Secundum atrial septal defect in the adult. Clinical, haemodynamic and electrophysiological aspects.

Thilén, Ulf

2009

Link to publication

Citation for published version (APA):

Total number of authors:
1

General rights
Unless other specific re-use rights are stated the following general rights apply:
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.
• Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
• You may not further distribute the material or use it for any profit-making activity or commercial gain
• You may freely distribute the URL identifying the publication in the public portal

Take down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Read more about Creative commons licenses: https://creativecommons.org/licenses/
SECUNDUM ATRIAL SEPTAL DEFECT
IN THE ADULT

Clinical, haemodynamic and electrophysiological aspects

Ulf Thilén

LUND UNIVERSITY

Department of Cardiology
Clinical Sciences, Lund
Lund University
Sweden
2009
To Britt, Maria and Johan

Difficult things take a long time;
the impossible takes a little longer
CONTENTS

Abstract 5
List of papers 7
Abbreviations 7
Introduction 8

Embryology 8
Genetics 10
Anatomy of the atrial septum 10
Classifications of shunt lesions at the atrial level 11
Incidence of atrial septal defect 13
Haemodynamics 15
Quantification of shunts – methodological aspects 19
Natural history 24
Clinical presentation 25
Atrial septal defect and pulmonary hypertension 26
Atrial septal defect and atrial fibrillation 27
Treatment 30
When to close an atrial septal defect 34

Aims of the study 35
Material and methods 36
Main results 43
General discussion 49
General conclusions 53
Populärvetenskaplig sammanfattning (Summary in Swedish) 54
Acknowledgements 56
References 58
Appendix: Original papers I-V 68
ABSTRACT

Background: Atrial septal defect (ASD) is the most common congenital heart malformation diagnosed in adult life. Usually the defect gives no or subtle signs and symptoms during childhood and young adult life. With increasing age symptoms frequently develop, particularly atrial fibrillation. The aim of this thesis is to analyse important clinical, haemodynamic and electrophysiological aspects of ASD in the adult.

Objectives: To analyse; 1) the diagnostic accuracy of MR velocity mapping (MRvm) in calculating the pulmonary/systemic flow ratio (QP/QS). 2) atrial electrophysiological properties before and after ASD closure in adults. 3) the remodelling process and its time course after ASD closure in the adult. 4) the haemodynamic outcome in the intermediate term and the clinical outcome in the very long-term after ASD closure in the adult.

Methods: 1) QP/QS was assessed by MRvm and compared to radionuclide angiography in 24 patients with a congenital left-to-right shunt lesion, mainly at the atrial level. The controls, 12 adult healthy volunteers, were only examined with MRvm. In a phantom study using an artificial shunt, flow assessed by MRvm was compared with the flow rate measured by means of a beaker and timer.

2) In 35 adult ASD patients (μ=53 years) and in 35 age- and sex-matched controls P-wave duration and P-wave morphology were obtained from high-resolution orthogonal P-wave signal-averaged ECG (PSA-ECG) derived retrospectively from conventional 12-lead ECG. In patients PSA-ECG was also analysed 8±6 months after ASD closure. The results in patients, were related to echocardiographic atrial and ventricular sizes and dimensions as well the systolic pulmonary pressure.

3) In 39 adult ASD patients (μ=54 years) who had the defect closed by surgery or catheter atrial and ventricular areas and dimensions, indexed to body surface area, were obtained by echoDopplercardiography before and repeatedly 1 day/week, 1 month, 4 months and 1 year after closure. Functional assessment in terms of NYHA was determined before and 1 year after closure. The control group consisted of 32 adults without cardiac disease.

4) The study group consisted of 24 patients who had repeated heart catheterisations performed in a standard way with a 2-9 year interval in the late 1950ies and 1960ies and who were able to trace in 1997 for a clinical follow-up survey focused on mortality and cardiovascular morbidity. Half of the patients had surgical repair between the heart catheterisations while the other 12 were medically managed.

Results: 1) In the phantom study the mean error of QP/QS by MRvm vs. beaker and timer was -1±1% and the maximal error was ≤4% in the whole range of different QP/QS. Radionuclide angiography yielded a higher QP/QS than MRvm, the mean difference was 14±13% and proportional to shunt size. Repeatability showed a difference of -1±5%. Interobserver variability was four times higher for radionuclide angiography than MRvm, 16% vs. 4%.

2) P-wave duration was significantly longer in ASD patients than in controls (148±16 vs.128±15 ms, p<0.0001) and neither related to atrial sizes, isolated or combined, nor to the systolic pulmonary pressure. Overall, P-wave duration was not affected by ASD closure (pre/post 148±16 vs.144±16 ms, p=0.07) while in patients without a history of atrial fibrillation P-wave duration was reduced after ASD closure (pre/post 145±14 vs. 138±12, p<0.05). The changes in P-wave duration did not relate to any changes of left or right atrial size.
3) ASD closure significantly and markedly reduced right ventricular and atrial sizes as well as the pulmonary pressure levels. A normal-sized right ventricle and atrium was found in 82% and 72% respectively one year after ASD closure. Before closure the left ventricle was undersized but became normal after ASD closure, while left atrial size remained unchanged. The changes that occurred came early and the speed of changes declined with time. From 4 months after closure and on no important changes were observed. The NYHA class improved after ASD closure (p=0.01).

4) ASD closure was associated with a significant reduction of total heart volume (557 vs. 439 ml/m², p<0.001) and right ventricular systolic pressure (31 vs. 19 mm Hg, p<0.001) at the first postoperative evaluation while a further but non-significant progression of cardiac size occurred in the medically managed group. At late follow-up cardiovascular mortality (5 vs.2 patients), cerebrovascular incidents (5 vs.1) and atrial fibrillation (7 vs.5) were more frequent in the medically than in the surgically managed group, in spite of the fact that 2/3 of the patients in the medical group had had later surgical closure of the ASD on symptomatic grounds 1.4-19.6 years after the second catheterisation.

Conclusions: 1) MR velocity mapping is accurate and precise for measurements of shunt magnitude over the whole range of possible QP/QS values.
2) ASD in the adult is characterised by a prolonged P-wave duration which is not related to atrial enlargement but rather to conduction delay. In middle-aged patients ASD closure does not influence P-wave duration, suggesting irreversible electrophysiological abnormalities known to be associated with the development of atrial fibrillation. This would favour early intervention in order to prevent late atrial fibrillation in ASD.
3) Cardiac remodelling after ASD closure in the adult is a common and early event that seems by and large completed within the first half year after closure. In contrast to the other heart chambers and of unclear reasons the left atrial size does not change after ASD closure.
4) In the adult, timely closure of the ASD seems to reduce the risk of late mortality and morbidity. A “delayed surgical strategy”, intervening when clear symptoms appear, does not seem to match early closure of the defect.
LIST OF PAPERS

This thesis is based on the following papers, referred to in the text by their Roman numerals:


ABBREVIATIONS

AF Atrial fibrillation
ASD Atrial septal defect
AV-valves Atrio-ventricular valves
ECG Electrocardiogram
LA Left atrium
LV Left ventricle
MRI Magnetic resonance imaging
NYHA Functional classification according to the New York Heart Association
PAH Pulmonary arterial hypertension
PSA-ECG High-resolution orthogonal P-wave signal-averaged ECG
QP/QS Pulmonary – systemic flow ratio
QRS The QRS complex of the electrocardiogram
RA Right atrium
RV Right ventricle
INTRODUCTION

Atrial septal defect (ASD) as an isolated cardiac malformation is the most common congenital heart defect, besides bicuspid aortic valve, diagnosed in adult life. ASD is also a common feature in more complex malformations like Fallot’s anomaly, tricuspid atresia and Ebstein’s anomaly, however, that is out of the scope of this thesis.

ASD was first described by Rokitansky in 1875. However, already 1513 Leonardo da Vinci had demonstrated a patent foramen ovale, a “perforating channel” in the atrial septum. In 1916 Lutembacher described the combination of atrial septal defect and mitral stenosis. The first systematic report on the clinical features of ASD was made by Bedford in 1941.

When cardiac surgery and particularly extra-corporal circulation was introduced in the 1950ies a new era started making surgical relief of ASD possible. Since the first report of a successful case in the mid-1970ies, catheter-based techniques for ASD closure have rapidly developed and a major breakthrough was 1997-98 when the self-centering Amplatzer® Septal Occluder reached the market.

EMBRYOLOGY

When the embryo is around 23 days and 2.2 mm long a straight primitive heart tube has been formed. The next days the cardiac looping takes place and parallel to this the caudal inlet portion expands. The latter will form the primary common atrium and due to the looping it will have a posterior and superior position. At this stage there are two venous channels connected to the atrium, the right and left sinus horns. The former will develop to the right-sided caval veins while the left sinus horn will diminish in size and become the coronary sinus. Behind the heart a single pulmonary venous channel develops and joins the left part of the primary atrium which at the same time is expanding forming the right and left atrial appendages.

In the end of the 4th week atrial septation starts. From the roof of the atrium, between the systemic and pulmonary venous openings a muscular shelf - “septum primum” - grows towards and later fuses with the superior endocardial cushion at the atrioventricular level (Fig 1 b-e). The interatrial communication that exists before this fusion is called “ostium primum”. However, before closure of the ostium primum, the upper part of the primary septum is broken down creating a new interatrial communication – the “ostium secundum” (Fig 1 d-e). When the ostium primum is obliterated, expansion of a posterior structure, spina vestibuli, also plays an important role. It becomes muscularised, thus making the base of the primary septum stronger. The upper and thinner part of the fibromuscular primary septum will later serve as the flap valve of foramen ovale. At this point, the roof of the primary atrium, between the systemic and pulmonary venous entrances, starts to infold thereby creating the secondary septum -“septum secundum” - which will form the upper rims of the foramen ovale (Fig 1 f-h). However, the secondary septum is not a true septum but rather a sandwich-like infolding of the atrial wall filled with extracardiac adipose tissue. This interatrial groove is often referred to as Søndergaard’s or Waterston’s groove”. Atrial septal “lipoma” or “lipomateous hypertrophy” is not an uncommon echocardiographic finding and, the denomination suggests involvement of...
the septum while it actually is extracardiac fat. By the 12th week of development the right and left pulmonary venous returns have become separated and the atrial septation is completed.

Fig 1. Schematic illustration of the embryology of atrial septation from a right atrial and a frontal view.
GENETICS

Most cases of ASD secundum are isolated without a family history and their genetic background is still obscure. However, there are families with recurrent ASD secundum having a pattern suggesting autosomal dominant inheritance. In a report on two Swedish families with recurrent ASD secundum showing an autosomal dominant inheritance, a common ancestor could be tracked down to the 18th century⁹. The Holt-Oram syndrome is an autosomal dominant trait, described 1960, characterised by congenital heart disease, most often ASD secundum, combined with delayed electrical atrio-ventricular conduction and forelimb malformations, triphalangeal or hypoplastic thumbs being the most typical features. Modern genetics has shown that the syndrome is caused by a mutation in the TBX5 gene encoding a transcription factor that controls the α-myosin heavy chain¹⁰. ASD secundum has also been associated with mutations in other transcription factors like NKX2-5 and GATA4. Recently, another specific haplotype was identified in chromosome 15q13-q21, a mutation of the gene for encoding the α-cardiac actin (ACTC1)¹¹. Lack of the α-cardiac actin induces apoptosis and it is thought that this would lead to excessive absorption or apoptosis of the primary atrial septum thereby causing an atrial septal defect of the secundum type.

ANATOMY OF THE ATRIAL SEPTUM

The atrial septum is made up of different components, a central true septum including the fossa ovalis as well as folds of the atrial walls. When describing cardiac structures in terms of anterior, superior, inferior etc. some confusion may occur because it is not clear to what they refer¹². For the atrial septum this could be circumvented by instead relating the structures to cardiac landmarks as suggested by Cook¹³. When viewed from the right atrial aspect the atrial septum and the fossa ovalis can be divided into six different segments according to their relationship with other cardiac structures (Fig 2).

![Atrial septal anatomy related to cardiac landmarks as seen from a right atrial view.](image_url)
CLASSIFICATION OF SHUNT LESIONS AT THE ATRIAL LEVEL

There is a number of different cardiac malformations causing a shunt lesion at the atrial level. The three most common are:

- Atrial septal defect of the ostium secundum type (ASD secundum)
- Atrial septal defect of the ostium primum type (ASD primum)
- The superior vena cava form of the sinus venosus defect (sinus venosus ASD)

Uncommon types are:

- The inferior vena cava form of the sinus venosus defect
- Unroofed coronary sinus
- Single atrium – complete absence of the septum
- Isolated partial anomalous pulmonary venous drainage

---

**Fig 3. The location of different types of atrial septal defects.**

**ASD secundum** makes up more than 2/3 of all ASDs and is a centrally located defect involving the fossa ovalis. Extension outside the true limits of the fossa ovalis due to a deficiency of the infolding of the atrial wall is common. It is called secundum defect because of its presence at the site of the embryologic ostium secundum although it is by and large due to deficiencies in the primary atrial septum. The shape of the defect is often oval and sometimes very irregular. Secundum defects with multiple perforations of the membrane in the fossa ovalis may also occur.
**ASD primum** constitutes up to 20% of ASDs and it is a partial form of atrio-ventricular canal defect (endocardial cushion defect). In ASD primum, the atrial septum superior to the AV valves is deficient making the AV valves to insert at the same level, the normal “off-set” between the tricuspid and the mitral valve is lacking. Usually the defect is associated with a cleft in the anterior mitral leaflet causing mitral regurgitation. ASD primum is typically associated with a left-axis deviation on the ECG. This is due to the arrangement of the conduction tissue and not a damage of a fascicle.

