 divers with their history of decompression illness. Even though the presence of a PFO was related to a low absolute risk of suffering a major decompression illness of 5/10,000 dives, the risk was increased five times in this group, compared to those without a PFO. The risk of a major decompression illness increased with increasing PFO size, as shown in Figure 1-5 [38].
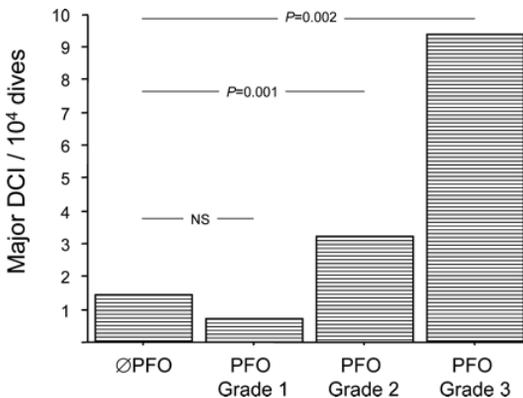

Figure 1-5. Mean number of decompression illness (DCI) events per 10,000 dives in relation to different PFO sizes.
Ø=no PFO,
PFO grade 1= only a few bubbles,
PFO grade 2= intermediate,
PFO grade 3= an entire cloud of bubbles.
Reprinted with permission, European Heart Journal April 2004.

Magnetic resonance imaging can detect hyperintense spots thought to be subclinical brain lesions and, as shown in Figure 1-6, an increased prevalence of hyperintense spots has been found in divers [76].
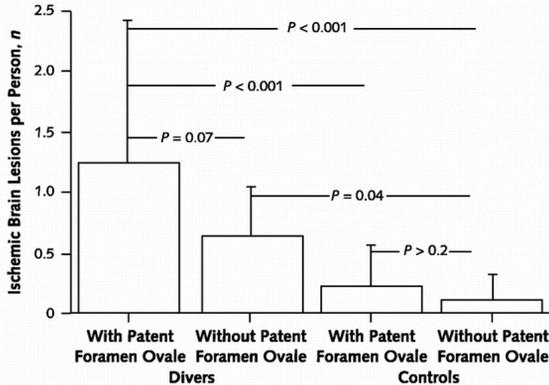

Figure 1-6.

Average number of ischemic brain lesions seen on magnetic resonance imaging.

Adapted from Schwerzmann, Annals of Internal Medicine, January 2001 [76]. Reprinted with permission.

The current European clinical fitness to dive praxis does not include PFO screening before diving [77]. The reasons are the low incidence of major decompression illness and the fact there is a good and well-established cure. Almost all patients treated in a recompression chamber recover completely. The estimated number of dives in Sweden is 500,000 per year and fatal accidents are rare with only about six cases per year [75]. Most of them probably have other causes than right-to-left shunting. Divers treated with recompression, on the other hand, are screened with contrast TE for the presence of a PFO. Those with a PFO are strongly advised to refrain from diving.

PFO and migraine

An association between PFO and migraine with aura was described in 1998 when Del Sette found a higher prevalence of PFO in a migraine group than in healthy controls (41% vs. 16%, p<0.005) [15]. This association between PFO and migraine with aura has since then been confirmed in several studies as described in a recent review [78]. The total PFO prevalence in migraine with aura was 54% as compared to 16% in migraine without aura and 24% in the control. A relationship between migraine and right-to-left shunts has also been found in divers treated for decompression illness. Among 200 treated divers, 27 described a migraine aura occurring 10 minutes to 4 hours after the ascent, and 26 of those had a PFO [79]. All of these 26 subjects described a migraine aura occurring after a deep dive

although not after a shallow dive. Analysis of their depth-time profiles showed that the dives could have provoked venous bubbles. A postulated mechanism for the association between PFO and migraine with aura is that circulating substances, such as serotonin or micro-thrombi, which normally are cleared when the blood passes the lungs, act as triggers for migraine if they reach the brain in sufficiently large amounts.

PFO closure and migraine

Improvement of migraine symptoms has been reported among patients undergoing PFO closure after cryptogenic stroke [78]. The scientific evidence of these studies is, however, limited for several reasons. They are only observational without a control group. Migraine symptoms often change spontaneously over time and the placebo effect in migraine can be as high as 70% [78]. Conflicting results with new-onset migraine have also been reported after closure [80]. A proposed mechanism is serotonin release from activated platelets as there is a significant rise in plasma serotonin at the start of a migraine attack. Platelets contain most of the serotonin normally present in the blood and aggregating platelets release serotonin. Initially, after device closure, platelets aggregate and form a thrombus in the discs. The discs are subsequently covered by endothelium within three months. In order to reduce the risk of new emboli, patients are treated with aspirin and sometimes also with clopidogrel for 6 months after closure, which may also have a beneficial effect on migraine symptoms [81].

The results from these descriptive studies have increased the need for randomised interventional trials. To date, only one randomised trial of PFO closure in migraineurs has been performed, the MIST trial (Migraine Intervention with Starflex Technology) [82]. The results have not been published but were reported at a meeting in 2006. The trial included 147 PFO patients with migraine with aura, which was refractory to preventive treatment. They were randomised to PFO closure or to a sham procedure, with incision in the groin under anaesthesia. The primary endpoint was complete freedom from migraine for 3-6 months after closure. The result was that only 3 patients, in each groups, achieved the primary endpoint, without any difference between groups [83]. Two out of six secondary endpoints were presented and showed a larger decrease in symptoms in the closure group than in the sham group. There are many possible reasons for this lack of effect of closure on the primary endpoint. One being a common genetic factor, that could explain the association between PFO and migraine, without a direct causal relationship [84].

PFO and hypoxaemia

Interatrial shunting can contribute to oxygen desaturation in conditions with disturbed intrathoracic pressure conditions, such as chronic obstructive pulmonary disease [18] and in conditions with distorted anatomy of the atrial septum as in platypnoea-orthodeoxia [85]. This is a rare disorder with incapacitating symptoms usually occurring in elderly subjects, with a mean age of approx 70 years [86]. Breathlessness is precipitated in the upright position (platypnoea) and hypoxia induced or aggravated in the upright position (orthodeoxia). Continuous right-to-left shunting occurs despite normal right-sided pressure, that is, the blood seems to flow uphill [87].

It is usually described in cases with some condition that distorts the relationship between the inferior vena cava, the interatrial septum and aorta. The flow from the inferior vena cava is directed more perpendicular towards the interatrial septum right through a PFO that is held open by a rightward shift of the fossa ovalis. A dilated aorta, or an aorta that is elongated in relation to the body, encroach on the atria. The distance between the aorta and the atrial free wall is reduced, and the relation between the membranous septum primum and the surrounding rim is distorted. Described conditions include aortic root dilatation, aorta elongation, kyphoscoliosis, spine compression fracture pericardial effusion, right-sided pneumonectomy and diaphragmatic paralysis [85-88].

PFO and obstructive pulmonary disease

Failure to reach full oxygen saturation despite administration of 100% oxygen is a sign of admixture of venous blood to the arterial circulation. This can be seen in chronic obstructive pulmonary disease (COPD) and is mostly due to perfusion of unventilated alveoli but intra cardiac shunting has also been discussed [89]. A study on 20 subjects with severe COPD and 20 healthy controls found an increased PFO prevalence in COPD, (70% versus 35% $p<0.05$) [90]. Greater oxygen desaturation after Valsalva maneuver was noted in COPD subjects with a PFO than in those without PFO ($-3.1\% \pm 1.4\%$ vs. $-1.5 \pm 0.5\%$, $p<0.05$). However, the clinical significance of a PFO in COPD was unknown until 2005, when a study shed new light on the issue [18]. The PFO prevalence was again higher in COPD, 23 out of 52 vs. 10 out of 50 controls. Those with a PFO only during Valsalva maneuver had similar clinical characteristics as those without a PFO. However, 11 subjects with shunting already during resting respiration were clinically more impaired than those without a PFO, as shown in Table 1-2. Shunting during resting respiration produces a continuous right-to-left flow that can contribute to oxygen desaturation. The decrease in oxygen saturation during Valsalva implies that the magnitude of the shunt is dynamic and dependent on the interatrial pressure gradient. Hypoxia seems to start a vicious circle with

pulmonary vasoconstriction; higher intracardiac right-sided pressure and increased shunt which may be further accelerated by exacerbation of COPD and exercise. Whether PFO closure is beneficial has yet to be shown.

Table 1-2. Comparison of groups of patients with Chronic Obstructive Pulmonary Disease according to presence of PFO. Adapted from Respiratory Medicine, 2006 [18].

Characteristics	Patients without PFO or with PFO only during Valsalva (n=41)	Patients with PFO during resting respiration (n=11)	P
Disease duration (y)	10.6 ± 7.2	15.4 ± 5.4	0.006
Oxygen saturation (%)	91.5 ± 5.7	84.1 ± 6.0	0.001
MMRC dyspnea scale	2.78 ± 0.93	3.55 ± 0.68	0.015
PAPs (mmHg)	48.0 ± 15.4	64.2 ± 25.5	0.01
Change in oxygen desaturation (%) during Valsalva maneuver	-0.41 ± 0.81	-2.91 ± 1.14	0.001

MMRC= Modified Medical Research Council; PAPs = Pulmonary Artery Pressure in systole.

PFO in severe asthma

PFO-related shunting has been discussed in a few case reports, some with a fatal outcome [91, 92]. Despite high concentrations of inhaled oxygen, patients have remained severely hypoxic and contrast echo has revealed a right-to-left shunt. Asthma is characterised by increased airway resistance. To overcome the resistance, the respiratory effort is enhanced. The intrathoracic pressure difference between inspiration and expiration get larger and these pressure swings affect the venous inflow to the heart [93]. During inspiration the venous inflow increases with increased right ventricular volumes and reciprocally diminishing left ventricular volumes, indicating higher right atrial than left atrial pressures. In the presence of a PFO the result will be right-to-left shunting [91]. Another sign of the respiratory pressure effect is pulsus paradoxus - decreased blood pressure on inspiration and increased blood pressure during expiration. Pulsus paradoxus can be seen also in other situations where spontaneous right to left shunt through PFO has been noted: pericardial tamponade [88, 94], pericardial constriction [95], and obstructive sleep apnea [96, 97].

PFO and high altitude pulmonary oedema

This is a potentially fatal condition that may occur after rapid ascent to high altitude [98]. Susceptible persons are characterised by hypoxia, pulmonary vasoconstriction and exaggerated pulmonary hypertension at high altitudes. In 2006, Alleman and co-workers presented a case control study, with 16 susceptible persons and 19 mountaineers who had been found to be resistant to high-altitude pulmonary oedema during repeated climbing to peaks above 4,000 meters [19]. The PFO prevalence was 4 times higher among susceptible participants than in resistant mountaineers, 56% vs. 11%. The subjects were also examined after ascent to a high altitude of 4,559 meters and the PFO prevalence had then risen to 69% vs. 16%. Oxygen saturation was studied at high altitude prior to the onset of pulmonary oedema. In the susceptible group, participants with a large PFO had significantly lower arterial oxygen saturation than those without a PFO or only a small PFO (65 vs. 77%, p=0.02). Spontaneous shunting during resting respiration was observed in the susceptible group in 4 of 5 subjects with a large PFO at high altitude. It seems that an otherwise silent PFO becomes a part of a vicious circle at high altitude [99]. Hypoxia induces vasoreactive pulmonary hypertension and when there is a concomitant PFO, interatrial right-to-left shunting is provoked, which then aggravates the hypoxia.

Diagnosis, significance and treatment of ASD

Atrial septal defect (ASD) is a congenital heart disease. The prevalence has been estimated to be about 4 per 10.000 live births, accounting for about 6% of all congenital heart defects [100]. A majority of all ASDs have, however, no clinical importance in childhood and many ASDs are diagnosed in adulthood, often "en passant", so that the true prevalence of ASD is unknown. An ASD involves a left to right shunt that increases the right ventricular flow, causes dilatation of the right side of the heart and the left atrium and is thus suspected on routine transthoracic echo when there is dilatation of the right heart. A complete evaluation of the interatrial septal anatomy in adults often requires transesophageal echocardiography. Although most individuals are asymptomatic for many years almost all eventually develop symptoms such as arrhythmias, exertional dyspnea or fatigue and untreated ASD patients have a shortened life expectancy [101]. Surgical closure increases functional capacity and reduces mortality even when it is performed on patients over the age of 40 [102, 103]. Technological development in resent years has made percutaneous closure of interatrial defects an alternative to open heart surgery [104-106].

Percutaneous closure and sizing of ASD

Since King and co-workers performed the first successful closure of an ASD in 1976, a number of investigators have developed devices for transcatheter closure of ASDs [107-111]. Today, the Amplatzer device (AGA Medical Corporation, Golden Valley, Minn., USA) is used by most centres, although there are other types which are currently in use or still under investigation. The Amplatzer device is a self-centring device, the centre of which has to fit perfectly in the defect to ensure an effective closure [105]. Therefore, an accurate measurement of the diameter is the key to successful closure. If the device is too large, it will not fold completely into the proper position, and if it is too small, there is a risk of embolisation and/or of not completely covering the defect. The balloon-stretched diameter (BSD) of the ASD by balloon sizing is used as a guide to select the size of the device for implantation. A balloon catheter is placed across the defect; the balloon is inflated and the indentation into the balloon is measured as the stretched diameter of the defect. Care is taken not to overinflate the balloon. Previous investigators have suggested using the pre-catheterisation, transesophageal echocardiography diameter as a guide to the size of the device and have suggested the following formula:

Formula 1: TE(X) x 1.05 + 5.49 = BSD(X) [112, 113]

where TE(X) is the size of the ASD measured by TE in millimetres and BSD(X) is the BSD of the ASD in millimetres.