Up to 10% of all ASDs are of the **superior sinus venosus type**. It is characterized by a defect in the most posterior and superior parts of the atrial septum at the junction of the superior vena cava and the right atrium. The superior vena cava overrides the defect and in a majority of cases there is anomalous right pulmonary vein connection. Embryologically, this is caused by a persisting interatrial channel in the groove between the right and left atria which also prevents a normal connection of the right pulmonary veins.

**Patent foramen ovale** is not a true atrial septal defect as there is no absence of tissue. The fibromuscular membrane covering the fossa ovalis serves as a flap valve permitting right-to-left atrial shunting which is essential during foetal life. After birth, due to the change of the interatrial pressure gradient, the foramen ovale becomes functionally closed and eventually anatomically fused. However, in around 25% of the population the anatomical fusion fails leaving a potential for right-to-left shunting when the pressure of the right atrium exceeds that of the left atrium. However, there are rare cases when there is a stretch of the atrial septum due to left heart disease with increased left atrial pressures, making a patent foramen ovale to become a true defect and thereby permitting left-to-right shunting. Considering the embryology of atrial septation it is not surprising that the patency of foramen ovale usually is located in the cranial part of the fossa ovalis.
INCIDENCE OF ATRIAL SEPTAL DEFECT

By definition, calculation of the incidence of congenital heart disease is often restricted to “a gross structural abnormality of the heart or intrathoracic great vessels with actual or potential functional significance” \(^\text{17}\). This usually excludes congenital arrhythmias and cardiomyopathies with genetic background, the latter because they are seldom detected at birth or in infancy. Bicuspid aortic valve, found in 2% of the population, is as a rule not included in series reporting the incidence of congenital heart disease. The reported incidence of congenital heart disease varies a lot, from 4 to 50/1000 live births and there are several reasons for this \(^\text{17}\). Most studies are restricted to infancy or childhood and will not count lesions detected later in life. This is of special relevance for ASD which often is diagnosed in adult life. Studies reporting the highest incidences are characterized by a frequent use of echocardiography in a neonatal setting or during infancy and, it is very obvious that the principal reason for the increase of the incidence of congenital heart disease depicted in recent years is the finding of mild forms, particularly small ventricular septal defects \(^\text{17}\). Small ASDs of the secundum type are also frequently found, however it seems that the spontaneous closure rate is higher than formerly thought. Besides diagnostic methodology and the age profile of the investigated population, referral patterns will play a role in retrospective studies based on a huge population.

In a retrospective study confined to children born 1941-1950 in Gothenburg, Sweden, the incidence of congenital heart disease was 6.4/1000 live births and the proportion of ASD of all forms was 8.8%, corresponding to an incidence of around 0.6/1000 live births\(^{18}\). The follow-up time was 7-16 years, thus no adults were included. In around 1/3 of cases the diagnosis was made at autopsy, in around 1/3 by invasive diagnostic measures and in 1/3 on clinical grounds (ECG, phonocardiogram and chest X-ray).

All children born 1980 in Bohemia participated in a prospective survey with repeated clinical examinations during the first four years of life\(^{19}\). All deceased children had an autopsy. The overall incidence of congenital cardiac malformations was 6.4/1000 live births, ASD constituting 11.4% (0.7/1000). In Malta the incidence of ASD during the period 1990-1994 was 2.7/1000 live births, a considerable increase compared to the preceding time periods\(^{20}\). However, only 15% (0.4/1000) required intervention and it was found that the incidence of ASDs in need of intervention had been stable for a long time. Thus, the observed sharp rise in incidence was solely caused by haemodynamically insignificant ASDs.

A recent retrospective study on all children born 1990-1999 in Iceland used the diagnosis in medical reports to calculate the overall incidence of congenital heart disease and it was found to be as high as 17/1000 live-born\(^{21}\). All cases were confirmed by echocardiography, cardiac catheterisation or autopsy. In this study also bicuspid aortic valve was included, however, even when excluding that diagnosis the incidence remained high, 16/1000 live births. Only 30 % of the malformations were classified as “major”. Small ASDs, less than 4 mm, were not included as they were considered irrelevant for the purpose of the study. The proportion of ASD, thus ≥ 4 mm, was 12.2%, corresponding to an incidence of 2/1000 live births. Besides an Australian study from the 1950ies, there are no published data on the prevalence of ASD in adults or in all age groups. In that report, the prevalence of ASD in people over 14 years of age was estimated to be 0.15/1000 by using a mass X–ray survey for tuberculosis to catch radiological signs of ASD\(^{22}\). Patients older than 14 years of age and already diagnosed with ASD were also included.
while deceased patients were not considered. It is reasonable to believe that such a low figure is a reflection of the diagnostic inferiority of chest X-ray compared to echocardiography, rather than something else.

With easy access to echocardiography the incidence of ASD in children reaches 2/1000 live births\textsuperscript{21}. However, spontaneous closure of ASD takes place. In a tertiary centre study on ASDs 4 mm or larger and diagnosed at a mean age of 5 months, 34\% closed spontaneously during a 3.8 years observation period\textsuperscript{23}. Assuming that modern diagnostics reveal all ASDs already in childhood and that ASD does not cause death during childhood, the prevalence of ASD in early adulthood, irrespective if intervention has been performed or not, would be around 1.3/1000. In the pre-echocardiographic era the diagnosis was suspected and established during childhood in 0.7/1000\textsuperscript{19}. Thus, in the adult population born before echocardiography was easy available, the prevalence of ASD not diagnosed during childhood would be 0.6/1000. In Sweden, with 8 million adults, that corresponds to nearly 5000 patients.

There is no evidence for differences in incidence of congenital heart disease in different countries and time periods\textsuperscript{17}.
HAEMODYNAMICS

Ventricular compliance determines the shunt magnitude

In the uncomplicated case an ASD is characterised by left-to-right shunting. When large, the defect does not restrict flow, there is no or nearly no pressure gradient between the atria and functionally the two atria can be regarded as a common chamber. The proportions of flow out of this common chamber will be determined by which ventricle is most easily filled, thus the ventricular diastolic properties are of paramount importance in this context. Early clinical and experimental studies have confirmed the relative compliance of the ventricles being the determinant of the degree of shunting as soon as the ASD is large enough not to restrict the flow through the defect. There is a number of studies supporting this concept as they demonstrate a poor correlation between the defect size and the magnitude of the left-to-right shunt in terms of pulmonary – systemic flow ratio (QP/QS).

The relative thin-walled right ventricle is more compliant than its left counterpart and thus there is a preference for left-to-right shunting. Initially, the increased volume load dilates the right ventricle making it thinner and even more compliant. In experiments in dogs, the acute creation of an ASD increased pulmonary blood flow as expected but, it also reduced aortic flow, indicating reduced filling of the left ventricle. Although not very emphasized, it has been known for a long time that a reduced left ventricular dimension, because of inadequate filling, is a typical feature of an ASD. At cardiac catheterisation it has been shown that closure of an ASD reverses the hypokinetic systemic circulation seen preoperatively by demonstrating a substantial increase in systemic cardiac output and a rise in venous oxygen saturation.

When accepting the concept of the relative compliance of the ventricles as the determinant of shunt magnitude, it is important to realise that this is a dynamic relation. In a newborn the right ventricular wall is as thick as that of the left ventricle and accordingly the degree of left-to-right shunting is low. After birth, parallel to the gradual reduction of pulmonary vascular resistance, the right ventricular wall becomes thinner and the left-to-right shunt augments. When ASD is associated with right ventricular hypertrophy secondary to right ventricular outflow obstruction or pulmonary vascular hypertensive disease the degree of left-to-right shunting becomes lower or even reversed. As many ASD patients are middle-aged or older, superimposed acquired left-sided cardio-vascular conditions such as systemic hypertension, coronary artery or aortic valve disease may have relevance. When left ventricular compliance becomes impaired the left-to-right shunt increases and the left ventricular stroke volume goes down. Experimentally this has been shown to take place in dogs with an ASD when the aorta was externally constricted. Clinically, there are just anecdotal reports on increased left-to-right shunting in patients with an ASD and acquired left heart disease like myocardial infarction. In a study on children and young adults with a small ASD, defined as QP/QS< 2:1, and followed for 5-21 years nearly 25% had a QP/QS ≥ 2:1 at follow-up suggesting that age-related cardiac functional alterations influence the degree of shunting.

Although not systematically studied, there seems to be a surprisingly high prevalence of systemic hypertension in ASD. In a study confined to ASD patients over the age of 60 years the prevalence of systemic hypertension was 38%, much higher than in an age-matched normal population. In another study comparing medical and surgical treatment of ASD 36% of the
patients, being in their mid-50’s, had a diagnosis of systemic hypertension. In the Euro Heart Survey on adult congenital heart disease, 17% of the ASD patients (mean age 39 years) had systemic hypertension. Besides a true association between ASD and systemic hypertension, one might speculate that hypertension causing left ventricular diastolic dysfunction and increased left-to-right shunting unmasks an ASD that otherwise would have gone undiagnosed.

If there is an inadequate systemic venous return the left-to-right shunting will increase in ASD thereby profoundly compromising left ventricular filling and systemic cardiac output. Administration of epinephrine will augment both pulmonary and aortic flow, however the latter to a greater extent indicating diminished left-to-right shunt. These observations demonstrate the potential of extrinsic stimuli to influence the degree of shunting. There are scarce data on what happens to the shunt during exercise in ASD patients and some inconsistencies exist between the studies. Both pulmonary and systemic output increase during exercise but it seems that the left-to-right shunt decreases, thereby promoting left ventricular output. That would fit to the observation that many ASD patients are asymptomatic and have a normal physical working capacity.

An ASD is restrictive by definition when there is a significant pressure gradient between the two atria. This is of course influenced by the size of the ASD but also by the flow volume that has to pass the defect. Therefore, restrictiveness of an ASD is not defined by a sharp cut-off point in ASD size, but rather in a range of sizes. Depending on body size and haemodynamics it seems that an ASD diameter less than 5-10 mm has a potential to be restrictive.

The pulmonary – systemic flow ratio, QP/QS, is a ratio and it is important to understand that it does not reflect the absolute volume load of the right heart. An increase of QP/QS could as well be attributed to the increase of pulmonary flow as the reduction of systemic flow. In most cases of ASD the obtained QP/QS seems to be a combination of the two.

**Flow direction as a determinant of shunting**

In patients with an ASD secundum or a patent foramen ovale and a very horizontally oriented atrial septum, the inferior vena cava flow may stream into the left atrium and cause hypoxemia in spite of a normal pressure gradient between the atria and a normal pulmonary pressure. This flow-directed shunt can be further promoted if there is a remaining prominent Eustachian valve. During foetal life the Eustachian valve directs the inferior vena cava flow towards the fossa ovalis. This arrangement has a survival value as the inferior vena cava blood to a large extent consists of highly saturated blood from the placenta which by the described mechanism will enter the left atrium and support the coronary and cerebral circulations. The above described phenomena of hypoxemia with normal pulmonary pressures in an interatrial communication is often termed the platypnoea-orthodeoxia syndrome as it is characterized by dyspnoea and hypoxemia in the upright position and relieved by recumbency.

In isolated secundum ASD the right pulmonary venous connection has a much closer relation to the defect than the left pulmonary venous return. When performing echo-Dopplercardiography in ASD secundum it is not uncommon to find the inflow of the upper right pulmonary vein going through the ASD and directly into the right atrium. One would be inclined to regard it as a functional, but not anatomical, anomalous pulmonary venous return. If so, the volume load of
the left atrium, which may affect left atrial size, may vary between ASD patients with the same degree of overall left-to-right shunting.

The abnormal volume load – influence on heart chamber size

When myocardial systolic function is intact, as it usually is in ASD, it seems reasonable to believe that the sizes of the heart chambers are related to the volume load. Concerning atrial size the ventricular diastolic properties and filling pressures must also be taken into account. As illustrated (Fig 4) assessment of the chamber sizes by echocardiography from an apical 4-chamber provides a very typical pattern in haemodynamically important shunts at the atrial level\textsuperscript{42,43}. The right ventricle and atrium are enlarged, the left atrium is also enlarged but, the left ventricle is smaller than normal. Due to the excessive flow, the pulmonary artery is wider than normal. In cases with isolated partial anomalous pulmonary venous return there is no extra volume load of the left atrium and hence, it does not become enlarged. There are cases with secundum ASD in whom the left atrial dilation is subtle and less pronounced than the right atrial enlargement. Whether the mechanism described above, that the right pulmonary venous return goes directly to the right atrium via the ASD, would be of relevance in this context is unknown. While right heart dilatation is stressed as a hallmark of ASD in textbooks of cardiology, the changes on the left side of the heart have been less emphasized, if at all\textsuperscript{1,44}.

![Fig 4. Schematic illustration of heart chamber areas in an echocardiographic 4-chamber view in normals and in ASD. When measured as largest – end-diastole for ventricles and end-systole for atria – the normal approximate area relations are: RV=RA=LA and LV=2RV.](image-url)
Paradoxical septal movement

When the right ventricle is volume overloaded the interventricular septum bulges towards the left ventricle in diastole and moves inversely towards the right ventricle in systole. However, this paradoxical septal movement is rather a quantitative than qualitative abnormality. Even normally in systole, the very upper basal part of the interventricular septum moves anteriorly (towards the right ventricle) while the rest of the septum moves posteriorly. This hinge point of anterior and posterior septal wall motion has been called the pivot point and in ASD it is displaced in an apical direction. Furthermore, the degree of displacement seems to correlate fairly well to the shunt magnitude, the larger shunt the more apical displacement. In a majority of patients the paradoxical septal movement disappears after ASD closure.
QUANTIFICATION OF SHUNTS – METHODOLOGICAL ASPECTS

The term left-to-right shunting refers to recirculated pulmonary flow, which means that a part of the pulmonary venous blood bypasses the systemic circulation. Right-to-left shunt is the recirculation of systemic flow, when systemic venous blood bypasses the lungs. Principally both left-to-right and right-to-left shunts can be calculated, however, in most cases of ASD there is left-to-right shunting which will be the main focus of the following presentation. Most methods will tell the direction of the shunt, some of them may also discriminate at what level the shunt occurs and they may quantify the shunt.

The magnitude of the shunt can be described in several ways;

- As the absolute value of the shunt flow
- The shunt flow as a percentage of pulmonary or systemic flow
- As a ratio between pulmonary and systemic flow (QP/QS)

The basis for shunt quantification by the oximetric and indicator-dilution techniques is either the conservation of blood volume or the conservation of indicator content, in the Fick method this indicator is oxygen$^1$. The amount of an indicator leaving the circulation must equal the amount entering the circulation plus any amount added during transit. In echoDopplercardiography and magnetic resonance imaging shunt quantification is derived from direct flow measurement in the systemic and pulmonary circulations.

The oximetric method - the Fick principle

In the Fick method the oxygen uptake by the lungs and the oxygen content of blood at different locations during cardiac catheterisation are measured. To calculate the QP/QS the following formula is used:

$$\frac{QP}{QS} = \frac{SAO_2 - MVO_2}{PVO_2 - PAO_2}$$

where $SAO_2$, $MVO_2$, $PVO_2$, and $PAO_2$ are the oxygen contents in systemic arterial, mixed systemic venous, pulmonary venous and pulmonary arterial blood. Note, when calculating the QP/QS there is no requirement to measure oxygen consumption and no information about flows in absolute terms is given. Usually the oxygen content is assessed in terms of oxygen saturation which reflects the haemoglobin-bound oxygen and disregards the dissolved oxygen. When breathing room air the amount of dissolved oxygen is very small and, from a practical and clinical point it can be ignored when quantifying the shunt. Furthermore, measuring the oxygen saturation, rather than the oxygen content, is often preferred because it is not influenced by the haemoglobin concentration$^{48}$.

The oxygen saturation of mixed systemic venous blood is an essential component in assessing QP/QS with the oximetric method. The right atrium receives venous blood from three sources, the inferior vena cava, the superior vena cava and the coronary sinus. As there are venous streams, samples from the right atrium are less reliable when determining mixed systemic venous oxygen content$^{48}$. When reaching the pulmonary artery these components of systemic venous return are mixed and in the normal case, without a shunt lesion, pulmonary artery
samples will provide an accurate basis for the estimate of mixed systemic venous oxygen content. However, when there is a left-to-right shunt the mixed systemic venous oxygen content must be based on samples obtained from a pre-shunt location. The vena cava inferior flow is larger than that of vena cava superior and at rest the oxygen saturation of the inferior caval blood is usually around 5%-units higher than that of the vena cava superior. In the coronary circulation oxygen extraction is high, hence the oxygen content of the coronary sinus blood is low. There is a number of formula suggestions how to weight the contribution of the inferior and superior caval blood in order to calculate mixed systemic venous oxygen content ($MVO_2$)\textsuperscript{49}. The oxygen content of the coronary sinus is not considered because it is not measured routinely. On empiric grounds the most frequently used formula, at rest, is:

$$MVO_2 = \frac{3 \times SVCO_2 + IVCO_2}{4}$$

where $SVCO_2$ and $IVCO_2$ are the oxygen contents or saturations from vena cava superior and inferior samples respectively\textsuperscript{50}. However, it has even been suggested that the oxygen saturation of the vena cava inferior can be completely ignored\textsuperscript{51}.

The drawback of the oximetric method is the low sensitivity to detect small shunts. The interobservational error has a mean variance of 2% saturation, changes in the physiologic state may affect oxygen saturation and venous streams may make measurements less representative\textsuperscript{48}. However, the level of systemic flow must also be taken into account\textsuperscript{48, 52}. In a low systemic output state the peripheral oxygen extraction is high and the oxygen content of returning venous blood is low making the nominator ($SAO_2 - MVO_2$) in the formula for calculating $QP/QS$ large. A considerable step-up of $PAO_2$ is then necessary for a reliable diagnosis of a left-to-right shunt. Vice versa, in systemic high output states, the nominator is small and even a small step-up of $PAO_2$ will result in a significant increase of the $QP/QS$. Usually there must be a minimal step-up of 5-7% saturation in the pulmonary artery compared to that of the mixed systemic venous return for the firm diagnosis of a left-to-right shunt at the atrial level and it is estimated that a minimal $QP/QS$ of 1.5-1.9 is required to reliably diagnose a shunt at the atrial level with the oximetric method\textsuperscript{48, 51}.

**Indicator-dilution methods and radionuclide angiography**

The basic principle of an *indicator-dilution* method is to inject an indicator substance at one point in the circulation and measure its concentration continuously at another point. This will yield a time-concentration curve of the indicator which demonstrates an exponential fall until the recirculation of the indicator appears (Fig 5). By manual or mathematical extrapolation of the downslope of the curve to zero an area ($A_1$) is obtained. This area corresponds to the first pass amount of the indicator which is proportional to pulmonary flow. In the case of a left-to-right shunt there will be early recirculation indicated by a secondary peak breaking the harmonic exponential downslope of the curve. When the obtained curve is subtracted by the estimated first pass curve ($A_1$) a new curve is generated and the area ($A_2$) of this curve corresponds to the shunt flow. Systemic flow will then be defined as $A_1 - A_2$ and hence; $QP/QS = A_1 / (A_1 - A_2)$.

A single-bolus of the indicator is used and the more central venous injection the better. One frequently employed dye indicator is indocyanine green. After a central venous injection continuous or multiple systemic arterial blood samples are withdrawn for spectrophotometric
analyses of dye concentration to make up a time-concentration curve. Cases with a right-to-left shunt are also discovered, provided the injection site is before the level of the shunt, as an extremely early peak will appear before that of the true first pass peak in the time-concentration curve.

**Fig 5. Indicator-dilution and radionuclide tests.**

Schematic illustration of the concentration/activity-time curve in a left-to-right shunt. The area \( A_1 \) represents pulmonary flow and \( A_2 \) the shunt flow, hence, \( A_1 - A_2 \) equals systemic flow.

The principles of the radionuclide technique are very similar to those of an indicator dye. However, it is less invasive as a peripheral vein can be used for injection. A radioisotope bound to the circulation and not filtered by the pulmonary circulation, usually \(^{99m}\)Tc pertechnetate, is injected and a time-activity curve of the lung is constructed. In cases with a left-to-right shunt an early recirculation peak will appear. In the same manner as described above, the QP/QS is obtained from the curve areas representing the pulmonary and the shunt flow (\( A_1 \) and \( A_2 \)). Although theoretically possible, it is problematic to detect right-to-left shunts with the radionuclide technique when the indicator passes the pulmonary circulation. In such cases a radioisotope that does not pass the pulmonary circulation, like that used in the diagnosis of pulmonary embolism, would be superior.

The curve fitting methods have several limitations and they do not provide information about the site of the shunt\(^ {49, 53} \). Low output states, right ventricular dysfunction, tricuspid and pulmonary regurgitation will all prolong the pulmonary transit time which makes the time-concentration/activity curve more flat. When the peaks are less distinguished, analysis becomes more difficult and the result less precise. The same phenomena occurs if the bolus injection is fragmented. Although detected by the method, large shunts (QP/QS > 3) can not be precisely quantified because the inability to fit an accurate downslope of the first pass peak. Quantification of the shunt is restricted to patients with exclusive left-to-right shunts, as they are invalid when shunting is bidirectional.

Although the curve fitting methods require experience and are operator dependent they are more sensitive than oximetry to reliably pick up small left-to-right shunts, the level of discrimination is approximately QP/QS exceeding 1.2:1. In healthy subjects, without a shunt, curves obtained by the radionuclide method, often generates a QP/QS between 1-1.2:1, at least partly this has been attributed to arterial bronchial and chest wall blood flow. When compared to oximetry in

21
assessing QP/QS in adults and children with shunt lesions including ASD, the radionuclide method has shown a good agreement\textsuperscript{54, 55}. However, in studies restricted solely to ASD patients the agreement was found to be not so good (\textit{r}=0.40-0.64) and, it was suggested that the outcome was a result rather of problems with the oximetric method than inferiority of the radionuclide method\textsuperscript{53, 56}. Having in mind the potential influence on the shunt by a change in the physiologic state, there is a methodological problem in the quoted studies as the methods compared are not made simultaneously, in the best performing 81% had the two investigations in the same day.

\textit{EchoDopplercardiography}

Echocardiography and colour flow Doppler have a high sensitivity to detect shunts at the atrial level by direct assessment of morphology and flow. The introduction of transesophageal echocardiography has circumvented the shortcoming of poor image quality sometimes encountered in transthoracic echocardiography. A right-to-left shunt is easily demonstrated by echocardiography when combined with a venous injection of echo-contrast that does not pass the lungs, e.g., agitated saline. The appearance of “bubbles” in the left heart within 3 cardiac cycles after the contrast has reached the heart proves that there is an intracardiac right-to-left shunt. Although regarded as a very sensitive method, sensitivity is influenced by the number of injections, the site of injection and the physiologic state, for instance if the Valsalva manoeuvre is done\textsuperscript{57}.

Shunt quantification by echoDopplercardiography is based upon the calculation of the systemic and pulmonary flow volumes. The flow velocity integral of the right and left ventricular outflow or the very proximal part of the pulmonary artery and the aorta are obtained by pulsed Doppler, and when multiplied with the cross-sectional area of the sample site the stroke volume of the right and left heart is obtained. However, flow velocity is not measured at every point of the cross-sectional area but just centrally and the assumption that the velocity is uniform is not completely true. The calculation of the cross-sectional area uses the diameter of the sample site assuming that is round and that it does not change in size during systole. Again, this simplification is not always true as the pulmonary artery may have an oval form. Delineation of the anterior or lateral aspect of the pulmonary orifice is often problematic in transthoracic echocardiography, making the measurement of the diameter less reliable. The use of transesophageal echocardiography would get round this but, surprisingly, there are no published reports using transesophageal echocardiography to measure the outflow diameters combined with transthoracic echocardiography for the flow measurements to assess QP/QS in ASD patients. Furthermore, even with good image quality echocardiographic dimensional measurements has a certain interobservational variation and, besides, when calculating the cross-sectional area any error will be squared. It is also very obvious that aortic and pulmonary regurgitation of importance will seriously disturb a correct quantification of the shunt.

Using high quality transthoracic echoDopplercardiography to calculate QP/QS in adult patients with ASD, a reasonable agreement (\textit{r}=0.82) when compared to oximetry has been demonstrated\textsuperscript{58}. An echoDopplercardiographic QP/QS exceeding 1.2:1, separated correctly all patients from controls. With increasing shunt size the random error between the two methods tended to increase and the intraobserver variability was reported to be around 4\% for the time-velocity integrals and nearly 5\% for the assessment of the outflow orifices. In a study on ASD patients using oximetry, radionuclide and echoDopplercardiography to quantify QP/QS, the
disparity between all the methods, including echoDopplercardiography, was high. Simplifying the method, by using only the flow velocity integrals of the right and left heart, thus disregarding the cross-sectional area, to estimate QP/QS, makes the correlation to oximetry poorer.

Magnetic resonance imaging (MRI)

MRI can accurately calculate the pulmonary and systemic flows either by volumetric assessment of ventricular stroke volumes or by velocity mapping of the pulmonary trunk and the proximal aorta. The former is not frequently used to calculate QP/QS and focus will therefore be on velocity mapping. In velocity mapping the flow velocity integral and the cross-sectional area of the flow are determined to generate QP/QS. When it is compared and matched to established investigations like oximetry and indicator dilution there is good agreement and, in contrast to other methods, MR velocity mapping seems precise over the whole range of possible QP/QS values. However, the robustness of QP/QS calculations of MR velocity mapping in terms of interobserver variability has not been very well validated. Besides shunt evaluation MRI also provides excellent and clinically important anatomic information. Due to the acquisition time at present, reliable QP/QS quantification by MR velocity mapping is restricted to patients with a reasonable regular heart rhythm, although not necessarily sinus rhythm.

Other and indirect methods of assessment of shunt magnitude

Besides what has already been described, some other methods of assessing shunt magnitude in ASD have been investigated and suggested. However, none of them seems to have reached clinical recognition as they do not match the established methods.

Echocardiographic right ventricular size expressed as a dimension was not significantly different in ASD patients with a QP/QS less than 2:1 compared to those with a QP/QS greater than 2:1. In another application of echocardiography, the ratio of the end-diastolic diameter of the right and left ventricle obtained from a 4-chamber view just below the AV-valves, was used to predict oximetric QP/QS. In spite of a fair correlation (r=0.83) there was a substantial and clinically important overlap, a certain ratio of the right and left ventricular dimensions could correspond to a QP/QS ranging from 1.25 - 2:1.

The poor correlation between oximetric QP/QS and the size of the ASD (r=0.43-0.76) is not surprising considering that shunt magnitude is dependent on ventricular compliances. With colour flow Doppler the area of the jet crossing the atrial septum can be measured and conceptually it seems reasonable to believe that it in some way is related to volume. However, the correlation between maximal jet area and oximetric QP/QS was found to be poor (r=0.65) in a series of adult patients with ASD. Furthermore, due to a substantial overlap, clinically less important lesions could not be accurately sorted out.