Other non-invasive methods have also been studied; Durongpisitkul and co-workers suggested using magnetic resonance imaging for accurate sizing [114, 115], whereas Zhu et al. [116] suggested using 3-dimensional TE, providing excellent correlation. Intracardiac echo provides accurate measurement as well and allows the procedure to be carried out without anaesthesia [117]. Percutaneous closure needs a sufficient rim around the defect and an anatomical position that does not interfere with AV-valves, pulmonary veins or sinus coronarius [118].

Pulmonary right-to-left shunts

Intrapulmonary arteriovenous malformations result in right-to-left shunting, resembling the PFO situation, but with a constant flow from right to left. Such malformations exist in about 25% of the patients with the rare genetic condition Hereditary Haemorrhagic Teleangiectasia, also called Rendu-Osler-Weber syndrome [119]. Clinical manifestations are similar, but more common, to those in PFO: hypoxia, cerebral infarctions and migraine. In addition, seizures and cerebral abscesses also occur. These manifestations are more common in patients with multiple arteriovenous connections than in simple connections, with an odds ratio of 4.5 (95%CI: 1.47-14) [120]. Cerebral infarctions were detected in 27 of 45 (60%) patients with multiple arteriovenous connections.

Obstructive sleep apnea

Historical remarks

Excessive daytime sleepiness in extreme obesitas was described in 1810 in London [121] and may have been an inspiration for Charles Dicken's success story: "The Posthumous Papers of the Pickwick Club" from 1837. He refers to Joe, the "fat boy" who consumes great quantities of food and constantly falls asleep in any situation at any time of the day. This text gave rise to the term "Pickwickian syndrome," claimed to be the origin of obstructive sleep apnea, as it combines extreme obesity with excessive sleepiness [122]. But the condition also included alveolar hypoventilation with chronic hypoxaemia and hypercapnia [121], and in current medical terminology this coincides better with obesity-hypoventilation syndrome [123].

The characteristic appearance of an obstructive sleep apnea event was described by Broadbent in the Lancet in 1877 [124]: "When a person, especially in advanced years, is lying on his back in heavy sleep and snoring loudly, it very commonly happens that every now and then, the inspiration fails to overcome the resistance in the pharynx of which stertor or snoring is the audible sign, and there will be perfect silence through two, three, or four respiratory periods, in which there are ineffectual chest movements; finally, air enters with a loud snort, after which there are several compensatory deep inspirations before the breathing settles down to its usual rhythm."

This description is still valid in several respects. The condition is common; apneas are intermittent, associated with snoring and the patient lying on his back. The mechanism is increased resistance (collapse) of the upper airways, which was confirmed in a cineradiography study in 1967 [125]. But it fails to connect sleep apnea with the major symptom of excessive daytime sleepiness [123]. The connection between sleep apnea and excessive daytime sleepiness was overlooked until it was discovered in 1965 by Gastout [126].

History of treatment

The effectiveness of tracheostomy in resolving obstructive sleep apnea (OSA) was described in 1969 [125]. The current OSA treatment, Continuous Positive Airway Pressure (CPAP) was first described in 1981 [127]. CPAP is delivered through a nasal or facial mask and provides a pneumatic splint for the nasopharyngeal airway that completely prevents upper airway occlusion and allows the patient to have a whole night of uninterrupted sleep [127].

Figure 1-6.

Nasal Continuous Positive Airway Pressure (CPAP)

photo courtesy of the American Sleep Apnea Association

Definition of obstructive sleep apnea

Obstructive sleep apnea is characterised by repetitive breathing pauses due to collapse of the upper airways. An apnea [128] is the absence of airflow for at least 10 seconds and a hypopnea is a significant reduction (30-50%) in airflow for at least 10 seconds. The combination with oxygen desaturation of 3% - 4% or arousal is usually required to define a hypopnea [129]. The number of apneas and hypopneas per hour of sleep is defined as the apnea-hypopnea index (AHI). A recent definition of OSA from the American Academy of Sleep Medicine is an event number of at least 15, regardless of symptoms, or a score of at least 5 together with symptoms [130]. When the patient is symptomatic, with excessive daytime sleepiness, the condition can also be defined as obstructive sleep apnea syndrome (OSAS).

Prevalence of OSA

The prevalence of OSA in the middle-aged population is 9% of women and 24% of men, when defined as an AHI of at least 5 [131]. The prevalence

in young women is low (6.5% among 30-39 year-olds) and increases after the menopause (16% among 50-59 year-olds). Also in men there is an increase with age (17% among 30-39 year-olds vs. 31% among those 50-60 years of age). After 65 years of age the prevalence does not increase further [132].

Patophysiology of OSA

Although the primary cause of OSA is uncertain, the patophysiological mechanism is intermittent collapse of the upper airways. Inspiration is initiated by contraction of the diaphragm, generating a negative pressure in the airways, which draws air into the lungs and also generates a collapsing force on the upper airways. To overcome this collapsing force, oropharyngeal dilator muscles contract during inspiration. Four different traits are common in OSA subjects and their interaction can probably explain the occurrence of obstructive apneas [133].

1. Anatomy

The upper airways are narrowed in OSA. Fat deposits laterally of the airways and mucosal inflammatory oedema are commonly seen in OSA [134, 135].
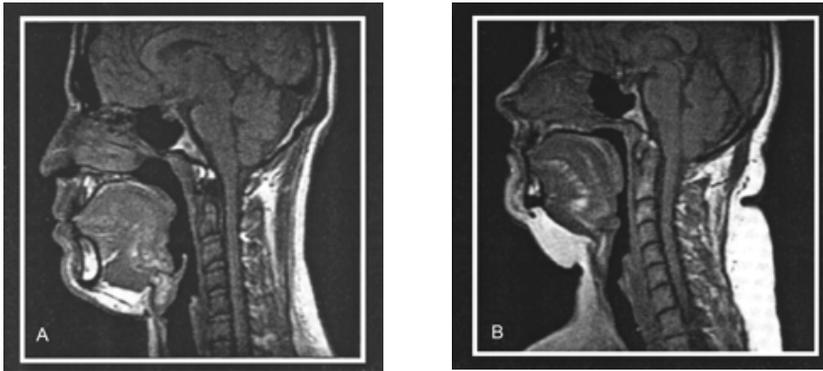
Normal subject   Patient with obstructive sleep apnea

Figure 1-7. Sagittal magnetic resonance image. Note that the airway behind the uvula, soft palate, and tongue are considerably smaller in the patient with apnea than in the normal control subject. This is the site of pharyngeal collapse in the patient with apnea. Reprinted by permission, from Schwab RJ. Upper airway imaging. Clin Chest Med 1998; 19:33–54.

2. Pharyngeal dilator muscle control during sleep

In order to maintain airway patency, the activity of the pharyngeal dilating muscles is augmented during wakefulness in OSA subjects as compared to normal controls [134]. On sleep onset the muscle activity decreases and OSA subjects are then more prone to airway collapse, which occurs when the negative pressure within the airway exceeds the dilating forces. The consequent apnea is resolved by dilator muscle contraction, often initiated by a short arousal from sleep causing disrupted sleep.

3. Arousal threshold

The respiratory arousal threshold varies between individuals. A subject with low threshold will suffer from frequent arousals and more disrupted sleep. With a higher threshold, longer apneas will be tolerated before an arousal is initiated.

4. Ventilatory control

OSA subjects seem to have more unstable central respiratory control and this may contribute to obstructive apneas. Increased central respiratory drive will result in increased ventilation and pharyngeal dilator muscle activity. Reduced drive decreases pharyngeal muscle dilator activity and airway occlusion may occur if the upper airways are susceptible to collapse. Hypoxia can induce unstable respiratory control with periodic breathing. One study showed periodic breathing in 7 of 9 healthy snoring subjects during hypoxic sleep and resulting in obstructed breaths in 6 of these 7 subjects [136]. Intermittent hypoxia may also reduce upper airway muscle endurance, impair central control of upper airway muscles and these mechanisms may induce a vicious circle [137].

Predisposing factors

Obesity, large neck circumference, male gender and smoking predispose to OSA [131, 138-141]. A weight increase by 10%, will result in a 6 fold increase in risk for developing moderate or severe OSA [138]. A large neck circumference increases the likelihood of OSA; ≥43 cm corresponded to a positive predicted value of 57%, tested prospectively [141]. There is also a hereditary predisposing factor, which can not be explained by obesity alone, and supports the importance of facial structure. The odds were 1.3 for having OSA when one first relative was diagnosed with OSA [139]. Absence of habitual snoring makes a diagnosis of OSA unlikely; only 6% and 16% of non-snoring women and men respectively, were found to have an AHI ≥ 5 [131]. OSA is more common in men than in women and the ratio is approximately 3:1, in age range 30-60 years [131]. The OSA prevalence in women is lower before than after the menopause and during hormone replacement therapy after the menopause, implying a protective role of

female hormones [142]. The upper airways in women are less prone to collapse than in men, probably due to different tissue characteristics and not to reduced airways size or dilator muscle activity [143].

Symptoms and clinical presentation of OSA

Excessive daytime sleepiness is the main symptom but also headache, gastroesophageal reflux and depression are prevalent [144]. Many subjects with high AHI do however, not suffer from excessive sleepiness. In a population based survey, only 35% of subjects with AHI ≥30 reported excessive daytime sleepiness, as did 21% of those with an AHI ≤5 [145]. The symptoms of OSAS are nonspecific and OSAS is a health problem that are unrecognised in 80-90% of cases [146]. However, these patients seek medical treatment more than twice as often as patients without OSAS [146]. Irrespective of daytime sleepiness, OSA is associated with an increased risk of traffic accidents. After adjustment for confounding factors such as, alcohol, visual refraction disorders, BMI, km of driving a year and work schedules, the odds ratio, for having a traffic accident was 11.1 (95%CI: 4.0-30.5), in subjects with AHI≥5 vs. subjects with AHI<5 [147].

Treatment of OSA

Weight reduction is recommended in overweight subjects with OSA, as a 10% reduction in body weight decreased the AHI by 26% in one study [132]. Surgery (uvulopalatopharyngo-plasty) has been used, but side effects occur and the long-term efficiency is questionable [148]. Nocturnal CPAP is the most effective treatment. CPAP eliminates the upper airway obstruction and improves daytime symptoms [132]. The compliance is good. According to a recent review, 69% of patients still used CPAP after 1-4 years of follow-up, during a mean of 5.2 hours per night (range 4.4-6.2) in an intention to treat analysis [144]. An alternative to CPAP is oral devices that advance the position of the lower jaw during sleep [149]. These devices have been shown to reduce the upper airway resistance and to alleviate daytime symptoms. However, CPAP is more efficacious in reducing the AHI.

OSA and cardiovascular disease

While the initial interest was OSA as a cause of daytime sleepiness there is currently also a great research interest in OSA as a risk factor for cardiovascular disease. OSA and cardiovascular diseases share many predisposing factors such as obesity, age and male gender. There is however, mounting evidence of OSA as a risk factor, independently of obesity at least in men [150]. Due to the low number of women included in published studies, the strength of the scientific evidence is less in women than in men. A review of the literature, published until March 1, 2006, by The Nordic Health Technology Assessment Agencies, judged the evidence of OSA as an independent risk factor for cardiovascular disease as insufficient in women [144]. Many studies on the effect of CPAP treatment on cardiovascular risk are nonrandomised, which could have introduced a bias. OSA patients have been offered CPAP and the incidence of cardiovascular events compared between those who have used the CPAP and those who did not use it.

OSA and mortality

An increased mortality in OSA subjects was reported in 1988 [151] and that CPAP treatment improves prognosis in 2005 [152]. The cardiovascular mortality during 7.5 year of follow-up in CPAP treated subjects was 1.9% as compared to 14.8% in subjects who failed to use the CPAP. Moreover, the diurnal pattern of sudden cardiac death is different in OSA vs. non-OSA subjects. In non-OSA and in the general population there is a peak in the risk of sudden cardiac death during the morning hours after awakening (6-12 a.m.) and a nadir during the night. In OSA subjects, however, 46% of the sudden cardiac deaths were found between midnight and 6 a.m., vs. 21% in non-OSA subjects and 16% in the general population [153]. The relative risk of sudden cardiac death 00-06 a.m. (as compared with the remaining 18 hours) was 2.57 in OSA subjects (95%CI: 1.87-3.52) vs. 0.77 (95%CI: 0.36-1.66) in non-OSA subjects and the relative risk increased with increasing AHI.

OSA and stroke

Following the first report in 1985 on snoring as a risk factor for stroke, multiple studies have provided evidence of a causal relationship between OSA and stroke [154]. In 2005, OSA was reported to be an independent risk factor for adverse cardiovascular events. In a cohort of patients, free from stroke and myocardial infarction at baseline, an AHI ≥5 vs. <5, predicted an adverse outcome during a median follow-up time of 3.4 years. After adjustment for known risk factors, the hazard ratio for stroke or death was 1.97 (95%CI: 1.12-3.48) [155]. In a cohort of men, severe OSA was found to be an independent risk factor for cardiovascular events including stroke

compared to healthy controls, matched for age and BMI. The incidence of fatal events, was per 100 patient years, in severe OSA 1.06 vs. 0.3 in healthy controls (p=0.0012) and the incidence of non-fatal events was 2.13 vs. 0.45 (p<0.0001). The risk increased with increasing severity of OSA. Furthermore, treatment with CPAP reduced the risk, per 100 patient years, of fatal events to 0.35 (p=0.0008) and for non fatal events to 0.64 p<0.0001) [156]. More than half of all stroke victims have OSA and it may affect their prognosis [157]. In a group of stroke victims, 53.7% were found to have an AHI ≥20. Those who tolerated CPAP had a better prognosis after 18 months of follow-up. Among CPAP-treated subjects 6.7% suffered one new cerebrovascular or coronary event vs. 36.1% among those who could not tolerate CPAP [158].

OSA and hypertension

There is increasing evidence that OSA is a cause of hypertension, independent of confounding factors such as obesity [159]. In a prospective study on subjects free from hypertension at baseline, the adjusted odds ratio for the presence of hypertension after four years was 2.89 (95%CI: 1.46-5.64) for AHI ≥15 vs. an AHI of zero [160]. The prevalence of OSA in hypertensive subjects is high. In one study, 47% of the hypertensive middle aged men had an AHI of at least 30 [161]. The evidence of OSA as a cause of hypertension was, however, judged as insufficient in the review of literature until 1 March 2006, from the Nordic Health Technology Assessment Agencies [144]. Several randomised trials have studied the effect of CPAP on 24-hour blood pressure in OSA subjects, who had sought medical attention due to suspicion of sleep apnea. The studies included both hypertensive and normotensive subjects [162-164]. The degree of blood pressure reduction varied and was larger in patients with hypertension and with frequent desaturations, and was noted both during the night and during daytime. However, in 2007 a meta analysis showed an overall, small, but significant reduction in 24 hour blood pressure of 1.69 mmHg (95% CI: - 2-69 to -0.69) [165].

OSA and coronary artery disease

The presence of OSA at baseline increased the risk of developing coronary artery disease in a group of patients free from coronary disease at baseline. At 7 years of follow-up the incidence of coronary disease was 16.2% in OSA vs. 5.4% in snoring subjects without OSA at baseline (p=0.003). Among efficiently treated OSA subjects the incidence of coronary disease after 7 years was lower, 3.9% as compared to 24.6% among incompletely treated OSA subjects (p=0.022) [166]. Furthermore, OSA patients with coronary disease who accept treatment have a better prognosis than those who decline treatment. OSA treatment significantly reduced the

risk of occurrence of the composite end point of cardiovascular death, acute coronary syndrome, hospitalisation for heart failure, or need for coronary revascularisation. The hazard ratio in treated vs. non treated subjects was 0.24 (95%CI: 0.09 to 0.62) [167].

OSA and atrial fibrillation

A high prevalence of OSA has been reported in patients with atrial fibrillation. One study found an OSA prevalence of 49% in atrial fibrillation patients, as compared to 32% in general cardiology patients without atrial fibrillation. After adjustment for co-variates the odds ratio for the association between OSA and atrial fibrillation was 2.19 (95%CI: 1.40-3.43) [168]. Moreover, the recurrence rate after cardio-version is much higher among OSA subjects. At 12 months, the recurrence rate was 82% as compared to 42% in treated OSA subjects and 53% in non-OSA subjects. Interestingly, non-treated OSA subjects with recurrence had a larger nocturnal fall in oxygen saturation than in those without recurrence (p=0.034), but similar AHI and arousal index [169].

OSA and congestive heart failure

Bearing in mind that OSA is associated with hypertension, the most common long-term risk factor for developing heart failure [170], it is conceivable that a 2.38 fold relative increase in OSA prevalence has been found in heart failure patients [171]. The influence of OSA on mortality in heart failure patients with reduced ejection fraction was reported on in 2007. The presence of an AHI≥15 vs. an AHI<15, entailed increased mortality. After correction for confounding factors, the hazard ratio for death was 2.81 (p=0.029) and the mortality rate was 8.7/100 patient years vs. 4.2 [172]. Randomised studies have reported some beneficial effects of CPAP in heart failure patients with concomitant OSA, regardless of excessive daytime sleepiness. In patients with heart failure and an AHI ≥20, one month of CPAP treatment increased the ejection fraction from a mean of 25.0±2.8% to 33.8±2.4% (p<0.001), reduced systolic blood pressure from 126±6 mmHg to 116±5 mmHg (p=0.02) [173]. Another randomised study with 3 months of CPAP in patients with AHI>5 and heart failure also found an increased ejection fraction. Furthermore, the report included, a decrease in urinary norepinephrine excretion (-9.9±3.6 nmol/mmol creatinine vs. 1.6±3.7; p=0.036) and improvement in quality of life [174]. However, no effect of CPAP on mortality has been found. A randomised study on heart failure patients with predominantly central sleep apnea, designed to study the effect on survival without need for heart transplant, did not found any effect on mortality [175].

Patophysiology of cardiovascular morbidity in OSA

Several factors, involved in the atherosclerotic process are commonly found in OSA subjects and some of them are described in brief here. Which aspects of OSA that are the most potent activators of these factors is currently unknown. There is, however, some evidence that chronic intermittent hypoxia is a potent activator [176]. Other trigger mechanisms could be the frequent arousals or the excessive intrathoracic pressure swings that are seen in OSA.

Sympathetic activation

In 1988, Hedner and co-workers found an increased and fluctuating sympathetic nerve activity during obstructive apneas [177]. It is now known that a generally increased sympathetic activity is present in OSA, also during daytime wakefulness, and this is an important mechanism linking OSA to cardiovascular disease [178]. CPAP treatment reduced sympathetic activity measured as daytime plasma nor epinephrine by approximately 50% [179].

Inflammation and oxidative stress

Inflammatory activity is implicated in the pathogenesis of atherosclerosis. There is evidence from several, although not all studies, that the inflammatory activity is increased in OSA and may be reduced during CPAP treatment [180, 181]. The intermittent hypoxia/re-oxygenation in OSA has also been implied in free radical formation. Free oxygen radicals are highly reactive molecules that are proposed to play an important role in the early inflammatory process that characterizes several forms of cardiovascular disease. The mechanisms are similar to the ischaemia/reperfusion injury seen in coronary artery disease. [182].

Insulin resistance and type II diabetes

In cross sectional studies, have insulin resistance and type II diabetes, been found to be associated with OSA, independently of obesity. The odds ratio for insulin resistance was 2.15 (95%CI: 1.05-4.38) after adjustment for BMI and percentage of body fat in patients with AHI≥5 vs. AHI<5 [183]. The odds ratio for type II diabetes, with an AHI ≥15 vs. an AHI<5 was 2.3 (95% CI, 1.28-4.11, p=0.005) after adjustment for age, sex and body habitus. The risk of developing new onset type II diabetes was, however, not significantly increased in OSA independent of confounding factors [184].

Platelet function

Increased activation and aggregation of platelets may also be a link between OSA and the risk of cardiovascular events. A non-randomised study found that an index of platelet activation was correlated to the AHI (r=0.3;

p=0.022) and was significantly reduced after one night of CPAP and with a further decrease after 3 months [185].

Endothelial function

Endothelial function has been found to be impaired in OSA and CPAP treatment may improve endothelium dependent vasodilatation. The percentage of flow-mediated vasodilatation improved with CPAP from a baseline value of 3.3±0.3%, to 5.8±0.4% after one week (p<0.01) and further to 6.6±0.3% after 4 weeks (p<0.01) in a non-randomised study [186].

Left ventricular hypertrophy and diastolic function

Left ventricular hypertrophy is common in OSA. In a cross-sectional study, oxygen desaturation was the strongest independent predictor of hypertrophy, and increased systolic blood pressure had an amplifying effect [187]. Six months of CPAP reduced left ventricular hypertrophy, with 0.7 mm reduction in septal thickness (p=0.011), in a non-randomised study [188]. Diastolic dysfunction is also common in OSA. A randomised crossover study showed improved diastolic filling with less impaired relaxation after 3 months of CPAP (increased E/A ratio, reduced mitral deceleration time, p<0.01) [189].

The combination of OSA and PFO

OSA and PFO are mostly considered to be two separate entities that are not interrelated. However, as both conditions are common, they sometimes coexist. The combined presence of both OSA and PFO may influence the pathophysiology in either of the two conditions. OSA is characterised by repetitive breathing pauses due to collapse of the upper airways and concomitant oxygen desaturation of varying degree [131, 190]. A PFO is a potential pathway for a right-to-left shunt, directing deoxygenated blood into the arterial circulation, without passing through the lungs. Such shunting may occasionally be so large that it causes arterial desaturation [18, 86]. An increased prevalence of PFO in OSA was found by Shanoudy and co-workers in 1998, with a prevalence of 69% in OSA subjects vs. 17% in controls [191]. During the Valsalva maneuver, the OSA subjects with a PFO, reduced their oxygen saturation more than the OSA subjects without a PFO (-2.4±1.5% vs. -1.3±0.6%, p= 0.007).

The inspiratory effort during obstructive apneas creates negative intrathoracic pressure swings, which greatly influence the central haemodynamics, as shown by Shiomi and co-workers [96]. During obstructive apneas, pulsus paradoxus and a leftward shift of the interventricular septum were seen in a group of OSA subjects, with a high peak negative intrathoracic pressure of 62±15 cm of water. A leftward shift of the septum indicates augmented venous inflow to the right heart and reduced filling of the left heart and is a sign of higher right atrial than left atrial pressure. In the presence of a PFO the consequence will be a right-to-left shunt. The subjects without a leftward shift of the interventricular septum had a lower peak intrathoracic pressure of 22±16 cm of water.

Beelke and co-workers found that nocturnal obstructive apneas actually provoked right to left shunting in OSA subjects with a concomitant PFO. In this study, the apnea definition, included a 4% reduction in oxygen saturation [97]. Right-to-left shunting may explain why more severe desaturation than predicted from alveolar hypoventilation has been demonstrated in OSA patients [192-195].

2. Aims

- To report the availability for percutaneous closure of interatrial shunts in adult patients with indication for closure, referred to a Grown-Up Congenital Heart Disease Unit in Sweden, during 1997-2003.

- To test a previously published formula that uses the pre-catheterisation, TE-measured ASD diameter and has been suggested for use to determine the appropriate occluder diameter during percutaneous closure.

- To evaluate whether the pre-catheterisation, TE-measured ASD diameter can be used to determine the appropriate occluder diameter and the balloon sizing be omitted during percutaneous closure.

- To test the hypothesis that nocturnal oxygen desaturations in OSA subjects occur more often in proportion to the frequency of respiratory disturbances in OSA subjects with a large PFO than in those without.

- To evaluate whether the oxygen desaturation index/apnea hypopnea index (ODI/AHI) ratio might be a clinically useful screening tool, for selection of OSA subjects with a high likelihood of PFO.

- To test the hypothesis that the sensitivity for PFO detection during contrast TE increases when additional contrast injections are given.

- To compare the sensitivity of different provocations for PFO detection during contrast TE.

- To determine the number of contrast injections needed during contrast TE, to achieve reasonably high sensitivity for PFO detection.

3. Methods

Study populations

Paper I

From January 1997 to December 2000, in period 1, 66 patients were consecutively referred to the Grown-up Congenital Heart Disease Unit in Göteborg with an indication for closure of a foramen ovale atrial septal defect (ASD secundum) or a PFO. Transesophageal echocardiography (TE) was used to evaluate the suitability of percutaneous closure. The indications were:

- Shunting of hemodynamic significance defined as a calculated ratio between lung and systemic circulation >1. 5 and/or dilated right heart chambers.
- Embolic indication defined as a cryptogenic cerebrovascular event in the presence of an ASD or PFO and right to left shunting demonstrated on contrast echo.

Table 3-1. Patient characteristics, paper I, period 1

	All patients n=66	Patients receiving device n=38
Age, y	47 [18-74]	47 [19-74]
Age at diagnosis, y	43 [5-73]	44 [15-73]
Diagnosis known, y	4 [0-41]	3,2 [0-41]
Height, cm	174 [160-192]	174 [160-192]
Weight, kg	71 [53-102]	71 [53-102]
Men / Women, n	25/41	17/21
QRS width, msec	103 [74-154]	103 [74-154]
Embolic indication, n	18	17
Hemodynamic indication, n	48	21

All data are presented as mean and [range], except numbers (n).

Period 2: February 2001 became occluders with a diameter up to 40 mm available; otherwise were the methodology the same as during the first period. From February 2001 to June 2003, 64 consecutive patients were referred, 47 with ASD and 17 with PFO. Patient characteristics have not been worked up for this patient group.

Paper II

Fifty-eight consecutive patients (20 men and 38 women) underwent transcatheter closure of ASDs between 2001 and 2003 at the Grown-up Congenital Heart Disease Unit in Göteborg. There were missing data on 7 patients so the study group consisted eventually of 51 patients. The patient characteristics and the results of the cardiac catheterisation for men and women are listed in Table 3-2.