By using systolic time intervals and the ratios of the pre-ejection period/ventricular ejection time of the right and left ventricle respectively a haemodynamic ratio can be constructed. It correlates fairly well (r=0.80) with oximetric QP/QS.
NATURAL HISTORY

It is problematic to describe the natural history of ASD in the 21\textsuperscript{st} century as a large number of patients has had or will have their defect closed. As a surrogate, studies from a pre-interventional era have been used and are often referred to\textsuperscript{66, 67}. According to them, the prognosis of ASD is very poor, more than half of the patients will die before the age of 40 years and 90\% are expected to pass away before the age of 60 years. It has also been stated that symptoms develop progressively whereby nearly no ASD patient aged 60-70 years is free of symptoms\textsuperscript{1}. However, considering the diagnostic tools of that time, it is very plausible that these studies consisted of patients with obvious symptoms or signs indicating advanced disease which logically, would be associated with a high risk of a fatal outcome. Today, the ASD patient that goes undiagnosed until adult life, belongs to a subset of the ASD population characterised by less symptoms and probably a much better prognosis than was depicted in the studies from the 1960ies. There are anecdotal reports about ASD patients who have reached 87 and 94 years of age\textsuperscript{3}. In a cohort of medically treated adult ASD patients followed for 25 years, cardiovascular mortality was 3\%\textsuperscript{68}. More than half of the patients were asymptomatic (=NYHA I) and 44\% were free from atrial fibrillation at a mean age of 63 years. In another study on ASD patients with a mean age of around 56 years at presentation only 6\% were free of symptoms, however, the symptoms were mild as ¾ of the patients were in functional class I or II\textsuperscript{37}. So, there are reasons to believe that the prognosis of ASD in the 21\textsuperscript{st} century is less pessimistic than formerly thought.

Spontaneous closure

According to retrospective studies containing 100-200 subjects having a secundum ASD diagnosed during early childhood or infancy, around ¼ of the ASDs will close spontaneously within 4-5 years\textsuperscript{23, 69, 70}. In all these studies ASDs < 3 mm in diameter had been excluded. The main predictor of spontaneous closure was the initial ASD size, in ASDs 3-4 mm in diameter the reported closure rate was 65-82\% and in ASDs 5-8 mm around 40\%. When the initial ASD diameter exceeded 8 mm spontaneous closure was rare, less than 10 \%. In a series where the ASD was diagnosed at a mean age of 4.5 years, spontaneous closure was rare, 4\%, illustrating the importance of age\textsuperscript{71}. Besides complete closure ASDs may also decrease in size and lose haemodynamic significance, however, ASD size could also increase and, it seems the larger ASD, the higher risk for further enlargement\textsuperscript{70}. The considerable rate of spontaneous closure during the first five years of life suggests that elective closure of the ASD in an asymptomatic child should not be performed before the age of five or six years. The spontaneous closure rate in adults is unknown, however, when it comes to haemodynamically significant defects the clinical experience is that they will remain haemodynamically important.
CLINICAL PRESENTATION

Symptoms

An ASD seldom causes symptoms during childhood, however, it has been associated with frequent respiratory infections and failure to thrive manifested as underweight\(^6^9\). Overt heart failure is rare and when it occurs it is by and large restricted to infancy\(^6^9\). In the adult symptoms are rare before the age of 40 years but from then, symptoms increase with advancing age, exertional dyspnoea and palpitations due atrial arrhythmias being the most common\(^1\). As described below a majority of the patients have experienced atrial fibrillation when reaching their 60’s. Angina-like chest pain of unknown cause but disappearing after ASD closure has been described\(^7^2\). In the orthodeoxia – platypnea syndrome (see page 16) cyanosis may develop in spite of normal pulmonary pressures. In long-standing right ventricular volume overload or when hypertensive pulmonary vascular disease complicates the ASD right ventricular failure may cause peripheral oedema, pleural effusion and ascites. In the presence of an ASD there is a potential for paradoxical embolism, however, considering that a majority of ASD patients are females, many undergoing the thrombogenic state of pregnancy, reports on paradoxical embolism are astonishingly rare.

Physical signs

In ASD the shunt flow per se does not cause any cardiac murmur because the pressure gradient between the atria is very low. The murmurs associated with ASD are due to the increased volume flow passing the tricuspid and pulmonary orifices. Hence, the relative tricuspid stenosis causes a diastolic filling murmur and the relative pulmonary stenosis a systolic murmur. In around 2/3 there is a fixed splitting of the second heart sound as a consequence of the right ventricular volume load\(^7^3\).

ECG

Although a rSR’ pattern in the QRS of lead V1 is found in nearly all patients with ASD, it is not very specific as it also is found in normals\(^7^3, 7^4\). The rSR’ pattern is not caused by bundle branch block but rather right ventricular dilation, hypertrophy and stretching. In ASD of the primum type, in contrast to other forms of ASD, there is characteristically a marked left-axis deviation of the QRS.

Chest X-ray

Before the echocardiographic era, chest X-ray was an essential part of the diagnostic workup in ASD\(^1^8, 7^5\). Typical findings are heart enlargement, particularly right atrial enlargement and prominent central pulmonary vasculature as a sign of increased pulmonary blood flow. On fluoroscopy “hilar dance” – increased pulsation of the main pulmonary artery branches – can be seen. In former times chest x-ray was widely used in mass surveys for tuberculosis and it was also routinely performed in a number of clinical settings. At that time the accidental finding of abnormalities was an important way to catch the asymptomatic ASD patient\(^1^8, 2^2\). Still, sometimes the diagnosis of ASD starts with a chest X-ray performed on another indication.
ATRIAL SEPTAL DEFECT AND PULMONARY HYPERTENSION

Pulmonary arterial hypertension (PAH) is defined as mean pulmonary pressure > 25 mm Hg at rest or > 30 mm Hg at exercise. Principally, PAH can be caused by either increased flow or, increased vascular resistance. In order to cause forward flow pulmonary pressure must exceed the filling pressure on the left side of the heart and left heart disease may therefore also contribute to PAH. In his Croonian lecture Paul Wood introduced the expression “Eisenmenger syndrome” to describe a shunt lesion, irrespective of level, complicated by hypertensive pulmonary vascular disease with reversed or bidirectional shunt. In this late stage of the pulmonary vascular disorder it is considered to be irreversible.

When defined as a systolic pulmonary pressure > 50 mm Hg or a mean pulmonary pressure > 30 mm Hg, PAH has been found in 9-17% of patients with ASD secundum. When defined as systolic pulmonary pressure ≥ 40 mm Hg, the prevalence of PAH is nearly 30% in ASD. The PAH is often regarded as caused by increased pulmonary flow due to the left-to-right shunt and substantially increased pulmonary vascular resistance (≈ 4 Wood units or more) is less frequent, found in 5-10% of ASD patients. An Eisenmenger reaction is even less common, although it has been reported in as much as 6-9% of patients. Although the high pulmonary flow in uncomplicated ASD is thought to promote the development of PAH there must also be other factors of importance as not all ASD patients develop PAH. Most studies on ASD do not differ between ASD secundum and ASD of the sinus venosus type, however, when done, the sinus venous type seems more prone to develop increased pulmonary vascular resistance and PAH.

Some features of the Eisenmenger syndrome are strikingly different when associated with ASD as compared to other underlying shunt lesions. It has even been suggested that it is not a “true” Eisenmenger syndrome but, rather a coincidental finding of an ASD in a patient with idiopathic PAH. The proportion of females in ASD-associated Eisenmenger syndrome is higher than expected and resembles that found in idiopathic PAH, 80%. Compared to other shunt lesions, symptoms develops later when the Eisenmenger syndrome is linked to an ASD and it is assumed that there is a transient period during childhood with a fairly normal pulmonary pressure in ASD, not found when the shunt has a post-tricuspid location. Genetically, a mutation in the bone morphogenetic protein receptor II (BMPR2) is linked to familial PAH and it is also common in idiopathic PAH. However, when tested for in patients with ASD and the Eisenmenger syndrome that mutation was not detected in a single case. However, other genetic mutations can not be ruled out.

When the pulmonary vascular resistance exceeds 12-15 Wood units/m² body surface area (in a normal adult that would be around 6-8 Wood units) surgical closure of the ASD is associated with high mortality and morbidity. In idiopathic and scleroderma associated PAH, selective pulmonary vasodilators like endothelin antagonists and sildenafil have shown symptomatic and prognostic benefits. When applied to patients with the Eisenmenger syndrome, there was a fear of worsening cyanosis due to increased right-to-left shunting as these vasodilators are not completely selective. They would induce systemic vasodilatation while the pulmonary vascular resistance was presumed to be fixed. However, when tested this did not occur, pulmonary vascular resistance was reduced and cardiac output increased. Although intended as a safety study, symptomatic improvement was also demonstrated.
ATRIAL SEPTAL DEFECT AND ATRIAL FIBRILLATION

In the initiation of atrial fibrillation (AF) an atrial ectopy serves as a trigger factor. It usually starts in the right atrium or around the pulmonary veins. When spread it comes across refractory tissue from the proceeding beat and becomes fractionated. AF sustains when these multiple fractionated waves circulate around constantly changing areas of conduction block, thereby restarting themselves or others. Increased electric heterogenicity of the atria, shortening of the atrial refractory period and impaired intratrial conduction will therefore play an important role in the development of AF. Atrial enlargement is associated with atrial fibrillation and has been suggested as a pathophysiologic prerequisite. However, in lone atrial fibrillation there are no macroscopic structural cardiac abnormalities but, infrastructural abnormalities assumed to alter atrial electrophysiology have been found.

In the general population the prevalence of AF increases exponentially with age and, in all age groups AF is more common in men than in women. Before the age of 55 years the prevalence of AF is 0.1% for women and 0.2% for men, when reaching the 70’s around 5% of the population has experienced AF (Table 1a). With AF follows a substantial risk of thromboembolism often necessitating anticoagulant therapy. AF is extremely common in adults with unrepaired ASD. Being very rare during childhood, AF starts to develop at the age of 30-40 years (Table 1b). From then and on the prevalence of AF shows an exponential increase by age, being 25 – 150 times higher than that of the general population. One should also consider that females, less prone than men to develop AF in the general population, constitutes 2/3 or more of the patients in most ASD series.

<table>
<thead>
<tr>
<th>Author</th>
<th>Age group, years</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>Go92</td>
<td>&lt;55</td>
<td>0.1</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td>55-59</td>
<td>0.4</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td>60-64</td>
<td>1.0</td>
<td>1.7</td>
</tr>
<tr>
<td></td>
<td>65-69</td>
<td>1.7</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td>70-74</td>
<td>3.4</td>
<td>5.0</td>
</tr>
<tr>
<td></td>
<td>75-79</td>
<td>5.0</td>
<td>7.3</td>
</tr>
<tr>
<td></td>
<td>80-85</td>
<td>7.2</td>
<td>10.3</td>
</tr>
<tr>
<td></td>
<td>&gt;85</td>
<td>9.1</td>
<td>11.1</td>
</tr>
</tbody>
</table>

Table 1a. Prevalence of atrial fibrillation (%) related to age and gender in the normal population.
<table>
<thead>
<tr>
<th>Author</th>
<th>N of pat</th>
<th>Age of study population, years</th>
<th>Prevalence, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Murphy</td>
<td>62</td>
<td>&lt; 24</td>
<td>0</td>
</tr>
<tr>
<td>Roos-Hesselink</td>
<td>135</td>
<td>&lt; 15 (mean 7.5)</td>
<td>0</td>
</tr>
<tr>
<td>Popelova</td>
<td>21</td>
<td>&lt; 40 (mean 29)</td>
<td>0</td>
</tr>
<tr>
<td>Vogel</td>
<td>101</td>
<td>18-40</td>
<td>1</td>
</tr>
<tr>
<td>Murphy</td>
<td>32</td>
<td>25-41</td>
<td>6</td>
</tr>
<tr>
<td>Mantovan</td>
<td>136</td>
<td>mean 37</td>
<td>8</td>
</tr>
<tr>
<td>Shah</td>
<td>82</td>
<td>25-54 (mean 37)</td>
<td>23</td>
</tr>
<tr>
<td>Oliver</td>
<td>94</td>
<td>mean 47</td>
<td>14</td>
</tr>
<tr>
<td>Gatzoulius</td>
<td>213</td>
<td>16-80 (mean 47)</td>
<td>19</td>
</tr>
<tr>
<td>Popelova</td>
<td>19</td>
<td>&gt; 40 (mean 51)</td>
<td>10</td>
</tr>
<tr>
<td>Vogel</td>
<td>79</td>
<td>40-60</td>
<td>30</td>
</tr>
<tr>
<td>Konstantinides</td>
<td>179</td>
<td>41-79 (mean 56)</td>
<td>22</td>
</tr>
<tr>
<td>Shibata</td>
<td>49</td>
<td>&gt;50 (mean 57)</td>
<td>49</td>
</tr>
<tr>
<td>Cowen</td>
<td>31</td>
<td>&gt;50 (mean 57)</td>
<td>53</td>
</tr>
<tr>
<td>Fiore</td>
<td>51</td>
<td>&gt;50 (mean 60)</td>
<td>42</td>
</tr>
<tr>
<td>St John Sutton</td>
<td>66</td>
<td>&gt;60 (mean 65)</td>
<td>54</td>
</tr>
<tr>
<td>Murphy</td>
<td>29</td>
<td>&gt;41</td>
<td>59</td>
</tr>
<tr>
<td>Vogel</td>
<td>25</td>
<td>&gt;60</td>
<td>80</td>
</tr>
<tr>
<td>Shah</td>
<td>34</td>
<td>46-83 (mean 63)</td>
<td>56</td>
</tr>
</tbody>
</table>

**Table 1b.** Prevalence of atrial fibrillation and flutter related to age in different series of unrepaired ASD.
Reports on the AF prevalence in ASD seldom analyse atrial fibrillation and atrial flutter separately. However, when done, atrial fibrillation is the dominating type, making up ¾ or more \[36, 96, 98, 102\]. As most data are derived from studies on surgical outcome there might be some bias in selection when reporting the AF prevalence. Often all kinds of ASD are included in these studies, however ASD secundum is by far the most frequent type. The diagnosis of arrhythmia is usually a clinically relevant event and based on clinical findings and ECG.