Table 3-2. Patient characteristics of study population, paper II

	All	Women	Men	p value
Patients	51	34	17	
Age, years	51±15	53±14.9	49±15.9	0.4 (NS)
Height, cm	n.a.	165±7.5	178±8.5	<0.001
Weight, kg	n.a.	67±9.3	83±13.2	<0.001
QRS duration, ms	105±18	104±20	106±12	0.7 (NS)
Implanted device size, mm	23.0±6.1	24.0±6.2	21.5±6.0	0.15 (NS)
Pulmonary artery pressure, mmHg	29.0±9.0	28±9	30±10	0.21 (NS)
Qp:Qs	2.3±0.9	2.4±1.0	2.1±1.5	0.23 (NS)

Paper III and IV

The two papers contain the same study population, selected from a community-based sample described in the Skaraborg sleep study [161]. Briefly, 161 patients with and 183 subjects without hypertension were subjected to polysomnography, without consideration of any clinical symptoms of sleep apnea. In total, 209 subjects were diagnosed with OSA using polysomnography. The apnea–hypopnea index (AHI) was calculated as the number of episodes per of hour of sleep with apnea or hypopnea. The oxygen desaturation index (ODI) was calculated as the number of episodes per hour of sleep with ≥4% reduction in oxygen saturation.

The ODI/AHI ratio was calculated for each of the 209 subjects. They were then ranked in accordance with their ODI/AHI ratios, divided into three groups and the subjects with the lowest and highest ratio (≤0.33 and ≥0.66) were considered for inclusion (Figure 3-1). The 54 subjects with a ratio ≤0.33 were defined as low proportional desaturation (PD) and those 57 subjects with a ratio ≥0.66, as high PD.
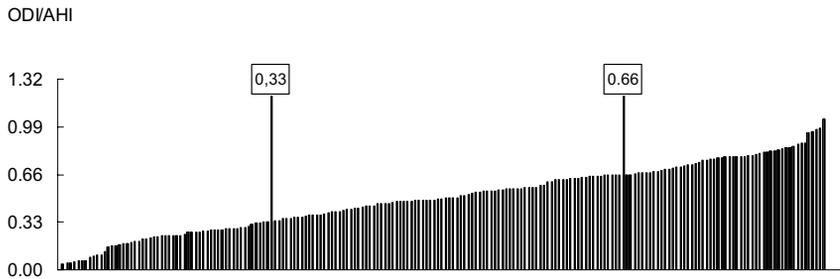
ODI/AHI

Figure 3-1 Distribution of ODI/AHI ratio among the 209 subjects diagnosed with OSA. ODI: oxygen desaturation index; AHI: apnea hypopnea index. Six subjects with an ODI/AHI ratio ranging between 1.1 and 3.8 were not considered for matching and are not shown in the graph.

Study participants were divided into pairs by contrasting their ODI/AHI ratio, and 15 pairs with the highest and the lowest ratio were chosen with the aim of maximising the difference in desaturation between the subjects within each pair in order to test the study hypothesis. The subjects were matched for the presence of hypertension (with or without diabetes), body mass index (within 3 kg/m²) and age (within 5 yrs). When more than one match was available, the minimum oxygen saturation and the mean overnight oxygen saturation were also considered in a manner that generated maximum difference. When a pair was split due to a participant being excluded or not giving consent, a second best match for the first subject was chosen. Following this procedure, 64 subjects were evaluated for participation before the final 15 matched pairs were finally identified. Exclusions were based on: death (n=2), obstructive pulmonary disease (n=7), other diseases (n=3), or subjects not giving consent (n=22). Characteristics of the subjects are described in Table 3-3. All participants gave written informed consent to participate.

Table 3-3. Characteristics of population in paper III and IV according to high and low PD.

	High PD n=15	Low PD n=15	P
Age, y	60.3 ±5.2	61.0±5.8	n.s.
Male, n. (%)	12 (80.0)	8 (53.3)	0.13
BMI, kg/m²	29.6±3.8	29.8±3.7	n.s.
Hypertension, n (%)	8 (53.3)	8 (53.3)	n.s.
SBP, mmHg	141±16	141±18	n.s.
DBP, mmHg	81±10	80±8	n.s.
Diabetes n (%)	2 (13.3)	2 (13.3)	n.s.
Smoking n (%)	1 (6.7)	2 (13.3)	n.s.
ESS	6.3±3.5	6.7±3.4	n.s.

High PD=High Proportional Desaturation= ODI/AHI ≥0.66; Low PD=Low proportional desaturation=ODI/AHI≤0.33; BMI=Body Mass Index, SBP=Systolic Blood Pressure; DBP=Diastolic Blood Pressure; ESS= Epworth Sleepiness Scale; n.s.=non-significant; P value unless p>0.2.

Table 3-4. Subject characteristics in paper III and IV according to the presence of PFO.

Subject characteristics	PFO n=14	No PFO n=16	All
Age, y	61 (53–68)	60 (50–71)	61 (50–71)
Male, n (%)	9 (64)	11 (69)	20 (67)
BMI, kg/m²	30.9±4.3	28.6±2.7	29.7±3.7
Hypertension, n (%)	9 (64)	7 (44)	16 (53)
Diabetes, n (%)	4 (29)	0 (0)	4 (13)

BMI = body mass index, PFO = patent foramen ovale. BMI given as mean value ± standard deviation and age as mean value and range.

Methods paper I and II

A TE performed in the referring hospital was reviewed. The patients were classified as suitable for percutaneous closure or not on the basis of clinical information and the echo evaluation. Patients judged as unsuitable for percutaneous closure were those with multiple defects, or unsuitable localization. In paper II patients with large defects, diameter >26 mm, were not included since this was the largest occluder diameter available at the time. There has to be a rim around the defect and the distance to the valves has to be at least 5 mm. If the defect was judged to be suitable for percutaneous closure the patient went to cardiac catheterisation with the intention of implanting a device for closure of the defect.
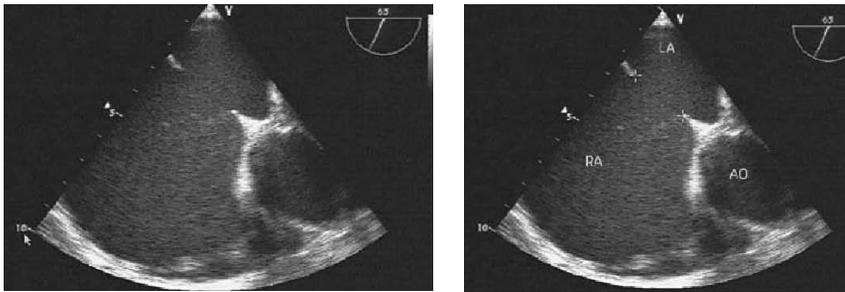

Figure 3-2. Measurement of ASD by TE. The distance between the two crosses is the measured TE diameter. AO = Aortic root; RA = enlarged right atrium; LA = left atrium.

The Amplatzer device

An Amplatzer septal occluder (AGA Medical, Golden Valley, Minnesota, USA) was used in patients in paper I and II. It consists of thin nitinol wires braided into two discs with a short connecting waist plugging the defect. Nitinol is memory metal alloy of 55% nickel and 45% titanium [196]. The occluder is a self centering, self expanding device due to the nitinol characteristics of super memory and super elasticity. The left atrial disc is 10-16 mm larger than the waist depending on device size that nowadays ranges from 4 to 40 mm [105, 196]. The device is covered by endothelium within three months [197] with a high rate of total ASD closure within 12 months [198]. Ten of the patients in paper I with PFO were closed with the Amplatzer PFO-occluder which has a thinner waist and larger discs. The remaining 7 patients with PFO were closed with the Amplatzer ASD-occluder, because the Amplatzer PFO-occluder was not available at that time.

Figure 3-3. The Amplatzer septal occluder.
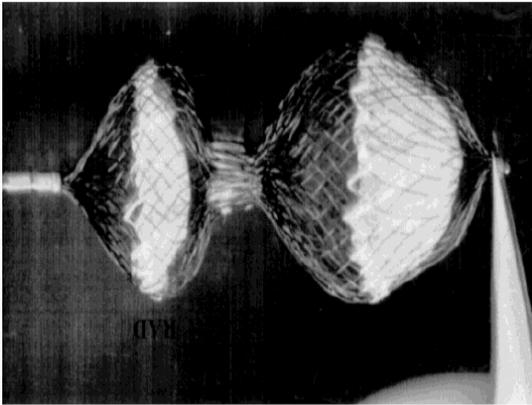
The delivery cable attached to the microscrew on the right atrial disc seen on the left side of the image. Note that there is polyester material sewn in the left and right atrial discs as well in the waist to enhance thrombogenicity and to augment rapid closure. The device is easily stretchable.
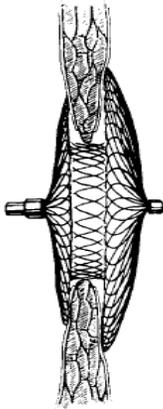
Schematic view of a deployed occluder.

Note the two flat discs with the connecting waist in between. The left atrial disc is slightly bigger than the right. There is a microscrew adapter mounted in the right disc for attachment of the delivery cable, seen on the left side of the image.

Images reprinted with permission. Catheterisation and Cardiovascular Diagnosis, December 1997, Pages: 388-393

Cardiac catheterisation

Venous access was gained via the femoral vein through an 8-12 French sheet. A hemodynamic investigation was carried out measuring pressure and saturation in a standard fashion. The degree of left-to-right shunting was determined in accordance with the Fick principle. The patients were subsequently given a general anaesthesia, intubated and a multiplane transesophageal probe was inserted into the oesophagus to monitor the procedure. (Sequoia Acuson, Mountain View, Calif.) A catheter was passed through the defect and a stiff wire was placed in the left upper pulmonary vein. A seizing balloon (PTA-OS, NuMED Inc., N.Y.) was placed in the

defect and filled with radiopaque contrast fluid (Omnipaque, Nycomed Amersham, Little Chalfond, United Kingdom), mixed with saline as seen in Figure 3-4. While the inflated balloon closed the defect a thorough look with colour Doppler-TE was done to see that no residual flow over the atrial septum was present. The stretched waist diameter was measured on both fluoroscopy and TE and the occluder was chosen to be the same or one mm larger than this. No sizing was done in the 10 patients closed with the Amplatzer PFO-occluder. The Amplatzer PFO-occluder comes in two sizes; 25 and 35 mm. The larger size was used if an atrial septal aneurysm was present. After this procedure a final decision was made whether to continue immediately with defect closure or not.

Figure 3-4.

Balloon measurement of ASD. The indentation at the centre of the balloon defines the stretched diameter.

Follow up

Patients treated with anticoagulation preoperatively continued this for at last six months. The other patients received acetylsalicylic acid 160 mg p.o. for a minimum of six months. The patients were followed for up to 18 months and any adverse event was considered. A transesophageal contrast echo was performed three months after the closure. As contrast was a gelatine-based plasma expander used (3.5% polygelin, Aventis Pharma, Frankfurt am Main, Germany). Together with a small amount of air (5–10% mixture) it was agitated between two syringes, mounted on a three way stop-cock, immediately before a bolus injection via a venous cannula. Two ml echo contrast was injected during a Valsalva maneuver (VM) 2-4 times. If this examination showed residual leakage a second follow up was performed 12 months after the closure. All clinical events were recorded.

Methods paper III and IV

Polysomnography

A polysomnography was performed in the 30 subjects. The in-home, full-night polysomnography recording used a computerised recording system (Embla A10 ©; Embla, Reykjavik, Iceland), which consisted of the following: 1) sleep monitoring through three-channel electro-encephalography, two-channel electro-oculography, and one-channel submental electromyography; 2) bilateral tibial electromyography and a body-position detector; 3) two-lead ECG; and 4) respiration monitoring through an oro-nasal thermistor as well as nasal pressure sensor for apnea–hypopnea detection. Piezo crystal effort belts were used for thoracic–abdominal movement detection and a pulse oximeter (Embla Oximeter-XN; Embla) was applied. The sensors were applied and the equipment calibrated at the primary care centre by a certified sleep technician or specially trained local staff. Data were subsequently scored, based on 30-s epochs according to the Rechtschaffen and Kales criteria [199]. An overall sleep stage report and accurate measures of respiratory events during the sleeping period were generated. Respiratory events were scored in accordance with guidelines for measurements in clinical research [129]. Obstructive apnea (hypopnea) was defined as a flat (≥40% reduction of) nasal pressure signal accompanied by respiratory effort movements for ≥10s and desaturation ≥3% from the immediately preceding baseline, or arousal. The definition of both apnea and hypopnea included the same requirement of ≥3% desaturation and/or arousal. The apnea-hypopnea index (AHI) was calculated to define the number of episodes of apnea and hypopnea per hour of sleep. OSA was defined as AHI ≥10 obtained through sleep recording with a total sleep time of ≥4 h. The oxygen desaturation index (ODI) was defined as the number of episodes per hour of sleep with a reduction in saturation of ≥4% from baseline, and ≥10 s.

Daytime sleepiness

Daytime sleepiness was assessed with the Epworth Sleepiness Scale, an eight-item self-administered questionnaire used for rating the likelihood of dozing in eight daily situations on a scale of 0–3. The final score ranged from 0 (no daytime sleepiness) to 24 (maximum daytime sleepiness) [200].

Spirometry

Standard dynamic spirometry (Spirotrac; Vitalograph, Ennis, Ireland) was performed on the same day as the transesophageal echocardiography (TE) examination. Values were calculated as percentages of predicted values [201, 202]. Daytime percutaneous oxygen saturation was measured with the Ohmeda Biox 3740 (Ohmeda, Louisville, CO, USA).