Like AF in other cardiac disease, the arrhythmia often starts in a paroxysmal form and later becomes persistent and chronic. Besides age, atrial sizes and AV-valve incompetence are the only independent factors that have been associated with AF in ASD \[97, 103\]. Defect size, QP/QS, pulmonary artery pressure, right ventricular dimension and left ventricular systolic function seems not to relate to AF in ASD \[97\].

Nowadays AF is often treated with pulmonary vein isolation by means of catheter ablation. This has relevance in this context as ASD closure counteracts the otherwise easy access to the left atrium by the catheters. It is therefore wise to consider the treatment sequence when ASD is complicated by AF.

Does ASD closure influence the prevalence of AF? To some extent this is still a controversial issue. It is well known that preoperative AF is a strong risk factor for postoperative persistent or recurrent AF and, although individual exceptions exist the arrhythmia course does not seem to change after ASD closure \[96, 102\]. Furthermore, in the long run after closure there is also a considerable number of new-onset atrial fibrillation or flutter \[37, 96, 98, 103, 104\]. In 62 patients aged 12-24 years at repair and without any preoperative history of AF, 17% experienced atrial fibrillation or flutter during a 27-32 year follow-up \[93\]. In a study comparing surgical and medical management of ASD presenting after the age of 25 years the prevalence of AF at start (25 vs. 20%, mean age 37 years) and 25 years later (53 vs. 56%, mean age 62 years) did not differ between the two groups \[68\]. It should be noted, that our knowledge is by and large based on surgical series and that the long-term impact on arrhythmia by catheter closure is unknown. Besides AF, a low incidence, far below 10%, of postoperative atypical atrial flutter is often reported \[94, 98, 102\]. The substrate of this macro-reentrant tachycardia, which is amenable to electrophysiologic ablation techniques, is thought to be the right atrial scar introduced by ASD surgery. This mechanism of arrhythmia would be avoided by catheter closure of the ASD.

There are many studies suggesting that timely closure of an ASD would reduce or prevent the occurrence of AF. However, when stating that age at ASD repair predicts the prevalence of late AF, the study design in most of them does not consider the close relationship between age at surgery and age at follow-up \[93, 94, 98\]. When this dependence has been accounted for, it has been shown that the age > 25 years, but not > 40 years, at surgery was the only predictor for late AF independent of the age at follow-up \[97\]. In a very long-term follow-up study on 135 patients that had the ASD closed during childhood 3% had experienced atrial flutter at a mean age of 34 years \[94\]. This prevalence of atrial arrhythmia is probably 100-fold that to be found in aged-matched controls but, it is reassuring that there were no cases of AF.

Occasionally pacemakers are implanted after ASD surgery because of complete heart block or important sinus node dysfunction \[94, 97, 99, 94\]. The risk of sudden death seems very low in ASD \[94, 105\].
TREATMENT

Surgical closure

Modern surgical closure of ASD secundum is performed during cardiopulmonary bypass through a right atriotomy. Thoracic access is usually through a median sternotomy or through a right antero-lateral thoracotomy. In order to minimize the cosmetic disturbance sometimes a submammary approach has been used. The defect may either be closed by direct suture or by patch. Different kinds of patch material have been used; patient’s own pericardium, Dacron and Gorex. Residual shunting warranting reoperation is rare while, mild or trivial residual shunts are encountered in 2 - 5%.

Most studies on surgical outcome of ASD repair comprise ASD secundum as well as ASD of the sinus venosus type. The proportion of ASD secundum in these reports varies from 83 to 93%. In some studies also a small number of ASD primum patients are included. In a number of reports of surgical ASD closure, in children and adults, the reported perioperative mortality is zero. However, there are studies with in-hospital mortality ranging from 1.2 to 6%, the highest rates found in reports including the surgical activity of the 1950 and 1960ies. Old age in combination with concomitant surgical procedures at the time of ASD repair and, the presence of advanced pulmonary hypertensive vascular disease seem to have had a major impact in these fatalities. Surgical ASD repair also carries early morbidity; bleeding necessitating reoperation, infection, pleural and pericardial effusion, thromboembolism, brady- or tachyarrhythmia. Due to definition the frequency of early complications varies between 3 to 47%. The highest rates are found in series on old patients with a high prevalence of postoperative atrial arrhythmias. ASD closure in children has been associated with a 3% complication rate and without perioperative arrhythmias.

When surgical ASD repair is performed during childhood, long-term follow-up (11-33 years) shows excellent survival, equivalent to that of the general population and much better than that of historic controls.

In adults, however, the survival benefit of ASD closure is not that clear-cut. In a non-randomised study with 179 patients comparing surgical treatment to medical management in adults older than 40 years the 10-year survival was superior in the surgical group. In 34 ASD patients with a preoperative systolic pulmonary pressure below 40 mm Hg and operated after the age of 24 years, survival matched that of the general population when followed for 27-32 years. In a study on 66 patients 60 years or older, postoperative survival rates at 5 and 10 years were not significantly different from those of an age-matched normal population and superior to that of historic controls. In the only randomised trial performed, comparing surgical and medical management in 473 ASD patients over the age 40 years, no clear survival benefit was demonstrated, although, surgery was superior to medical therapy for a composite clinical end point.

As symptoms develop late in ASD, the demonstration of symptomatic relief of ASD closure is more or less restricted to adults. Postoperative improvement of the functional capacity in terms of NYHA is a constant finding. A personal experience is, that even when in NYHA
I preoperatively, many patients report improved working capacity after the ASD closure. In a study testing physical performance, adult ASD patients preoperatively showed a low peak oxygen uptake which normalised within 10 years after the surgical repair\(^\text{112}\). In patients having the ASD closed during childhood, exercise capacity seems comparable with the normal population when tested 15 and 26 years after surgery\(^\text{94}\). In another study, on children some years after surgical closure of the ASD, this was confirmed, however, compared to controls, the ASD group had a greater stroke volume and a lower heart rate at a given exercise level\(^\text{113}\).

As closure of the ASD eliminates the volume load of the right heart and improves left ventricular filling, a resolution of the preoperative heart chamber abnormalities would be anticipated. Using 2D-echocardiography in 94 patients operated during childhood around 20\% of the patients showed right atrial and right ventricular enlargement and 6\% left atrial dilatation when examined 22 years after closure\(^\text{94}\). To some extent this might be a matter of methodology as, in a study using MRI after ASD closure during childhood, right and left ventricular volumes were normal in all patients\(^\text{107}\). Using 2D-echocardiography in children the right ventricular area from an apical 4-chamber view, representing the inflow and trabecular part of the right ventricle, normalised after surgical ASD closure but, the right ventricular outflow dimension did not\(^\text{114}\). Also in adults, ASD closure is associated with a substantial regression of right atrial and ventricular size as well as increased left ventricular size\(^\text{42, 115}\). However, the potential to normalise seems less when the defect is operated in adults compared to children. In a retrospective echocardiographic study on patients with ASD repair at a mean age of 35 years, enlargement of the right atrium, left atrium and right ventricle was found in 64\%, 44\% and 29\%, respectively, at follow-up 11 years later\(^\text{42}\). Age at follow-up, atrial fibrillation, degree of tricuspid regurgitation and pulmonary hypertension were identified as predictors for persistent heart chamber dilation.

In the short-term, and in contrast to what is found after catheter closure, surgical closure of the ASD impairs right ventricular systolic function as assessed by echocardiographic tricuspid annular plane motion and volumetric measurements\(^\text{115-117}\). However, in the long-term, right ventricular systolic function becomes normal in all or nearly all patients, irrespective of age at surgery\(^\text{42, 94}\).

**Percutaneous catheter closure**

The principle of percutaneous catheter closure of an ASD is to push a closing device inside a catheter to the site of the defect and, when deployed it remains in position covering the defect. During the two decades following its introduction in 1976, the “patch” concept reigned, that is umbrella-like devices with textile discs mounted on a metal frame and joined by a thin waist. In spite of different modifications they were not user-friendly and the complication rates and results did not match surgery. In 1997, the self-centering Amplatzer® Septal Occluder, representing a “patch and stent” concept, reached the market and it has become the dominating type in ASD catheter closure. The “patch and stent” concept means that the device besides covering the defect fills it up, stents it. It should be noticed that in catheter closure of a patent foramen ovale (PFO), often a narrow channel, the umbrella-type of device continues to play an important role.
The Amplatzer® Septal Occluder (AGA, Medical Corp., Golden Valley, MN, USA) is a self-expanding Nitinol wire mesh which forms two discs and a waist. The waist diameter should correspond to the size of the ASD. Depending on the diameter of the waist the diameters of the left and right atrial discs exceed that of the waist by 12-16 and 8-10 mm respectively. Inside the mesh there are three Dacron polyester patches. Nitinol, an alloy of nickel and titanium, is superelastic and has shape memory. Within three months after implantation the device is covered by endothelium. Until then there is some nickel release into the bloodstream. In most cases, including those with nickel hypersensitivity, it does not seem to cause any major harm. The device is connected to a wire and is unscrewed when released.

Vascular access is obtained by the femoral vein in most cases. The procedure is guided by fluoroscopy and echocardiography, transesophageal or intracardiac. General anaesthesia is used in children or when the transesophageal echo-probe is not tolerated. Before implantation, the ASD is balloon-sized to obtain the stretched diameter of the defect. A device, with a waist the same size or 2 mm larger, is then chosen. Before release the stability is checked by pushing and pulling. As an antithrombotic regimen aspirin is given 6 months after the procedure.

Percutaneous catheter closure of the ASD carries several obvious advantages when compared to surgery, it cause less patient pain and discomfort and it eliminates the cosmetic disturbance of a scar. Catheter-based closure is now considered as first-line treatment strategy for ASD secundum and, it is estimated that more than ¾ of all ASD secundum would be suitable for this technique. Catheter closure is said to be cost saving by the elimination of post-operative intensive care and shorter hospital stay. However, the cost of the device itself may alter the balance in different health care systems.

When considering catheter closure, a thorough anatomic preinterventional assessment is mandatory in order to delineate the morphology of the ASD and to reassure that the defect is sufficiently remote from the AV-valves, pulmonary and systemic veins. The defect must have a sufficient atrial septal rim (5-7 mm), although the retroaortic rim is of lesser importance and can be absent.
**Results and complications of catheter ASD closure**

Embolişation of the device is a serious complication occurring in around 1% \cite{106, 120, 121}. Cardiac perforation and tamponade are extremely infrequent (<0.1%) and often occur within 24-48 hours \cite{13}. However, erosions have been reported as late as three years after implantation. Usually they have occurred near the aortic root in patients with deficient anterior or superior rims and, the devices used have often been oversized. Other complications encountered are atrial arrhythmia, transient ST-elevation (inferior leads), transient cerebral ischemic attack, haemoptysis, pericardial effusion and bleeding complications related to the catheter insertion. When investigating late thrombus formation on different devices used for ASD closure, it was found in 1.2% of the patients, however no case was associated with the Amplatzer® device \cite{122}.

Fatal complications are extremely rare and the overall complication rate is around 6%, a majority of them being minor \cite{120, 121}.

Catheter-based closure of ASD carries a high success rate with complete closure in 93-100% after one year or later \cite{123-125}. During the first 24 hours trivial residual shunting is common but, it gradually disappears with time. For obvious reasons there are no very long-term results after ASD catheter closure. In two studies with a high number of patients, there were no deaths or complications of importance during a median follow-up time of 2.3 and 6.5 years, respectively \cite{124, 126}. Besides symptomatic relief in terms of NYHA, increased exercise capacity is found after closure by catheter \cite{127}.

There is a marked resolution of right heart dilation after catheter closure, similar to what is found after surgical closure \cite{46, 128, 129}. In a mainly paediatric series using echocardiography the right ventricular volume but not the right atrial size returned to normal over 24 months following catheter closure \cite{129}. In a retrospective study on adults mainly using the CardoSeal® device (umbrella-type) a considerable reduction of right ventricular and atrial size took place within one year \cite{47}. However, 29% showed persistent right ventricular enlargement which might be explained by the fact that residual shunting occurred in more than 50% of the patients. Regarding the speed of these changes, conclusions are hampered by a large loss of patients during follow-up, a high prevalence of residual shunting or infrequent exams \cite{46, 47, 129, 130}. However, it seems that the right heart remodelling is an early event which diminishes in rate and is more or less finished after 6 months \cite{131}. In contrast to the regression of right heart enlargement and increased left ventricular volume, left atrial size does not seem to react on ASD catheter closure and children do not differ from adults in this aspect \cite{130, 131}. It is a flaw that these studies did not contain controls but, the left atrial size seemed, from given values, to be rather normal before intervention, thus leaving a small potential for change.

As mentioned above, surgical closure of the ASD is associated with an early transient dysfunction of the right ventricle. This seems not to be the case with catheter closure \cite{116, 117}.
WHEN TO CLOSE AN ATRIAL SEPTAL DEFECT?

There are two main motives for ASD closure; to relieve symptoms or to improve prognosis. It would seem logical that prognostic expectations become weaker with increasing age. The indication for closure has varied during the years but the American Heart Association recommendations of 2008 are:\(^{132}\):

**CLASS I (Benefit >>> Risk)**

Closure of an ASD either percutaneously or surgically is indicated for right atrial and right ventricular enlargement with or without symptoms (Evidence level B=limited number of trials involving a comparatively small number of patients or well designed data analyses from non randomised or observational studies).

**CLASS IIA (Benefit >> Risk)**

Closure of an ASD either percutaneously or surgically is reasonable in the presence of: Paradoxical embolism (Evidence level C = consensus) or documented orthodeoxia-platypnoea.

**CLASS IIB (Benefit ≥ Risk)**

Closure of an ASD either percutaneously or surgically may be considered in the presence of net left-to-right shunting, pulmonary pressures < 2/3 systemic levels, pulmonary vascular resistance < 2/3 systemic vascular resistance or when responsive to either pulmonary vasodilator therapy or test occlusion of the defect (Evidence level C).

**CLASS III (Risk ≥ Benefit)**

Patients with severe irreversible pulmonary arterial hypertension and no evidence of a left-to-right shunt should not undergo ASD closure (Evidence level B).
AIMS OF THE STUDY

Since more than two decades I have had a deep and thorough interest in different clinical and scientific aspects of ASD in the adult. Recognising the importance of haemodynamic assessment in clinical judgement as well as the flaws of the existing methods there was a wish to explore what new technologies could provide. Traditionally, an ASD is regarded as a right heart disease. As atrial flutter rather than atrial fibrillation is associated with right atrial disease, the high prevalence of atrial fibrillation in ASD was intellectually disturbing. Consequently, exploring the underlying mechanisms of AF in ASD would be an intriguing and important field of research. It would be tempting to assume that long-standing haemodynamic abnormalities induces irreversible structural cardiac changes hampering remodelling after closure. From the point of science as well as the daily management, it would therefore be important to analyse the potential of ASD closure to normalise cardiac abnormalities in the adult as well as to describe the clinical outcome in the very long run.

The aims of these papers are:

- To evaluate the accuracy of MRI in calculating left-to-right shunts, including ASD.
- To describe the atrial electrophysiological abnormalities in adults with an ASD in order to better understand the association to atrial fibrillation.
- To analyse how ASD closure in the adult influences atrial electrophysiology.
- To analyse the haemodynamic consequences in terms of the remodelling process and its time course after ASD closure in the adult.
- To analyse the very long-term outcome and benefits of ASD closure in the adult.
MATERIAL AND METHODS

The studies enrolled patients at the Department of Cardiology at the Lund University Hospital (I-IV). Paper I also included patients from the service of paediatric cardiology at Lund University Hospital, as well as adult healthy volunteers. Paper V is confined to patients diagnosed with an atrial shunt at the Department of Medicine I, Sahlgrenska hospital, Gothenburg during the period 1958-1968.

The study protocols complied with the Declaration of Helsinki and were approved by the local Ethics Committee. The investigations in paper IV were all part of the routine clinical management and an application to the Ethics Committee was not considered necessary.

Patient characteristics

Paper I:

The control group consisted of 12 adult volunteers; six women and six men aged 20-53 years. They had no history of cardiovascular disease and had no direct or indirect signs of a shunt lesion when examined by echoDopplercardiography. The patient group consisted of 24 subjects with a congenital left-to-right shunt lesion determined on clinical grounds and by echoDopplercardiography. Eight of them were children (age range 2-17 years) and 16 were adults (age range 20-68 years). In a majority of the patients, 19, the shunt was at the atrial level. Only subjects with sinus rhythm were included.

Paper II-IV:

The patients in paper II-IV were all derived from the same pool, 47 adult patients with an isolated ASD secundum who were scheduled for and, later had the defect closed by surgery or catheter during the period 1996-2003. Twenty-seven of these were included in all three studies. In the studies on PSA-ECG (paper II-III) another 8 patients were included, making a total of 35 patients. The two main reasons for these not to be a part of the study on remodelling (paper IV) were the later start of that study or an inability to adjust to the follow-up protocol. Of the 39 patients in the study on remodelling 12 of them were not a part of the PSA-ECG studies mainly because of persistent atrial fibrillation, an exclusion criteria, or low quality of the ECG recordings making interpretation impossible.

In paper III clinical follow-up, focused on the appearance of atrial fibrillation, lasted 3.8±2.8 years after ASD closure. In the remodelling study (paper IV) 23% of the patients had a history of systemic hypertension and 38% had a history of paroxysmal or persistent atrial fibrillation.

In paper II-III the control group contained 35 age- and sex-matched healthy individuals without any history of cardiovascular disease.

The control group in paper IV consisted of 32 individuals who had been referred for echocardiography because of chest pain or suspected cardiac embolic source and, who were found to have no signs of cardiac disease or a shunt lesion. Characteristics of patients and controls are given in table 2.
<table>
<thead>
<tr>
<th></th>
<th><strong>PSA-ECG studies</strong></th>
<th></th>
<th><strong>ASD remodelling study</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>(paper II-III)</strong></td>
<td></td>
<td><strong>(paper IV)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>ASD group</strong></td>
<td>35</td>
<td>35</td>
<td>39</td>
</tr>
<tr>
<td><strong>Controls</strong></td>
<td>35</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gender (female/male)</strong></td>
<td>27/8</td>
<td>27/8</td>
<td>30/9</td>
</tr>
<tr>
<td><strong>Age, years (μ±SD, range)</strong></td>
<td>53±15 (20-75)</td>
<td>54±15 (20-74)</td>
<td>54±15 (19-73)</td>
</tr>
<tr>
<td><strong>Mode of closure, surg./cath.</strong></td>
<td>14/21</td>
<td></td>
<td>10/29</td>
</tr>
<tr>
<td><strong>QP/QS</strong></td>
<td></td>
<td></td>
<td>2.7</td>
</tr>
<tr>
<td><strong>ASD diameter, mm (μ±SD)</strong></td>
<td>17±5</td>
<td></td>
<td>17±5</td>
</tr>
</tbody>
</table>

**Table 2. Characteristics of patients and controls in paper II-IV.**

**Paper V:**

During 1958-1968, 75 adult patients were diagnosed with ASD and/or partial anomalous pulmonary venous return. Of these, 26 underwent repeated heart catheterisation, 2-9 years after the initial one. Two patients could not be traced in the follow-up part of the study. Of the remaining 24 patients 12 had successful surgical repair of the defect between the two catheterisations while 12 patients were medically managed. At diagnosis, all patients were in sinus rhythm and symptoms were absent or mild (NYHA I or II). In 1997 a follow-up survey was performed to create a non-randomized clinical observational study. The mean follow-up time from the 1st catheterisation was 30.3 years and if restricted to those alive at follow-up it was 36.3 years. In the medically managed group 8 patients had the ASD closed after the 2nd catheterisation, representing a delayed surgical strategy. Patient characteristics are given in table 3.
Table 3. Characteristics of patients in paper V.

<table>
<thead>
<tr>
<th></th>
<th>Surgical group (N=12)</th>
<th>Medical group (N=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (female/male)</td>
<td>11/1</td>
<td>9/3</td>
</tr>
<tr>
<td>Age at 1st catheterisation, years (µ±SD, range)</td>
<td>38±9 (18-48)</td>
<td>40±12 (21-58)</td>
</tr>
<tr>
<td>Interval 1st - 2nd catheterisation, years (µ)</td>
<td>5.9</td>
<td>5.6</td>
</tr>
<tr>
<td>Age at surgical repair, years (µ ±SD, range)</td>
<td>39±9 (18-50)</td>
<td>-</td>
</tr>
<tr>
<td>Age at follow-up or death, years (µ ±SD, range)</td>
<td>71±8 (60-83)</td>
<td>67±12 (43-83)</td>
</tr>
</tbody>
</table>

Methods

Paper I:

MR velocity mapping

A 1.5-T magnetic resonance imaging system (Magnetom, Siemens, Erlangen, Germany) with a 25-mT/m gradient strength and a 600µs gradient ramp time was used. Gradient-echo velocity mapping sequences provided by the manufacturer were used to determine blood flow. A standard head coil was used in the phantom study and a phased-array body coil in the subjects.

In the phantom study an artificial shunt system with connecting 10 mm tubes was constructed. The system was filled with MnCl2-doped water to approximate the relaxation time of blood. The relation between the flow in one tube and the total flow was investigated by MR velocity mapping and compared with the flow rate measured by means of a beaker and timer. The whole range of different “QP/QS” ratios from 1 to 5 was investigated.

In subjects the ascending aorta and the pulmonary trunk were localised by MR imaging technique. By means of velocity mapping, through-plane flow was measured perpendicular to flow in the ascending aorta at the level of the pulmonary trunk and in the pulmonary trunk just
above the pulmonary valves. By means of prospective ECG-triggering but no respiratory gating, information covering the whole cardiac cycle, based on 512 heart beats, was obtained. The measurements started, randomly assigned, either in the aorta or the pulmonary trunk and when completed in both, a third measurement was made in the first vessel. This was done to avoid effects of physiologic shifts in cardiac output and to serve as a basis for calculation of repeatability. When calculating the QP/QS the average of the two measurements of the first vessel was used.

Radionuclide angiography

In patients, but not in the control group, first-pass radionuclide angiography was performed by means of a gamma camera system (GCA 901A/ECT, Toshiba, Tokyo, Japan) with a manufacturer-supplied evaluation system. $^{99m}$Tc pertechnetate was injected in the vena cava superior or in an arm vein during the early reactive hyperaemic phase induced by inflating a blood-pressure cuff for three minutes. QP/QS was calculated by a gamma-variate technique and a highest value of 3 was given, as QP/QS exceeding that can not be precisely assessed with the radionuclide method. In all patients the MR velocity mapping and the radionuclide angiography were performed on the same day.

Paper II-IV:

High-resolution orthogonal P-wave signal-averaged ECG (PSA-ECG)

Orthogonal P-waves were derived from signal-averaged P-wave triggered 12-lead ECG using an inverse Dower transformation. This methodology has earlier been described and analysed by our group. In short, following high-pass (0.5 Hz) and bandstop (50 Hz) filtering, QRS complexes were automatically identified and grouped according to similarity (a cross-correlation coefficient, $p > 0.9$). P waves were extracted using 250 ms wide signal windows preceding each QRS complex. The signal windows were then shifted in time to estimate the maximal correlation in each lead. Signal windows with a cross-correlation coefficient of $p > 0.9$ (analyzed separately in all leads) were grouped together and averaged. The actual P waves were defined by manual setting of the onset and end. From the obtained PSA-ECG, the total P-wave duration, the timing and the amplitude of the deflections in the orthogonal leads X,Y and Z were determined (Fig 7). The P-wave onset and end was manually defined as the earliest and the latest activation in any of the three orthogonal leads.

PSA-ECG was performed on recordings before and 8±6 months after ASD closure. The recordings were made at the same day as echocardiography in 29 of the 35 patients before closure and in 32 at the post-closure exam.
P wave morphology, based on the pattern in the three spatial planes was categorised into one of four different types:

*Type 1:* Positive deflection in leads X and Y and a completely negative deflection in lead Z.

*Type 2:* Positive deflection in leads X and Y, and a biphasic lead Z, starting with a negative and ending with a positive deflection.

*Type 3:* Positive lead X, biphasic (positive-negative) lead Y and biphasic (negative-positive) lead Z.

*Type 4, atypical:* Those who did not fit into Types 1-3.

*Figure 7.* Schematic illustration of a high resolution signal-averaged orthogonal P wave depicting the timing and amplitudes of maximal and minimal deflection and baseline crossover.

- A = $X_{\text{max}}$ position
- B = $X_{\text{max}}$ amplitude
- C = $Y_{\text{max}}$ position
- D = $Y_{\text{max}}$ amplitude
- E = $Z_{\text{min}}$ position
- F = $Z_{\text{min}}$ amplitude
- G = $Z_{\text{zero}}$ position
- H = $Z_{\text{max}}$ position
- I = $Z_{\text{max}}$ amplitude

The given example corresponds to “Type 2” morphology.
Before ASD closure all patients had had a full transthoracic and transesophageal echoDoppler cardiographic workout. Associated or valvular lesions of importance were ruled out. The diameter of the ASD was determined and, if oval the given diameter was the average of the long- and short-axis. After ASD closure only transthoracic echoDoppler cardiography was performed. In paper IV echoDoppler cardiography after ASD closure was done at four occasions; the 1st day after closure if closed by catheter and around 1 week after surgical closure, 1 month, 4 months and 1 year after closure. In the PSA-ECG study (paper III) there was just one echoDoppler cardiographic exam post-closure.

From a 2D-transthoracic 4-chamber view the areas of the four heart chambers were measured when the heart chamber was at its largest, that is pre-emptying for the atria and end-diastole for the ventricles. From a parasternal view, using a M-mode setting, left atrial, left and right ventricular end-diastolic dimensions were obtained. As no patient had pulmonary stenosis, the systolic right ventricular/right atrial Doppler pressure gradient derived from the tricuspid regurgitation served as an indicator of the pressure levels in the pulmonary circulation.

In paper IV, the obtained areas and dimensions were indexed to body surface area to allow comparison with controls. In the studies on PSA-ECG this was not done because, the absolute size of the atria was assumed to be more relevant in this context and, the patients served as their own controls regarding the exam after closure of the ASD. Body surface area (BSA in m²) was derived from weight (W in kg) and height (H in cm) by the formula:

$$BSA = \frac{(H+W-60)}{100}.$$

In paper IV the mean value of the chamber areas of the controls ± 2 standard deviations was defined as “normal”. EchoDoppler cardiography was made once in the controls of paper IV and not at all in the controls of papers II-III.

Other

In paper IV all patients but one had the QP/QS measured, either by oximetry or radionuclide angiography. Functional assessment was described in terms of the NYHA functional classification before and, one year after ASD closure.

Paper V:

Right heart catheterisations were performed in a standard fashion. The degree of left-to-right shunting was approximated by oximetry. As no patient had pulmonary stenosis only systolic right ventricular pressure was systematically measured at the 2nd catheterisation.

Heart volume, indexed for body surface area, was obtained by chest X-ray.

In the follow-up study clinical events were obtained from hospital reports and from the patients themselves by telephone and/or a questionnaire. In deceased patients the time and the cause of death were obtained from official death certificates.
**Statistical methods**

If not otherwise stated mean (μ) values ± SD are given.