Contrast transesophageal echocardiography

Subjects were thoroughly instructed and trained to perform the Valsalva maneuver (VM) and Mueller maneuver, with a constant pressure of at lest 40 mmHg, during a minimum of 8 seconds. The achieved pressure was measured with a manometer and shown to the subject. Multiplane transesophageal echocardiography in fundamental mode imaging was performed (Siemens, Acuson Sequoia 256 or General Electric, Vivid 7) after mild sedation with midazolam and local pharyngeal anaesthesia (lidocain). Images of fossa ovalis were obtained in midoesophageal view and mainly with a 50–100 degrees angle but other planes were also used to optimize the view of the septum primum overlapping the septum secundum. Colour Doppler of fossa ovalis was performed with reduced pulse repetition frequency to about 40cm/s during resting respiration. A gelatine-based plasma expander (3.5% polygelin, Aventis Pharma, Frankfurt am Main, Germany) was used as contrast. Together with a small amount of air (5–10% mixture) it was agitated between two syringes, mounted on a three way stop-cock, immediately before a bolus injection via a 20-gauge venous cannula [203]. A bolus injection of two ml was made antecubitally while 10ml bolus injection was made in a foot vein, in both cases, followed by a bolus injection of 5–10 ml of saline.

Contrast injections were given according to a standardised protocol with two injections during each of the provocations. The VM [34] was defined as "early" when it started 3–5 seconds before injection and "late" when it started 3–5 seconds after injection. Both maneuvers were maintained until the moment when the contrast had filled the right atrium. The aim was to maintain strain for about 10 seconds and make the septum primum bulge over towards the left atrium, at the very same moment as the region in the right atrium adjacent to the fossa ovalis had filled with contrast [204]. The sequence of injections was as it appears in Table 4-6, with the subject in left lateral decubitus position, and began with injections in a foot vein during late VM, followed by injections in the left arm during relaxed breathing, early VM, late VM, Mueller maneuver [205], early VM in combination with bed tilt [40], cough [39]. Then followed arm injections after nitro-glycerine spray during resting respiration and early VM. At last, two arm injections were made with the subject in supine position during rest.

Mueller maneuver was performed with an anaesthesia mask through which the transesophageal probe was thread with a tight fitting rubber ring. The subject pressed this mask towards his mouth and nose, with help of an assistant, while inhaling against this resistance for about 5 seconds. Contrast was injected when the subject began inhaling. Bed tilt started with a 10-degree foot down tilt during 60 seconds. Then the early VM was started,

contrast injected and about five seconds later, or when contrast was appearing in the right atrium, the bed was tilted to 10 degrees head down. Cough was performed with five consecutive coughs starting just when the contrast had filled the right atrium. In order to reduce preload, nitroglycerin (0.8 mg) was sprayed lingually, during constant 10-degree foot-down bed tilt and contrast was injected antecubitally during relaxed breathing and early VM. All examinations were performed by one person (Johansson) from March to December 2003.

PFO analysis

The echo evaluation was performed off-line from Super-VHS video. A single injection was defined as PFO positive if at least three bubbles appeared in the left atrium adjacent to the septum within three heartbeats from when contrast had filled the right atrium. A subject was defined as PFO positive if at least one of the injections was PFO positive and this was considered to be the gold standard [36]. Two persons made PFO analysis independently, during 2003 and 2004. Disparities were settled by consensus with a third observer. The total number of bubbles passing into the left atrium after a single injection was estimated and also those passing after the first three heart beats were accounted for. A large PFO was defined as a minimum of 20 accumulated bubbles passing over following a single injection [9, 206]. After injection of agitated solutions can, even in normal subjects, faint echoes be seen entering the left atrium through the pulmonary veins later than 3-5 beats after opacification of right atrium. Besides their late appearance, they were distinguished from PFO shunting by their faint, thin and smoke like characteristics and by their flow direction. We did not use second harmonic imaging, which makes these thin echoes appear brighter.

The current protocol includes cannulation of a foot vein. This is however more painful, than cannulation of an arm vein and not common in clinical practice. An explorative analysis using only arm injections was thus made. The traditional PFO definition requires that three bubbles reach the left atrium within three beats from opacification of the right atrium. This rule originates from a single case report [31] and is not always enough for distinguishing intracardiac from intrapulmonary shunts [207]. In cases were the PFO channel can be directly visualised this criterion also seems unnecessarily strict. For exploratory analysis we therefore created a novel PFO definition. A case is then classified as PFO positive if either the traditional criterion is met, or the PFO channel can be visualised at the site of contrast passage, even when the contrast appears in the left atrium after the three beats.

Transthoracic echocardiography

Standard echo-Doppler examinations were performed in the 30 subjects. Left ventricular mass was calculated according to the corrected formula of the American Society of Echocardiography and indexed for body surface area. The longitudinal, myocardial, peak systolic and early diastolic velocities were assessed in the base of the left ventricular lateral wall and in the base of the right ventricular wall with spectral, pulsed-wave tissue Doppler. The left ventricular ejection fraction was visually estimated. The systolic maximum tricuspid regurgitation gradient was assessed with and/or without signal amplification with agitated polygelin as echo contrast. Right atrial pressure was quantified on the basis of the respiratory variations of the inferior vena cava width and the right ventricular systolic pressure was calculated as the sum of the right atrial pressure and tricuspid regurgitation gradient. The left and right atrial area was measured in apical four-chamber view in end systole.

Statistical analysis

Data were analysed using SPSS version 12, SPSS, Chicago, Illinois. For quantitative parameters we used Pearson's test for correlation analysis and unpaired Student T-test for comparison between groups. A p value < 0.05 was considered statistically significant. All values are given as mean $\pm$ 1 standard deviation, if not otherwise stated.

In paper II the sizes of the ASDs by TE and by balloon sizing during catheterisation were further compared by plotting scatter grams and developing regression line.

In paper III a calculation of power was made as part of the study design. A minimum of 60% PFO prevalence in high PD subjects and a maximum of 15% in low PD subjects was hypothesised, and it was calculated that a sample of 15 pairs would give 80% power to detect any difference with a level of significance of $p<0.05$. McNemar's two-tailed test was used for paired proportions. For comparison of the prevalence between groups, Fischer's two-tailed exact test was used.

In paper IV, the agreement between the gold standard and each provocation was, with both contrast injections counted together, characterised by unweighted kappa values. Kappa scores between 0.21 and 0.40 indicate fair, 0.41-0.60 moderate, 0.61-0.80 good and above 0.8 very good agreement.

4. Results

Paper I: Availability for percutaneous closure

Period 1, 1997-2000: Out of the 66 TE that were reviewed 16 were considered unsuitable for catheter closure as shown in Figure 4-1. This was because the defect was considered too large in 13 patients. One defect because of no posterior rim and one because the defect was too close to the mitral valve. One patient had a dilated cardiomyopathy with mitral regurgitation and the ASD was judged mainly to serve as an overload valve for the dysfunctional left ventricle. All the remaining 50 patients went on to heart catheterisation with the intention of closing the defect. In seven patients the stretched diameter was over 26 mm and differed up to 17 mm from the initial TE estimation. In five patients additional defects were detected during balloon occlusion. So of 66 patients referred for closure 38 (58%) were considered suitable and were successfully closed by catheter intervention.
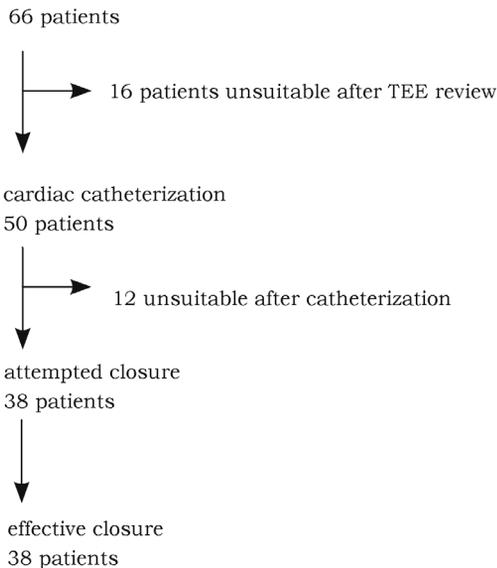
66 patients

→ 16 patients unsuitable after TEE review

cardiac catheterization
50 patients

→ 12 unsuitable after catheterization

attempted closure
38 patients

effective closure
38 patients

Figure 4-1.

Numbers of patients receiving a device of all consecutive referrals in period 1, 1997 to 2000.

Table 4-1. Number of patients available for percutaneous closure in period 1, 1997-2000, depending on type of defect.

Type of defect	TE-review	Catheterisation	Receiving device
ASD, n	48	32	21
PFO, n	18	18	17
Total, n	66	50	38

Per-procedural complications, period 1

Two patients had brachial plexus injury, related to positioning during the catheterisation, with a subsequent full recovery. No patient went to surgery. No arrhythmia and no thromboembolic event occurred during hospitalization.

Follow up, period 1, paper I.

After three months TE showed residual leakage in 7 patients and after 12 months only 1 patient had a residual leakage. It was a patient with a 22- mm ASD where a part of the defect rim was not placed in-between the two discs of the Amplatzer device. No signs of thrombi or device fracture were seen in any patient. The patients were followed for up to 18 months, with a mean follow-up of 6 months. Two patients developed atrial fibrillation 1 month after having the device and were successfully cardioverted. None of them had any recurrence of atrial fibrillation during the 12 months follow-up.

Table 4-2. Catheterisation data, period 1, paper I

Catheterisation data	All patients n=66	Patients receiving device n=38
Fluoroscopy time, min	23 [5-62]	22 [5-62]
Total time, min	94 [25-240]	92 [25-240]
Balloon stretched defect diameter, mm	15 [5-35]	12.7 [5-26]
Difference between balloon stretched diameter and TE, mm	5,6 [1 – 17]	4,5 [-1–17]
Qp/Qs †	2.4:1	1.9:1
Syst PAP <30 mmHg, n	31	29
Syst PAP 30-40 mmHg, n	15	6
Syst PAP >40 mmHg, n	4	3

† Catheterisation data from those with hemodynamic indication for closure. Qp/Qs=ratio between pulmonary and systemic blood flow.

Availability in Period 2

From February 2001 to June 2003, 64 consecutive patients were referred, resulting in 56 successful percutaneous closures as shown in Table 4-3. Follow up data are not available for patients in period 2.

Table 4-3. Availability for percutaneous closure depending on type of defect in the second period, February 2001 to June 2003.

Type of defect	TE-review	Catheterisation	Receiving device
ASD, n	47	44	39
PFO, n	17	17	17
Total, n	64	61	56

Paper II: ASD sizing

The echocardiographic size of the ASD for the whole group was 16.3±4.6 mm (range 3–22 mm). The stretched diameter of the ASD measured by balloon sizing was generally larger than the echocardiographic size, namely 22.5±6.0 mm (range 12–40 mm), p<0.001. There was no gender difference; for men, the values are 16.5±4.6 mm versus 22.2±5.4 mm (p<0.001), for women, the values are 16.3±4.6 mm versus 22.5±6.0 mm (p<0.001). The relationship of the TE diameter and the BSD diameter is shown in Figure 4-2 for all the patients, men and women. The regression line was y=0.94x+7 (Pearson's correlation coefficient r=0.65; p= 0.02). Thus, our formula can be displayed as: BSD(X)=TE(X)x0.94+7.0 (Formula 2) where TE(X) is the size of the ASD measured by TE in millimetres and BSD(X) is the BSD of the ASD in millimetres.
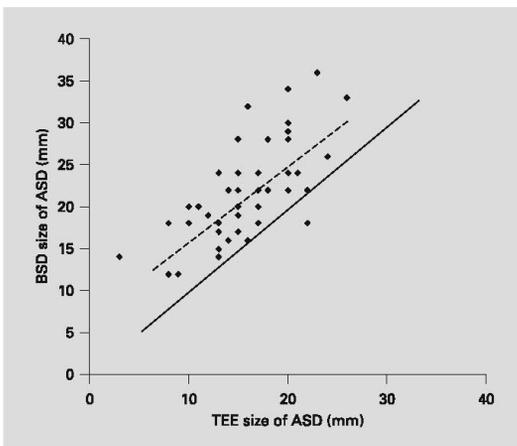

Figure 4-2. ASD sizing comparing transesophageal echocardiography (TEE) diameter and balloon sizing diameter (BSD).There are some identical points on the plot, thus displaying fewer points than there actually are. The solid line is y=x (line of equality) and the dotted line is the line that best describes the straight line through the points, y=0.94x + 7

We also explored the relationship between the Qp:Qs ratio (left-to-right shunt) and the size of the defect (balloon size) showing a great variability in the shunt when compared with the size of the defect (Figure 4-3) (Pearson's correlation coefficient r=0.52; p=0.04). The regression line was y= 0.07x–0.3.
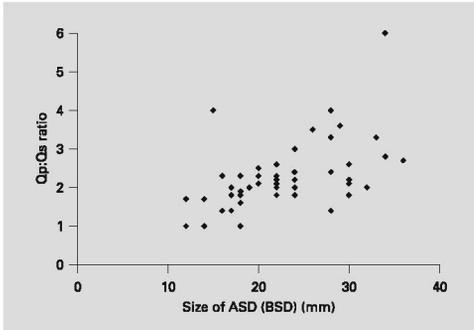

Figure 4-3. Relationship between the degree of shunting and the size of the ASD, according to balloon sizing diameter (BSD)

Qp/Qs=ratio between pulmonary and systemic blood flow.

Paper III: PFO in OSA

All 30 subjects completed contrast TE with 12–20 injections each. A PFO was found in 14 (47%) subjects and was classified as small in three and large in 11 subjects. The PFO subjects received 17.6±1.6 and the non-PFO subjects received 18.4 ±2.2 injections. A large PFO was found in nine out of the 15 (60%) high PD cases but only in two out of the 15 (13%) low PD controls (p=0.02), as shown in Figure 4-4. Furthermore, the PFOs were found in individuals with a large range of AHI values as shown in Figure 4-5.
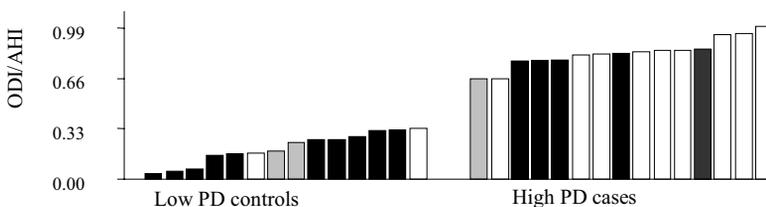

Figure 4-4. Distribution of subjects with a patent foramen ovale (PFO) according to oxygen desaturation index (ODI)/apnea–hypopnea index (AHI) ratio. White bars: subjects with large PFO; grey bars: subjects with small PFO; black bars: subjects without PFO. Low proportional desaturation (PD) ODI/AHI ≤0.33; high PD: ODI/AHI ≥0.66. One subject without PFO had ODI/AHI=0.

It was more likely that a subject in the upper part of the graph would have a PFO than a subject in the lower part, irrespective of AHI value.
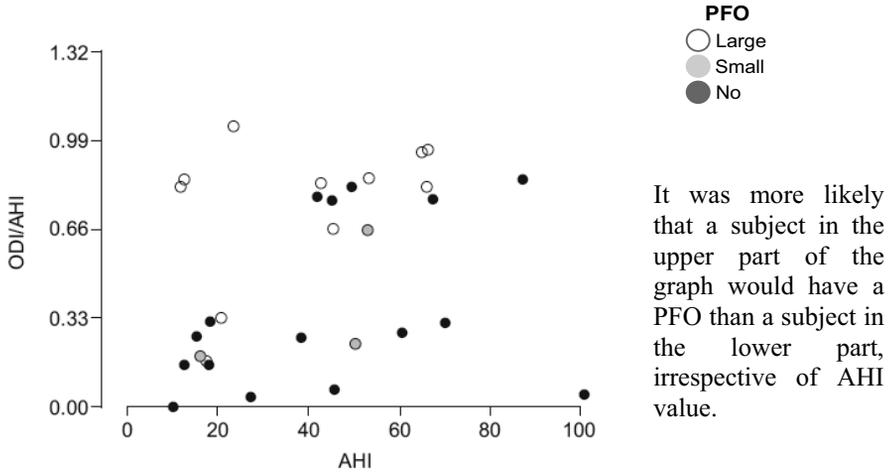
Figure 4-5. Correlation of OD/AHI ratio and AHI among subjects with large, small and without PFO. Abbreviations as in Figure 4-4.

The paired distribution showed a higher prevalence of large PFOs in high PD cases than in low PD controls. There were eight pairs in which only the high PD case had a large PFO, one pair in which both had a PFO, five pairs in which no large PFO was found, while in one pair only the low PD control had a large PFO (p<0.04). The paired distribution regarding all-size PFO did not reach a statistically significant difference (p=0.07). The predictive value of the ODI/AHI ratio for PFO detection was calculated. A high ratio ($\geq$0.66) had a sensitivity of 82% and a positive predictive value of 60%. A low ratio ($\leq$0.33) had a specificity of 68% and a negative predictive value of 87%.

The spirometry and polysomnography data for the groups are shown in Table 4-3. As expected, the ODI is higher in high PD cases than in low PD controls, but the significant difference is not explained by AHI. In fact, the AHI was not significantly different between groups. No significant difference in AHI, apnea index or apnea duration was found regarding the presence or absence of a large PFO. However, the ODI/AHI ratio in large PFO subjects was twice that found in subjects without a large PFO. The ODI/AHI ratio, but not the minimum oxygen saturation and ODI per se, was fairly well correlated to a large PFO (r=0.55, P=0.02). The median number of bubbles passing into the left atrium after an injection was significantly correlated among all 30 subjects with nocturnal minimum oxygen saturation (r=0.36, p=0.05) and among the 14 subjects with a PFO (r=0.62, p=0.02). However, age, body mass index, hypertension, diabetes and blood pressure did not

differ in accordance with the PFO diagnosis. The measured echo parameters did not differ between groups, as shown in Table 4-4. The characteristics of patients with high PD are shown in Table 4-5; patients with a high PD without a PFO had significantly more hypopneas than those with PFO.

Table: 4-3. Spirometry and polysomnography data in the matched groups and in subjects with vs. without large patent foramen ovale (PFO).

	Proportional Desaturation			Large PFO		
	High PD n=15	Low PD n=15	P	Yes n=11	No n=19	P
VC, %	87.9±12.1	85.5±17.4	n.s.	90.0±13.5	84.8±15.5	n.s.
FEV1, %	97.1±15.9	86.7±17.7	0.10	97.3±19.0	88.8±16.0	0.20
PEF, %	92.2±18.5	77.2±12.4	0.02	93.0±20.0	79.9±13.8	0.07
OS, % daytime	95.4±2.1	96.0±2.0	n.s.	95.4±2.3	95.9±1.9	n.s.
OS mean, %, sleep	93.0±1.7	95.2±1.7	0.02	93.3±1.8	94.5±2.0	0.09
OS min, %, sleep	75.4±7.5	84.7±2.9	<0.001	78.3±6.7	81.1±7.6	0.18
Desat, 10%	10.1±11.0	0.0±0.0	0.003	9.0±12.9	2.8±5.4	0.15
ODI, n/hour	40.5±18.4	6.5±6.2	<0.001	31.5±22.3	18.9±20.9	0.14
AHI, n/hour	48.9±20.8	34.9±26.1	0.12	38.8±22.0	43.7±25.90	n.s.
ODI/AHI	0.83±0.10	0.19±0.11	<0.001	0.75±0.27	0.37±0.30	0.001
AI, n/hour	26.7±20.7	9.9±16.6	0.021	23.6±21.9	15.2±19.2	n.s.
Apnea duration, s	25.0±9.1	16.8±8.0	0.014	23.3±12.6	19.5±6.9	n.s.
HI, n/hour	21.9±13.1	25.0±14.9	n.s.	14.7±7.2	28.5±14.4	0.007
Hypopnea duration, s	28.3±8.4	23.6±3.6	0.06	26.9±7.9	25.4±6.2	n.s.

Data are presented as n or mean±SD, unless otherwise stated. PD: Proportional Desaturation; VC: Vital Capacity; FEV1: Forced Expiratory Volume in 1 second; FEV%: FEV1/VC; PEF: Peak Expiratory Flow. All values for spirometry data given as percentage of predicted value. OS: oxygen saturation percutaneously measured; ODI: Oxygen Desaturation Index; AHI: Apnea Hypopnea index; AI: Apnea Index; HI: Hypopnea Index; Desat 10: episodes per hour of sleep with desaturation of more than 10%; n.s.: non significant. All p value are given unless p>0.2.

Table 4-4. Transthoracic echocardiography data in the matched groups and in subjects with vs. without large patent foramen ovale (PFO)

	Proportional Desaturation			Large PFO		
	High PD n=15	Low PD n=15	P	Yes n=11	No n=19	P
LVMI, g/m²	123±26	122±28	n.s.	117±26	126±28	n.s.
EF, %	58±3	58±4	n.s.	59±3	59±4	n.s.
Sm, cm/s	13.2±4.0	12.9±2.6	n.s.	12.8±2.9	13.5±4.1	n.s.
Em, cm/s	12.6±2.9	12.3±2.2	n.s.	12.3±2.9	12.6±2.4	n.s.
E/Em	5.7±1.3	6.0±1.4	n.s.	5.9±1.2	5.8±1.4	n.s.
Sm RV, cm/s	18.6±6.0	18.0±5.1	n.s.	19.3±5.3	17.8±4.8	n.s.
EmRV, cm/s	16.9±6.8	16.7±3.8	n.s.	16.6±8.0	17.0±3.5	n.s.
ERV/EmRV	3.3±1.1	3.1±0.7	n.s.	3.2±1.1	3.2±0.8	n.s.
RAP, mmHg	6.0±2.1	5.0±0	0.08	5.5±1.5	5.5±1.6	n.s.
RVSP, mmHg	27.8+6.5	26.8±3.3	n.s.	27.3±7.2	27.3±3.6	n.s.
LA area,cm²	20.4±4.6	21.5±4.3	n.s.	19.4±4.0	21.8±4.5	n.s.
RA area, cm²	16.9±3.6	16.2±2.7	n.s.	16.5±3.1	16.5±3.2	n.s.

Data are presented as n or mean±SD unless otherwise stated. PD: proportional desaturation LVMI: left ventricular mass index (gram/m² body surface area); EF: left ventricular ejection fraction; Sm: peak systolic velocity of LV myocardium; Em: early diastolic left ventricular myocardial relaxation velocity; E/Em= ratio between early diastolic transmitral inflow velocity and Em; SmRV = peak systolic velocity of the right ventricular myocardium; EmRV: early diastolic right ventricular myocardial relaxation velocity; ERV/EmRV=ratio between early diastolic transtricuspid inflow velocity and early myocardial right ventricular relaxation velocity; RAP: right atrial pressure; RVSP: right ventricular systolic pressure; LA area: left atrial area; RA area= right atrial area. All p-values are given unless p>0.2

Table 4-5. Characteristics of high PD cases according to presence of large PFO.

Large PFO	Yes=9	No=6	P
ODI/AHI	0.86±0.11	0.78±0.07	0.08
AHI, n	43±22	58±17.0	0.18
HI, n	14.0±7.7	34±10.3	0.003
AI, n	28.6±21.4	23.8±21.3	n.s.
Hypopnea, min per hour	5.8±2.4	14.8±5.1	0.006
Apnea, min per hour	14.0±12.9	9.2±8.9	n.s.

Abbreviations as in Table 4-3.

Paper IV: PFO detection

The number of detected PFOs increased as the number of injections increased, as shown in Figure 4-6. The correlation was statistically significant (r = 0.79, p < 0.01). A PFO was eventually found in 14 (47%) subjects and classified as small in 3 and large in 11 subjects. Five injections per patient were required to detect all the 11 large PFOs. Eleven injections per patient, counted in the order given, were required to detect all 14 PFOs but after that, no more PFOs could be detected, even though more injections were given. The small PFOs needed more injections to be detected (4.8 injections/small PFO) than the large PFOs (2.0 injections/large PFO). All 30 subjects completed contrast transesophageal echocardiography with 12 to 20 injections each. The PFO subjects received 17. 6±1.6 and non-PFO subjects received 18.4±2.2 injections. There were disparities in PFO detection between the two observers in one large PFO and two small PFOs, all settled in consensus with the third observer.
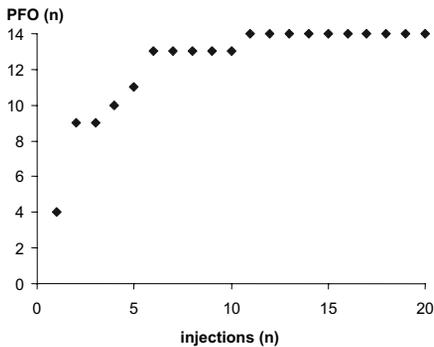

Figure 4-6.
Cumulative numbers of detected patent foramen ovale with increasing numbers of contrast injections.

Sensitivity for a single injection ranged from 29% to 77% as shown in Table 4-6. When the two injections during one provocation were evaluated together, the sensitivity ranged from 31% to 86%. The highest sensitivity reached was early VM, with or without the combinations with bed tilt or nitroglycerin, and detected 8 of the 11 large PFOs. These provocations also had the highest kappa values.

Table 4-6. Sensitivity (%) and kappa values for PFO detection with the different provocations used.

Inject-ion site	Provo-cation	Sensitivity (%)				Kappa
		Injection 1 all PFOs	Injection 2 all PFOs	Both injections all PFOs	Both injections large PFOs	Both injections all PFOs
Foot	Late Valsalva	29	64	64	82	0.66
Arm	Rest	29	43	43	46	0.44
Arm	Early Valsalva	57	77	79	73	0.80
Arm	Late Valsalva	42	42	58	56	0.60
Arm	Mueller	31	25	31	40	0.32
Arm	Bed tilt + early Valsalva	71	71	86	73	0.87
Arm	Cough	36	43	43	55	0.44
Arm	Nitro+ rest	30	40	40	57	0.49
Arm	Nitro + early Valsalva	71	71	79	73	0.80
Arm	Rest + supine	44	71	70	71	0.79

Arm injections were made in the left arm. Kappa values for comparison with gold standard; a subject was considered PFO positive when at least one of the injections was PFO positive. The differences in kappa values did not reach statistical significance.