In comparisons, paired and unpaired t-tests were used for continuous variables and a $\chi^2$ test for categorical variables. In the MR velocity mapping study (paper I) a paired t-test of differences between logarithmic measurements was used because the scatter of the differences between the two methods increased as QP/QS increased. In the MR velocity study (paper I) the agreement between the two methods, repeatability and interobserver variability were analyzed according to the method of Bland and Altman\textsuperscript{135}. In the analysis of agreement the mean value of the two methods was considered to be the “true” value. Repeatability was calculated as 100(1\textsuperscript{st} measurement – 2\textsuperscript{nd} measurement)/mean of the 1\textsuperscript{st} and 2\textsuperscript{nd} measurements. The proportional difference in QP/QS was calculated as 100(radionuclide QP/QS – MR velocity mapping QP/QS)/the mean QP/QS of the two methods. Error was calculated as 100(measured QP/QS - “true” QP/QS)/”true” QP/QS. Accuracy and precision were defined as 100% -error and 100% - SD respectively.

A $p$-value less than 0.05 was considered statistically significant.
MAIN RESULTS

Paper I:

In the phantom study the mean error of QP/QS by MR velocity mapping was -1±1% versus QP/QS determined by the beaker and timer and the maximal error was ≤ 4%. In this setting MR velocity mapping was precise in the whole clinically relevant range of different QP/QS.

MR velocity mapping QP/QS in control subjects was 1.03±0.03 (range 0.98-1.07) and in patients QP/QS ranged from 1.18-3.19. Repeatability, in controls and patients, showed a difference of -1±5%.

In most patients radionuclide angiography yielded higher QP/QS than MR velocity mapping, the mean difference between the methods was 14±13% and it was proportional to shunt size. Interobserver variability was four times higher for radionuclide angiography than MR velocity mapping, 0±16% vs. 0±4%.

Paper II and III:

Baseline

P-wave duration was significantly longer in the ASD patients than in the sex- and aged-matched controls (148±16 vs. 128±15 ms, p<0.0001). P-wave duration was not related to age or sex. In the ASD group, P-wave duration was neither related to right and left atrial sizes, isolated or combined, nor to the systolic pressure in the pulmonary circulation. A weak positive correlation between P-wave duration and ASD diameter was found (r=0.37, p=0.03). There were no consistent differences in the location and amplitude of the maxima and minima of the orthogonal leads when ASD patients were compared to controls. The distribution of P-wave morphology, in terms of type 1-4, did not differ between the two groups.

The influence of ASD closure

Overall, P-wave duration was not affected by ASD closure (pre;148±16 vs. post;144±16 ms, p=0.07). Although postclosure P-wave duration weakly correlated to postclosure left atrial area (r=0.39, p=0.02) the change in P-wave duration was not related to the change of left or right atrial size. Closure of the ASD reduced the maximal amplitude in X and Y leads but, did not affect their location. Pre- and postclosure amplitudes showed no consistent pattern when related to the matching right and left atrial areas. The mode of closure, surgery or catheter, did not influence changes in P-wave duration.

Paroxysmal atrial fibrillation

Before ASD closure 6 patients had a history of paroxysmal atrial fibrillation. During a follow-up of 3.8±2.8 years after closure another 4 patients experienced this arrhythmia. These 10 patients formed an “AF-group” and the remaining 25 patients without a history of atrial fibrillation formed the “Non-AF group”. As shown in table 4 the former group was significantly older and demonstrated no change in P-wave duration at all after ASD closure. In contrast, the P-wave...
duration in the “Non-AF group” was significantly reduced (145±14 vs. 138±12 ms, p<0.05) although not “normalised”. Furthermore, after ASD closure left atrial size and systolic pulmonary pressure were significantly lower in the “Non-AF group”, which was not the case before closure.

<table>
<thead>
<tr>
<th></th>
<th>AF group</th>
<th>Non – AF group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td>65±7</td>
<td>49±15</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>P-wave duration, ms</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>preclosure</td>
<td>158±18</td>
<td>145±14</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>postclosure</td>
<td>157±18</td>
<td>138±12</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Right atrial area, cm²</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>preclosure</td>
<td>29±5</td>
<td>25±4</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>postclosure</td>
<td>21±4</td>
<td>17±4</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>Left atrial area, cm²</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>preclosure</td>
<td>22±3</td>
<td>20±5</td>
<td>0.36</td>
</tr>
<tr>
<td>postclosure</td>
<td>24±3</td>
<td>18±4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Left atrial dimension, mm</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>preclosure</td>
<td>42±4</td>
<td>39±6</td>
<td>0.09</td>
</tr>
<tr>
<td>postclosure</td>
<td>43±4</td>
<td>38±5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>RV/RA pressure gradient, mm Hg</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>preclosure</td>
<td>38±12</td>
<td>33±9</td>
<td>0.18</td>
</tr>
<tr>
<td>postclosure</td>
<td>26±4</td>
<td>21±4</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Table 4. PSA-ECG and echocardiographic data in patients who had (AF-group) or had not (Non-AF group) experienced paroxysmal atrial fibrillation either before or during follow-up after ASD closure. Mean values ± SD. P-value refers to unpaired t-test between the two groups.

Paper IV:

Baseline

The mean ASD diameter was 17±5 mm and the mean QP/QS was 2.7:1 in patients. When compared to controls, irrespective if measured as an area or dimension, the ASD group was characterised by markedly and significantly larger right heart chambers and left atrium (Table 5). The left ventricle was significantly smaller and the systolic pulmonary pressure significantly higher in the ASD patients. A history among patients of atrial fibrillation (n=15), when compared to those free from arrhythmia (n=24), did not influence atrial or ventricular sizes.
### Table 5. Echocardiographic data in controls and patients before and one year after closure of the ASD.

<table>
<thead>
<tr>
<th></th>
<th>ASD Preclosure</th>
<th>Controls</th>
<th>ASD 1-year postclosure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=39</td>
<td>N=32</td>
<td>N=39</td>
</tr>
<tr>
<td>RV area, cm²/m², µ ± SD</td>
<td>14.3 ± 3.2***</td>
<td>7.8 ± 1.7</td>
<td>9.3 ± 2.2**</td>
</tr>
<tr>
<td>RVIDD, mm/m², µ ± SD</td>
<td>21 ± 5***</td>
<td>11 ± 2</td>
<td>16 ± 4***</td>
</tr>
<tr>
<td>RA area, cm²/m², µ ± SD</td>
<td>15.4 ± 3.6***</td>
<td>8.6 ± 1.9</td>
<td>11.4 ± 3.6**</td>
</tr>
<tr>
<td>LV area, cm²/m², µ ± SD</td>
<td>12.8 ± 2.4***</td>
<td>15.9 ± 2.6</td>
<td>15.4 ± 2.6NS</td>
</tr>
<tr>
<td>LVIDD, mm/m², µ ± SD</td>
<td>24 ± 3**</td>
<td>27 ± 3</td>
<td>27 ± 3NS</td>
</tr>
<tr>
<td>LA area, cm²/m², µ ± SD</td>
<td>11.8 ± 2.2***</td>
<td>8.5 ± 1.8</td>
<td>11.7 ± 3.4***</td>
</tr>
<tr>
<td>Tricuspid regurgitation</td>
<td>None-trivial/Mild/Moderate</td>
<td>8/28/3</td>
<td>30/2/0</td>
</tr>
<tr>
<td>Pulmonary regurgitation</td>
<td>None-trivial/Mild</td>
<td>33/6</td>
<td>32/0</td>
</tr>
<tr>
<td>RV-RA pressure gradient</td>
<td>mm Hg, µ ± SD †</td>
<td>33 ± 9***</td>
<td>21 ± 4</td>
</tr>
</tbody>
</table>

† = not obtainable in all subjects. Significance levels refer to comparison between controls and ASD-patients pre- and postclosure. NS = no statistical significant difference. ***p<0.001 and **p<0.01.

**Follow-up 1-year after ASD closure**

The “1-year” exam actually took place at a mean time of 16 months after closure. The functional capacity was significantly improved 1 year after ASD closure (p=0.01). At that time 32 of the 39 patients were in NYHA I and another 2 patients had improved from NYHA III to NYHA II. It should be noted that 16 patients were in NYHA I before ASD closure, making improvement in NYHA class impossible.
As seen in table 5, depicting the results at the final exam, closure of the ASD was associated with dramatic reductions of right ventricular and atrial sizes. Although right ventricular and atrial areas as well as right ventricular end-diastolic dimension were on the average still significantly larger than those of the controls, the right ventricle and the right atrium were normal-sized in 82% and 72% of the patients respectively.

The right ventricular/right atrial pressure gradient, indicating the pulmonary pressure level, was markedly reduced after ASD closure and not significantly different from controls at the final exam.

The left ventricular size increased after ASD closure and did not differ from controls one year after closure. However, left atrial size was not affected by ASD closure and remained enlarged in 44% of the patients. The potential to normalise right or left atrial size differed substantially between patients with a history of atrial fibrillation and those without arrhythmia (Table 6). Only around 1/3 of the patients with arrhythmia, compared to 80-90% in those without this, had normal left or right atrial size one year after ASD closure. Patients with arrhythmia were significantly older.

<table>
<thead>
<tr>
<th></th>
<th>AF</th>
<th>Sinus</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PRE-CLOSURE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial septal defect size, mm</td>
<td>17 ± 6</td>
<td>17 ± 4</td>
<td>NS</td>
</tr>
<tr>
<td>Age, years</td>
<td>65 ± 8</td>
<td>48 ± 15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left atrial dimension, mm/m² BSA</td>
<td>24 ± 4</td>
<td>22 ± 3</td>
<td>NS</td>
</tr>
<tr>
<td>Left atrial area, cm/m² BSA</td>
<td>12.4 ± 2.5</td>
<td>11.5 ± 2.1</td>
<td>NS</td>
</tr>
<tr>
<td>Right atrial area, cm/m² BSA</td>
<td>16.6 ± 4.5</td>
<td>14.6 ± 2.7</td>
<td>NS</td>
</tr>
<tr>
<td><strong>POST-CLOSURE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left atrial dimension, mm/m² BSA</td>
<td>24 ± 4</td>
<td>21 ± 3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Normal left atrial dimension, % of pat.</td>
<td>33</td>
<td>79</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Left atrial area, cm/m² BSA</td>
<td>14.0 ± 3.9</td>
<td>10.3 ± 2.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Normal left atrial area, % of pat.</td>
<td>20</td>
<td>79</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Right atrial area, cm/m² BSA</td>
<td>13.9 ± 4.2</td>
<td>9.8 ± 2.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Normal right atrial area, % of pat.</td>
<td>40</td>
<td>92</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 6. Atrial sizes before and one year after atrial septal defect closure related to the occurrence of atrial fibrillation. AF = patients who had a history of chronic or paroxysmal atrial fibrillation. Sinus = patients without a history of arrhythmia. Mean values ± SD. P-values refer to unpaired t-test between the groups.
The temporal profile of remodelling after ASD closure

As demonstrated below (Fig 8-10) it is obvious that when changes occurred they came early and that the rate of the changes was declining with time. Compared to the preclosure findings, right ventricular, right atrial and left ventricular sizes as well as the right ventricular/right atrial pressure gradient showed highly statistically changes already at the first test after closure (1st day/1st week). From 4 months after ASD closure and on, the measured variables showed only minor or no changes.

**Fig 8-10.** Heart chamber areas and dimensions indexed to body surface area (BSA) and the right ventricular – right atrial pressure gradient in patients before and after closure of the atrial septal defect and in controls. From left to right: Pre-closure, 1st day/1st week post-closure, one month post-closure, four months post-closure, one year post-closure and controls. Box-plots indicate 10th, 25th, 50th, 75th and 90th percentiles. *** = p<0.001, **= p<0.01, *= p<0.05 when compared to the test occasion just before (paired t-test), for controls the comparison refers to the final test of the patients, one year post-closure (unpaired t-test).
Paper V:

Early follow-up (the 2\textsuperscript{nd} heart catheterisation)

ASD closure was associated with a significant reduction of total heart volume and right ventricular systolic pressure as well as trend to symptomatic relief in terms of NYHA while, there were no significant changes in the medical group (*Table 7*).

<table>
<thead>
<tr>
<th></th>
<th><strong>Surgical group</strong></th>
<th><strong>Medical group</strong></th>
<th><strong>P-value</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heart volume, ml/m\textsuperscript{2}</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>\textsuperscript{1}\text{st} catheterisation</td>
<td>557±93</td>
<td>608±145</td>
<td>NS</td>
</tr>
<tr>
<td>\textsuperscript{2}\text{nd} catheterisation</td>
<td>439±65</td>
<td>663±231</td>
<td>0.004</td>
</tr>
<tr>
<td><strong>RV systolic pressure, mm Hg</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>\textsuperscript{1}\text{st} catheterisation</td>
<td>31±9</td>
<td>38±24</td>
<td>NS</td>
</tr>
<tr>
<td>\textsuperscript{2}\text{nd} catheterisation</td>
<td>19±4</td>
<td>39±15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>NYHA (I/II/III/IV)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>\textsuperscript{1}\text{st} catheterisation</td>
<td>6/6/0/0</td>
<td>6/5/1/0</td>
<td></td>
</tr>
<tr>
<td>\textsuperscript{2}\text{nd} catheterisation</td>
<td>10/2/0/0</td>
<td>6/5/1/0</td>
<td></td>
</tr>
</tbody>
</table>

*Table 7. Roentgenological heart volume, right ventricular (RV) systolic pressure and functional class at the \textsuperscript{1}\text{st} and \textsuperscript{2}\text{nd} catheterisations. Mean values±SD.*

Late follow-up

In the initially medically managed group, 8 of the 12 patients had surgical ASD repair 1.4-19.6 years after the \textsuperscript{2}\text{nd} catheterisation, mainly of symptomatic reasons. At late follow-up 5 patients in the originally medical group and 4 patients in the surgical group had died. In the medical group all and, in the surgical group two, of the deaths were cardio-vascular. Seven patients in the medical group and five patients in the surgical group had experienced atrial fibrillation during follow-up. The number of cerebro-vascular incidents seemed lower in the surgically than the medically managed group (1 vs. 5), where the only incident in the surgical group was due to air embolism during the cardiac surgery.