Colour Doppler imaging during resting respiration could not detect any of the PFOs. The PFO channel was directly visualised in 9 subjects, all with a large PFO, whereas in the other 5 PFO subjects the exact location of the communication could not be visualised, but contrast appeared in the left atrium, near the septum within three heartbeats from opacification the right atrium. No subject was judged to have an intrapulmonary shunt. In an exploratory analysis, direct visualisation the PFO channel was used as a criterion according to the novel PFO definition described in the methods. We the used this novel definition and confined the analysis to injections solely in the arm. A combination of four arm injections, with two during early VM, one during cough and one during bedtilt combined with early VM, could fully detect all 14 PFOs.

5. Discussion

Paper I: Availability of percutaneous closure

Of 66 consecutive referred patients in the first period 1997-2000, 58% could be closed percutaneously. The most common reason for not being suitable for percutaneous closure was too large defects in 20 (30%) of the 66 referred patients. The size of the defect can be measured by TE but the balloon-stretched diameter will mostly be significantly larger [112]. Seven (14%) of the 50 patients judged as suitable based on the TE (Figure 4-1) had too large a stretched diameter and differed up to 17 mm compared to the initial TE measurement and in a rather unpredictable way. The largest device available at the time of the study was 26 mm.

Of the 18 patients with PFO in the first period there was only one not available for closure. TE images during balloon occlusion revealed a fenestrated septal membrane, instead of single PFO. The total occlusion rate was high with only 1 patient (2.6%) with a residual shunt at 12 months. It was clinically insignificant with a residual leakage diameter of only 3 mm in a patient with a large ASD and thin adjacent tissue surrounding the defect. Control TE revealed juxtapositioning of the occluder with both discs on the right side of the septum in the antero-superior part of the circumference. Colour Doppler showed a small leakage at this site, adjacent to the occluder, but no other defect and the device has been stable in position during two years' follow-up. It is a known complication in patients with a superiorly located defect [105]. The route through vena cava inferior steers the guide wire and a large angle is created between the discs and the atrial septum. This complication focuses on the importance of visualizing the atrial septum on TE in order to direct the occluder so it will engage the atrial septum along the entire circumference of the defect.

TE is an excellent tool in evaluating the anatomy of the interatrial septum. The rims surrounding the defect can be visualized and distances can be measured to the mitral and tricuspid valves and to the entrance of sinus coronarius. The entrances of the pulmonary veins can be visualized in order to rule out anomalous pulmonary veins. Some features will however be visible first on catheterisation. Multiple defects will often be visualized with colour Doppler first when the balloon occludes the defect. The size of the defect can be measured, but the balloon-stretched diameter will mostly be significantly larger [112]. The anatomy of the fossa ovalis varies significantly [117]. The defect can be located close to the cava inferior with little or no inferoposterior rim, which will make device closure impossible. The rim towards the mitral valve must be sufficient while the anterior rim towards the aorta not is essential for closure. Visualization of the inferior part of the right atrium by TE is not always possible. Initial experience with three-dimensional TE has shown that this area is difficult to interrogate even with 3-D [208]. It may be better visualized by intracardiac ultrasound [209]. The incidence of total closure is higher than in some other studies using other devices [106, 210] and comparable to a study by Taeed using the Amplatzer device [198] where all the patients (n=16) had total closure at 12 months. Out of the 28 patients that were not closed, 23 have gone through surgery, 3 will be left with the defect open, two are waiting for catheter closure with a larger device.

Limitation

The population in paper I consisted of patients selected at different hospitals referred to a tertiary centre and is probably not representative of the total population with ASD/PFO.

Paper II: Sizing of ASD

Our results show that the difference between TE size and the BSD of the ASD is quite large (16.2 vs. 22.5). TE almost invariably underestimates the size of the ASD, at times up to 50%. There is also a great deal of variability in addition to the underestimation. Formulas 1 and 2 actually do correct the underestimation but not the variability. The variability of the two methods is too great to regard TE size useful for closure, without using a sizing balloon for accurate measurement. In our material, we would have chosen the correct device size in 3 of 51 patients by exclusively using formula 1.

There are several reasons for this discrepancy. The size and localization of fossa ovalis varies from one patient to another. Given the fact that the ASD is rarely a perfect circle, it may be difficult to precisely measure the correct largest diameter of the defect. There is also a certain amount of flexibility and

redundancy of the tissue surrounding the defect resulting in a larger defect when stretched with the balloon. The cardiac cycle might also affect the size when TE sizing is used [211]. Additionally, ASDs can be multiple, causing error in measurement [212]. The pre catheterisation TE exams were carried out at different institutions by different echocardiographers with different types of equipment, possibly causing some scatter which was, however, minimized by our review of the TE studies from the referring institutions. Other investigators have shown comparable difference and scatter [213]. Thus, for the individual patient, the use of these formulas is at best doubtful. In this context, it is also important to bear in mind that the balloon is inflated with low pressure, just enough to occlude the defect; thus, the pressure in the balloon does not exceed 15–20 mmHg. It is also easier to assess the presence or absence of additional defects when the largest ASD is occluded by a balloon.

Recently, Carcagni and Presbitero [214] suggested using the thickest part of the rim around the ASD (2.5 mm thick), providing much better correlation with the BSD and very little scatter. Their results need to be confirmed. The relationship between the size of left-to-right shunt (Qp:Qs) and the size of the ASD is poor. An ASD of more than 15 mm diameter is likely to be non-restrictive, and the degree of shunting will be decided by the difference in compliance between the right and the left ventricles. The difference in compliance is dynamic, influenced by the patient's physical situation as well as co morbidity. With increasing age and developing hypertension and ischemia, the left ventricle will lose compliance more than the right ventricle and thereby increase the degree of left-to-right shunting through an ASD. Thus, the pulmonary artery pressure seems to play a minor role.

We think it is very important to measure the size of PFO by balloon as well because of the variability in the anatomy of the fossa ovalis and due to the fact that a long slit-like PFO in the fossa ovalis might not adequately hold a PFO occluder.

Paper III: PFO and desaturations in OSA

To the best of our knowledge, this is the first study demonstrating an association between nocturnal desaturations in OSA and the existence of a PFO. In order to discriminate between desaturation caused by veno-arterial admixture and desaturation caused by apnea–hypopnea related interruption in alveolar ventilation, the ODI/AHI ratio was calculated for each OSA subject. This ratio is a novel construction that consists of two well-defined parameters with the same denomination: number per hour of sleep. The ODI and AHI values were fairly well correlated with each other among those 209 OSA subjects from whom the 30 study subjects were selected (r=0.8, p<0.01) as shown in Figure 5-2. Also in the literature, ODI is generally considered to be positively correlated with AHI in OSA subjects [190]. Due to this correlation, the ODI/AHI ratio was considered to be a factor that roughly corrects the desaturation frequency for the apnea–hypopnea frequency and that its variation reveals that factors other than ventilation could be involved. Although the correlation is good in a group of OSA subjects, large variations are actually found when AHI and ODI are compared between individual subjects [190]. In the whole group of 209 subjects with OSA, the AHI values were generally higher than the ODI values, with a mean difference of 15.8 and a considerable scatter (SD 13.7). According to the present hypothesis, a subject with an ODI of 16 and AHI of 20 (ODI/AHI 0.8) would be more likely to have a PFO than a subject with an ODI of 10 and an AHI of 40 (ODI/AHI 0.25), even though the OSA is more severe in this latter subject.
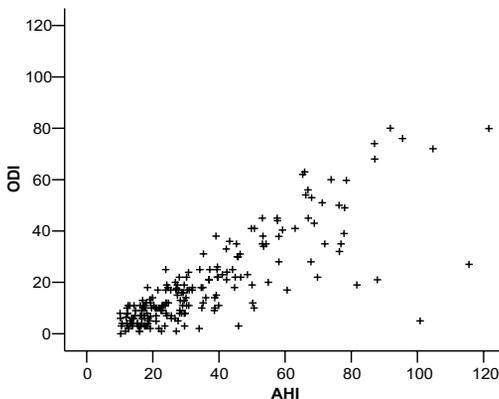

Figure 5-2. Correlation of ODI and AHI among the 209 subjects diagnosed with OSA.

As shown in Table 4-3, pulmonary function was significantly better in high PD cases than in low PD controls, supporting the hypothesis that other factors besides respiratory factors are involved. Moreover, the variation in

ODI/AHI ratio between groups was not explained by the AHI. However, the power of the ODI/AHI ratio to predict shunt-related desaturation is limited. The magnitude of desaturation from an interatrial shunt will depend on the size of the PFO and the interatrial pressure relation. The potential opening diameter of the PFO ranges ≥1–19 mm [13]. Since the number of bubbles passing through is only a rough estimate of the diameter during balloon sizing, and no catheterisation was performed, the exact maximum opening diameter is not known [47]. The interatrial pressure relationship will depend on the degree of right-heart loading during obstructive apnea but also on concomitant left-heart condition [203]. Shunt diagnosis was only performed with the subjects awake, for which reason the actual degree of shunting during sleep is unknown. In order to overcome this weakness the frequency of moderate desaturation (≥4%) rather than maximum desaturation was focused upon.

Beelke and co-workers [97] found right-to-left shunting in nine out of 10 PFO subjects during obstructive apnea lasting longer than 17 s but not during hypopnea. That study exclusively included OSA subjects with apnea–hypopnea and concomitant 4% desaturation, which would correspond to the high PD cases in the present study. One of the two low PD controls with PFO in the present study had only hypopnoeic and no apnoeic events, while the other had only three episodes of apnea per hour of sleep. The current results are in contrast, in part, to the study of Shanoudy and co-workers [191], which showed a generally increased prevalence of PFO in OSA, but did not consider the degree of desaturation in relation to apnoeic events. The present study showed a low prevalence of only 13% in the low PD group. It also seems logical that PFO is not a cause of upper airway obstruction, but its valve-like function permits unidirectional right-to-left shunting during right-heart loading, such as that occurring during obstructive apnea [96, 97, 205].

The analysis of PFO is not always distinct. There was disagreement in the analysis of one large PFO and three small PFOs; however, they were all solved through consensus. This is in concordance with Cabanes and co-workers [36] who found considerable variation in small-PFO analysis with only a few bubbles passing to the left atrium. However, the clinical significance of these small shunts is probably very limited [9]. In the current study, the PFO channel was visualized in nine subjects, all with large PFO, whereas in the other subjects, the exact location of the passage could not be visualized. Another route of contrast passage could hypothetically be intrapulmonary shunts, but this is probably not the case as contrast appeared in the left atrium adjacent to the septum within three heartbeats from contrast filling of the right atrium. The current sampling and classification procedure may have been skewed towards high AHI values in this population, as the

definition of respiratory events was based on nasal pressure cannula recording. Moreover, obstructive events were also scored when respiratory events included arousal but not necessarily desaturation. This practice may also have elevated the AHI value in patients with minor desaturation but frequent arousal responses. Apnea duration and the relationship between episodes of apnea and hypopnea may also have introduced a confounding influence.

The characteristics of patients with high PD are shown in Table 4-5; patients with a high PD without a PFO had significantly more hypopneas than those with PFO. Frequent hypopneas in OSA subjects have been associated with reduced hypoxic ventilatory drive [215]. This may cause a high ODI/AHI ratio because of reduced ventilation between events and relatively low respiratory event scoring, as the baseline respiratory flow is also reduced. In calculating ODI/AHI, apneas and hypopnea were counted together, although shunting seems only to occur during apneas [97].

The result supports the hypothesis that interatrial shunting gives a substantial increase in the number of desaturations in OSA subjects with PFO. Moreover, this may be the mechanism that explains the increased risk of stroke that is seen in OSA [155]. If this link could be established, percutaneous closure of a PFO may be a potential treatment option in the future [216].

Limitations

The study population in paper III was small. It was however based on a cross-sectional population sample randomly selected for polysomnography without prior knowledge of sleep disturbances. Subjects diagnosed with OSA were considered for inclusion on the basis of their ODI/AHI ratio and with obstructive pulmonary disease as the only exclusion criterion. The findings may therefore be regarded as reasonably applicable to a general population of OSA patients with healthy lungs.

Paper IV: Diagnosis of PFO

The results showed that the sensitivity for PFO detection increased with the number of contrast injections given. If only two contrast injections for PFO detection are used, this will result in a low sensitivity as shown in Figure 4-6. In order to yield a sensitivity of 100% for large size PFOs and 79% for all size PFOs, five contrast injections were needed. The effect that the number of contrast injections has on sensitivity for PFO detection has probably resulted in underestimation of the PFO prevalence in many previous studies. It might also be a reason to the high variation in PFO prevalence in previous studies. The reported prevalence of PFO amongst controls in transesophageal studies varies from 3 to 43% [217, 218]. The study by Fisher [41], with 1000 clinical transesophageal exams detected PFO in only 9% whereas the autopsy study by Hagen [13] showed a prevalence of 27% and about half of them with a diameter of at least 4 mm. The variation is also large between TE studies, even when population based control groups have been used, as shown in Table 5-1. In a group of healthy volunteers, Job and co-workers found a high PFO prevalence of 43% [218]. They used a large amount (10 ml) of agitated gelatine as contrast and a single bubble per stop frame in left atrium was enough for a PFO diagnosis.

Variation in the number of contrast injections might also have been a significant bias in previous studies, when controls and subjects have received different numbers of contrast injections. Even though study protocols often specify the number of contrast injections, the actual number of injections eventually given is usually missing. With a strict TE protocol including six contrast injections Petty and co-workers showed a PFO prevalence of 24.7% in a large group of over 500 subjects, without stroke, randomly selected from the population. However, in the groups examined without defining the number of injections, the prevalence was 14.9% in a clinical control group, 17.1% in a non-cryptogenic stroke group, and 24.8% in a cryptogenic stroke group. A retrospective analysis of this material by Agmon and co-workers [42], showed that adjustment for the number of contrast injections given greatly influenced the results. The odds ratio of PFO in cases versus controls changed significantly from 0.71 to 1.65 after adjustment for the number of injections given. Thus, in studies that not have used a strict protocol, with equal numbers of injections used in both cases and controls, differences in the effort taken to reveal PFO may have resulted in a significant bias.

Table 5-1. PFO prevalence in TE studies with population based control groups.

Author	No of subjects	Selection	PFO prevalence (%)	No of contrast injections	No of bubbles defining PFO
Job [218]	63	Healthy volunteers	43	3	1
Jones [219]	202	Advertising, stroke excluded.	15	2	2
Lindgren [220]	59	Random population sample, matched to stroke cases	25	Not specified	Not specified
Petty [221]	519	Random population sample, stroke excluded.	24,7	6	2
Roijer [222]	68	Random population sample, matched to stroke cases	22	Not specified	3
Schwerzmann [76]	50	Healthy hospital staff	17	Not specified	2

There are several reasons as to why a contrast injection during VM can be negative, even in the presence of a large PFO. Firstly, insufficient strain during VM may provide too little pressure gradient between the left and right atrium. We do not know which pressure the patients achieve during VM and patients with left heart disease may require a higher Valsalva pressure in order to reverse the interatrial pressure gradient since they have increased left atrial pressure [203, 223].

Readily identifiable signs of a significant strain during VM are leftward displacement of the atrial septum as the left atrium shrinks and undulation of the interatrial septum. Secondly, upon release of strain, the septum bulges towards the left. In this very moment, contrast should densely fill the region in the right atrium, adjacent to the bulging septum. Thus, entrance of contrast free blood from inferior vena cava on release of strain and insufficient strain i.e. absent bulging are two common causes of false negative contrast injections, as illustrated on the echo images.
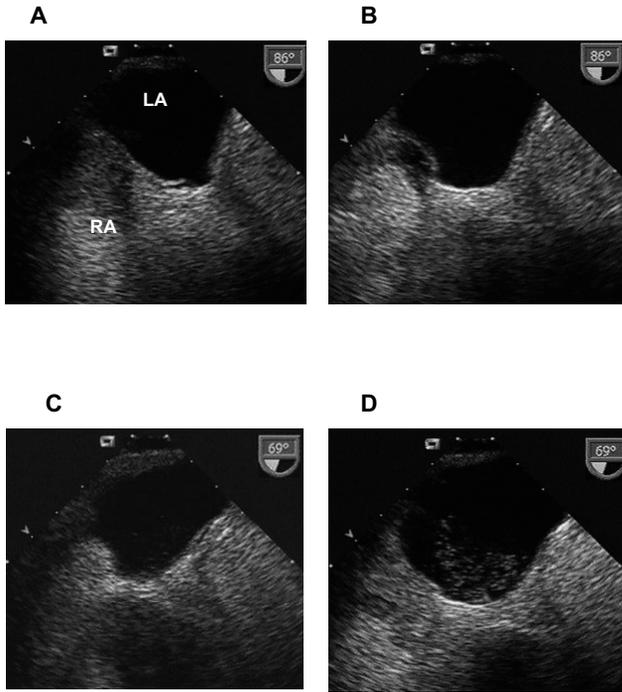
Discussion

Figure 5-3. Contrast transesophageal echo

A: False negative injection due to absence of leftward bulging of the interatrial septum. LA = left atrium. RA = right atrium.
B: False negative injection due to contrast free blood that surges in from inferior vena cava and sweeps the contrast away from the septum.
C and D: Both images are from the same injection.
C: The septum bulges clearly towards the left atrium.
D: A split second later than image C, contrast is seen in the left atrium.

However, even when contrast filling and bulging seem to occur simultaneously, later injections may occasionally be PFO positive. One possible explanation is that the PFO does not open up even though the septum primum bulges over towards the left atrium. Another that the opening of the PFO occurs along a part of the circumference of the septum primum that may be localised outside the image plane even when the septum primum is seen overlapping the septum secundum. Therefore, even when the echo image shows contrast filling and the PFO actually opens the blood passing over to the left atrium could be contrast free blood surging in from inferior cava.

The results also have important implications for the clinical use of contrast transesophageal echocardiography. Thorough search for PFO with additional contrast injections will increase the number of PFO positive patients. When the main indication for the exam is PFO detection, this should be noted in advance and the patient thoroughly instructed and trained to perform the VM that should last about 10 seconds. The physician or an assistant can hold his hand on the stomach of patient to check the continuity of the strain. For patients unable to perform a VM, bed tilt is an alternative. During mechanical ventilation, end inspiratory occlusion maneuver can be a substitute for VM [224]. Contrast is then injected after the appliances of an end inspiratory occlusion pressure of 20 cm of water. When the contrast fills the right atrium after about 10 seconds the pressure is released and ventilation resumed. When injections are made in the right arm, the patients can rise and move their arm between injections in order to empty remaining contrast into the central circulation.

Our results indicate that the early VM is more effective than late VM and more effective than cough, which is in contrast with the study by Stoddard and co-workers [39] which showed cough to be superior to the VM for PFO detection. An explanation could be different timing of contrast filling in relation to release of the VM. Pfleger and co-workers [34] showed that the dominant interatrial pressure reversal occurs only during roughly three seconds after the release of the VM strain phase. If the VM stops when contrast is injected this pressure reversal will probably have ceased by the time the contrast reaches the right atrium. Pfleger also showed the VM to be more effective than cough in producing inversed interatrial pressure. Our results are also in accordance with those of Zanette and co-workers [225], which also showed highest sensitivity for VM starting before contrast injection The injections with the subject in supine position during "resting respiration" had a rather high sensitivity. However, most subjects experienced excessive coughing so respiration was actually not "resting".

Previous studies has shown high sensitivity for PFO detection with femoral injection [43]. However, in our study, foot injections had only intermediate and highly variable sensitivity. All nine subjects that were PFO positive with foot injection were also positive with arm injection, but the remaining five subjects that were positive with arm injections were negative on both foot injections. The reason for this discrepancy was probably lack of timing between VM and contrast filling of the right atrium. The late VM started about 5 seconds after the foot injection, but the contrast did in most cases, not appear in the right atrium, during the 10–15 seconds the subject was able hold the strain. When the contrast eventually entered the right

atrium, the leftward bulging of the atrial septum, seen at the release of Valsalva strain, had already ceased.

In our experience, the strain almost stops the blood flow from inferior vena cava and allows the right atrium to be filled with contrast from superior vena cava. When strain continues, the contrast from cava superior will fill also the lower region of the right atrium that is close to the entrance of the inferior vena cava and often guarded by the Eustachian valve. Interatrial pressure seems to equalise during the strain phase [34]. Contrast often passes over to the left side already during the strain phase, when it is continued long enough. Since the echo image is more stable before the release of the VM, the PFO channel can be better visualised. The entrance of the cava inferior will then be filled with contrast and upon the release of strain, the contrast will surge towards the PFO channel. With this methodology the problem, with contrast free blood from inferior vena cava sweeping the contrast away from foramen ovale, during the release phase, will be dissolved. Even though more than three beats will elapse after contrast filling of the right atrium, those cases where the PFO channel is visualised can be classified as PFO positive with the novel PFO definition that is suggested. Thus, in a purely exploratory analysis, a combination of four arm injections, with two during early VM, one during cough and one during bedtilt combined with early VM, could fully detect all 14 PFOs in our study population.

We used colour Doppler of fossa ovalis with aliasing velocities about 40 cm/s only during resting respiration and not during VM, a technique that could be a useful complement to contrast, when the velocity is set low, about 25 cm/s [226]. Colour Doppler does not have the disadvantage of washout of contrast by the vivid flow of contrast free blood from the inferior vena cava after the release of VM.

The strength of this study is the large number of contrast injections given during many different provocations. As contrast agent, we used an agitated gelatine solution instead of the commonly used agitated saline. Gelatine solutions cause a more intense contrast effect than saline and increases the sensitivity for PFO detection [227, 228]. The main limitations are the small number of the study group, which makes the statistical power limited and that the presence or absence of PFO not was tested with any invasive method.

Remarks on the clinical use of contrast TE

Although contrast-TE is a valuable tool for PFO diagnosis, differences in methodology will influence the results. The experience from the work with this thesis will here be summarised as a guide to clinical contrast-TE for PFO diagnosis.

The indication for PFO diagnosis is preferably evaluated before the exam. The patient is instructed and trained to perform the Valsalva maneuver for about 10 seconds. The physician or an assistant checks the continuity of the maneuver by holding his/her hand on the patient's stomach.

After probe insertion, imaging at 45-90 degrees is focused on the thin membrane-like septum primum, overlapping the thicker septum secundum. Colour Doppler imaging with low aliasing velocity of this overlap may be used to detect a PFO by the appearance of a small left-to-right shunt through the PFO channel. A first Valsalva maneuver (VM) is performed without contrast injection in order to further train the patient and adjust the image during and after the VM. In the absence of leftward bulging of the interatrial septum the procedure is repeated.

Contrast injection is made a few seconds after the start of a VM. Two ml of agitated gelatine solution is injected, preferably in an antecubital right arm vein. When the contrast fills the right atrium, the patient is told to release the VM. The aim is to fill the region of the right atrium, adjacent to the thin membrane, densely, at the very same moment as when the membrane bulges over towards the left atrium. The procedure is repeated until a positive injection is obtained or up to a total of five injections. The patient may move his right arm between injections, in order to empty remaining contrast fluid into the central circulation.

When one injection during VM has been positive an injection is also made during resting breathing. A PFO can be risk-stratified according to the following factors:

- *o* The existence of a resting shunt.
- *o* The total number of bubbles passing as < 20 or≥20 bubbles.
- *o* The maximum opening diameter as <4 or ≥4 mm.
- *o* The maximum bulging of the thin membrane from side to side, or into one of the atria as less than or more than 10-15 mm.
- *o* The existence of a prominent Eustachian valve.

Sources of false negative injections and alternative suggestions

When no leftward bulging of the septum is seen after VM, repeat the procedure and encourage the patient to increase and maintain strain during VM. If this also has fails, consider alternatives such as coughing or bed-tilt.

Discussion

An alternative during mechanical ventilation is provocation with end inspiratory positive occlusion pressure maintained for about 10 seconds. Another source of false negative injections is inflow of contrast-free blood from the inferior vena cava. The alternative is then to repeat injections and let the patient maintain the VM longer. Contrast should fill also the region of the right atrium adjacent to the entrance of the inferior vena cava, inferior to the Eustachian valve, before the strain is released. Another alternative is to use colour Doppler imaging, with aliasing velocities reduced to about 25cm/s. During and after release of the VM, a right-to-left flow reveals the presence of a PFO.

Sources of false positive injections and alternative suggestions

There are some sources of contrast-like phenomena in the left atrium that are not related to pathological right-to-left shunting. Contrast may be due to low flow velocities, commonly seen in atrial fibrillation and congestive heart failure. Thin echoes may also be due to the machine setting such as high gain and high dynamic range. Late appearing, thin and smoke-like echoes may be seen entering the left atrium from the pulmonary veins also in normal subjects. Imaging in secondary harmonic (octave) mode will make these echoes appear brighter and denser. Adjust the machine settings to fundamental mode and repeat the contrast injection.

6. Conclusions

- The availability for percutaneous closure of interatrial shunts were:

  - 58% during 1997-2000, when occluders with a diameter of up to 26 mm were available;
  - 88% during 2001-2003, when occluders with a diameter of up to 40 mm were available;
  - 89% of ASDs judged suitable for closure at TE review were available for closure, during 2001-2003, when occluders with a diameter of up to 40 mm were available;
  - 97% of all PFOs during 1997-2003 were available for percutaneous closure.

- The previously published formula was not reliable enough to be used to determine the appropriate occluder diameter during percutaneous closure.

- The pre-catheterisation, TE-measured ASD diameter can not to be used to determine the appropriate occluder diameter, as the differences between the two measurements were too large in individual patients.

  - The balloon-stretched diameter cannot be omitted and should always be obtained and used to determine the appropriate occluder diameter during percutaneous closure of ASDs.

- Nocturnal oxygen desaturations occurred more often in proportion to the frequency of respiratory disturbances in OSA subjects with a large PFO than in those without a large PFO.

- The oxygen desaturation index/apnea hypopnea index (ODI/AHI) ratio seemed to be a clinically useful screening tool for selection of OSA patients with a high likelihood of PFO.

- The sensitivity for detection of PFO during contrast TE increased when additional contrast injections were given.

- Arm injection during early Valsalva, with or without combination with bed tilt or nitroglycerin, seemed to be the most sensitive method for PFO detection.

- During TE, five contrast injections were needed to achieve 79% sensitivity for detection of all size PFO and 100% sensitivity for large PFO.

7. Acknowledgements

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