Heart volume, as here determined by X-ray, seemed to influence late mortality. Irrespective if surgery took place before or after the \textsuperscript{2}\text{nd} catheterisation, all 6 patients with a heart volume < 500 ml/m\textsuperscript{2} at the preoperative exam were alive at late follow-up. In the surgical group there were two cardio-vascular deaths, one occurring among the 11 patients with a heart volume \leq 500 ml/m\textsuperscript{2} at the postoperative exam, the other in the only surgical patient who had a heart volume exceeding 500 ml/m\textsuperscript{2} at the \textsuperscript{2}\text{nd} catheterisation.
GENERAL DISCUSSION

Calculation of the shunt magnitude in ASD

QP/QS as a measure of the severity of an ASD should be regarded as an approximation due to three main reasons. Firstly, the former methods of quantifying QP/QS, although not appreciated by many clinicians, are imprecise. In atrial shunting the determination of mixed systemic venous blood oxygen saturation is a particular problem with the oximetric method and, the sensitivity to detect shunts of even a moderate degree is low\textsuperscript{48}. In large shunts, oximetry and indicator-dilution methods, including radionuclide angiography, are mathematically sensitive which contributes to the low precision. Secondly, variations in the physiologic state influence the degree of shunting\textsuperscript{25, 34, 39, 40}. Thirdly, QP/QS is a ratio and does not reflect the absolute volume load of the pulmonary circulation as changes in the systemic flow may also play a role.

The present study (paper I) demonstrates the high precision, accuracy and repeatability of MR velocity mapping in quantification of QP/QS of all degrees, superior to that of radionuclide angiography which in turn is held to be superior to oximetry, particularly when shunting occurs at the atrial level\textsuperscript{48, 53}. The results fit into earlier and later studies, including both adults and children, comparing MR velocity mapping with oximetry or indicator-dilution techniques\textsuperscript{61-63}. However, in these studies the superiority of MR velocity mapping has been difficult to demonstrate as repeatability and interobserver variability of the competitive methods were not assessed. Considering the theoretical background of these methods it seems likely that the demonstrated inconsistencies would rather be due to the shortcomings of the oximetric and indicator-dilution methods than imprecision of MR velocity mapping.

Oximetry was the first clinical method introduced to quantify shunts and, for a long time it has served as gold standard. Although more precise than oximetry, the radionuclide method has its limitations\textsuperscript{49, 53, 54}. QP/QS assessment by echoDopplercardiography may be limited by poor image quality and it is a highly operator dependent technique\textsuperscript{56, 58}. MR velocity mapping might therefore well be the future gold standard for quantifying QP/QS.

During recent years the QP/QS has lost some of its former importance in clinical decision-making in ASD\textsuperscript{132, 136, 137}. Before non-invasive cardiac imaging was available, the QP/QS held a central role in describing the severity of an ASD and, served as a major discriminator when to decide about intervention. With the introduction of echocardiography and later MRI other features of an ASD have gained attention, the significance of an ASD is rather described in terms of right heart dilatation than QP/QS. The recently published guidelines from the American Heart Association state “Closure of an ASD either percutaneously or surgically is indicated for right atrial and right ventricular enlargement with or without symptoms” and does not mention QP/QS\textsuperscript{132}. However, there are cases when the picture is blurred because of right-sided valvular incompetence, right ventricular dysfunction or hypertensive pulmonary vascular disease. In these, assessment of QP/QS is still clinically important. Besides providing excellent anatomical information, being non-invasive and without radiation exposure magnetic resonance seems to be the most precise method to determine QP/QS. Although irregular heart rhythm, pacemakers/internal cardiac defibrillators, metallic implants and claustrophobia may limit or prevent the use of magnetic resonance, it can be applied in a majority of ASD patients.
Atrial fibrillation and interatrial conduction in ASD

AF is a frequent and major complication in adults with ASD, however, the underlying mechanisms of the arrhythmia are poorly understood. Long-standing volume load, various degrees of pulmonary hypertension, ventricular dysfunction, surgical scars and congenital abnormalities in the atrial conduction tissue have all been implicated in the aetiology of late atrial arrhythmias in ASD. Moreover, the benefit of closing the defect, from the point of arrhythmia, is still not completely elucidated.

The present findings (paper II and III) suggest that atrial conduction disturbances play an important pathogenetic role in ASD, and furthermore, that these electrophysiologic abnormalities cannot be reversed in the middle-aged adult by closing the defect. Electrophysiologic alterations develops early as, atrial conduction abnormalities have been shown in children with ASD by means of invasive electrophysiology, as well as conventional ECG, demonstrating prolonged P-wave duration and increased P-wave dispersion. However, it can be extracted from studies that, when the ASD is closed during childhood the postoperative P-wave duration seems to be normal and stable over time. When the defect is closed in adults younger than in our series, two subsets of patients seems to form; one younger cohort free from postoperative AF in whom P-wave duration decreased after closure and one older group suffering from paroxysms of AF in whom P-wave duration did not change. Using a signal averaged technique the link between postoperative P-wave prolongation and the late occurrence of AF in adults with ASD has also been demonstrated. In that study no pre-closure measurements were made.

Thus, it seems that the reversibility of the atrial conduction disturbances in ASD is related to patient’s age at closure and that these abnormalities start to become irreversible in young adult life. If so, and assuming the pathogenic role of conduction abnormalities in AF, it would fit very well to the observation that ASD closure performed before the age of 25 years reduces the risk of late AF.

The pattern of increased prevalence of AF with age, recognised in the general population, is also found in patients with ASD but, at a much higher level. It would be plausible that the haemodynamic abnormalities of ASD markedly enhance the general age-related mechanisms causing atrial conduction alterations and AF. The potential to reverse the conduction disturbances declines with age. However, in ASD, age also is a measure of the duration of the abnormal volume load and, it is not possible to distinguish if the process of electrophysiologic irreversibility is a consequence of time per se, the volume load, or both. Considering the reports on ASD closure during childhood, there is no support that the atrial conduction disturbances associated with ASD would have a congenital origin.

An important finding in our studies is the absence of a mechano-electrical interaction as, relationships between P-wave duration and atrial sizes were lacking and that the marked reduction of right atrial size after ASD closure was not accompanied by changes in P-wave duration. However, patients with a history of paroxysmal AF were significantly older, had larger left and right atria as well as longer P-wave duration post closure than those without arrhythmia. Interpretation is difficult – what is the cause and what is the consequence? - as AF itself promotes electric remodelling and seems to contribute to increased atrial sizes. In our patients,
those with a history of paroxysmal AF even tended to increase left atrial size after ASD closure and the pulmonary pressure was significantly higher in that group when compared to those without AF. Although hypertensive pulmonary vascular disease has to be considered, this combination suggests that increased filling pressures on the left side of the heart may play a role. It might well be that closure of the ASD unmaskis impaired left ventricular filling and, the preclosure left atrial volume load is replaced by left atrial pressure load. If so, the left atrium would remain enlarged and mechanisms causing electrical conduction disturbances, although of a different character, would go on.

In ASD the increased pulmonary venous flow, as well as the above described possible risk of increased left atrial pressure after closure, may stretch and distend the mouths of the pulmonary veins. As that area is thought to be a major origin of ectopies triggering AF, this could have a potential to increase the “trigger load”. If this would be a mechanism contributing to the high frequency of AF in ASD is unknown.

In conclusion, there seem to be clinical and electrophysiologic data favouring timely intervention in ASD, if to prevent the development of late AF. The finding of late atrial flutter but, not atrial fibrillation, after surgical closure during childhood may suggest an arrhythmogenesis by surgical scar. However, it is still too early to decide, if the introduction of catheter-based ASD closure, as compared to surgery, is beneficial in the long-term from the point of arrhythmia.

**Cardiac remodelling after ASD closure**

Our study (paper IV) demonstrates the typical features of a significant ASD; right atrial and ventricular dilation, left atrial enlargement and a small left ventricle. These findings correspond well to our understanding of flows and volume loads in ASD and are in line with earlier reports, however, focusing on the right heart many of them have put less emphasis on the left ventricle and particularly the left atrium.

After ASD closure the resolution of these abnormalities, with the exception of the left atrium, shows a pattern consistent with the changes of volume load. Older age does not seem to preclude normalisation of right atrial and ventricular size, it occurred in around ¾ of our patients. In spite of our patients being considerably older (mean age 54 years) this outcome seems to match the findings in a number of studies on younger patients (mean ages 22-38 years). Even in children normalisation is not always complete. The clinical prognostic impact, per se, of persistent right heart enlargement is unclear because it is often associated with other signs of more advanced disease. Normalisation of left ventricular size and the maintenance of a normal left ventricular ejection fraction are consistent findings after ASD closure.

Regarding the left atrium, the absence of postclosure reduction of size is surprising and not well understood but, in accordance with earlier reports. Abnormal left atrial size was found in 44% of our patients one year after ASD closure. In a short-term study in young patients (mean age 22 years) right atrial size diminished markedly while left atrial size remained unchanged after catheter closure of the ASD. In long-term follow-up after surgical ASD closure, left atrial
enlargement was found in 44% in adults (mean age at surgery 35 years) and in 6% in a paediatric series\textsuperscript{42, 94}.

As ASD closure eliminates the abnormal volume load, other factors have to be taken into account when to explain the relative unresponsiveness of the left atrium. As the right atrium, exposed to the same unloading and having the same embryologic origin, is more reactive it seems unlikely that atrial cellular and muscular properties would play a role. Before closure, an ASD serves as a pop-off valve when left ventricular filling is impaired. ASD closure would then unmask superimposed left ventricular diastolic dysfunction and, it would be tempting to consider pressure load replacing volume load as a cause of the persistent left atrial dilation. This may be supported by the finding of increased levels of brain natriuretic peptide correlating with left atrial size after ASD closure in adults\textsuperscript{42}. However, it might also be that the atria at a certain point lose the potential to remodel completely. In a study on former professional cyclists assumed to have had athlete’s heart, the right and left atrial sizes were significantly larger than in controls when examined a long time after the professional career\textsuperscript{142}. This could not be explained by differences in ventricular filling pressures as the systolic pulmonary pressure and the concentration of brain natriuretic peptide were normal and similar to controls. Although within normal ranges, the left ventricular size, but not left ventricular mass or right ventricular size, was larger in former cyclist than in controls.

The prevalence of impaired left ventricular compliance in ASD has not been systematically studied but, what could the reasons be? Congenital? As a consequence of the left ventricle being “spoiled” by the ASD for a long time? Superimposed acquired left ventricular stiffness due to extrinsic factors that could be biologically associated with ASD or not? In this context the reports of a relative high prevalence of systemic hypertension in ASD is intriguing\textsuperscript{36, 38}.

When remodelling occurs it starts very early after closure and the speed of the changes are declining with time. At 6 months the remodelling process seems more or less to have been brought to an end. Although not studied, it is reasonable to believe that the early changes are functional to a high degree while, later changes tend to have a more structural background. Again, the lack of early change in left atrial size, provided that any structural abnormalities would be similar in both atria, suggests a functional cause, like pressure load.

**Long-term results of ASD closure**

There are a number of intermediate-term follow-up studies after ASD closure\textsuperscript{37, 99, 101, 104, 109}. Studies on the very long-term outcome, with follow-up 20-30 years after ASD closure are rare. Actually, there are only two, one confined to children and one including all age groups\textsuperscript{93, 94}. The present study (paper V) has a unique design as, it compares a surgical and medical treatment strategy by means of an intermediate haemodynamic and clinical assessment as well as an extremely long term clinical follow-up. Furthermore, the medically treated group would rather represent a delayed surgical strategy as, 2/3 of them were operated on symptomatic grounds after the intermediate follow-up. After five years, surgical closure, in contrast to medical management, was associated with improved symptoms, resolution of cardiac enlargement and normalisation of the pulmonary pressure, in agreement with many other studies. In the long-term, the medical group, in spite of later ASD closure, tended to do worse in terms of
cardiovascular mortality and morbidity. Thus, it seems that a delayed surgical strategy, waiting for obvious symptoms, is not superior to early intervention. However, as the numbers are small conclusions should be made with caution

In former times the perioperative risk was an important factor in the cost-benefit analysis when to decide about ASD closure. Nowadays, the peri-interventional risk in ASD closure is very low, thus, favouring intervention as soon as a significant ASD is found in the adult.

**GENERAL CONCLUSIONS**

MR velocity mapping provides accurate and precise measurements of shunt magnitude over the whole range of possible QP/QS values. Considering the flaws of the alternative methods, it seems appropriate to appoint MR velocity mapping as the “gold standard” when to calculate QP/QS.

P-wave prolongation, a marker of atrial conduction delay, is a common finding in adults with ASD. It is likely that the electrophysiologic abnormalities become irreversible with time as, closure of the defect in middle-aged or older patients does not influence P-wave duration. As atrial conduction delay is associated with the development of atrial fibrillation (AF), the high prevalence of this arrhythmia in ASD and the failure of ASD closure to prevent late postoperative AF in older patients will have a plausible explanation. This would favour early intervention, if to prevent late AF in ASD.

Cardiac remodelling towards “normality” after ASD closure in the adult, is a common and early event that seems by and large completed within the first half year after closure. Although having had an abnormal volume load for several decades, a majority of patients has the potential to normalise right atrial and ventricular sizes. Surprisingly, and for obscure reasons, left atrial size, in contrast to right atrial size, is not affected by ASD closure. One might speculate that concealed left ventricular diastolic impairment may play a role and future studies exploring that issue are warranted.

In the adult, timely closure of the ASD seems to reduce the risk of both intermediate and late morbidity as well as late cardio-vascular mortality. A delayed surgical strategy, intervening when clear symptoms appear, does not seem to be advantageous when compared to earlier closure of the defect.
POPULÄRVETENSKAPLIG SAMMANFATTNING
(Summary in Swedish)

Förmakseptumdefekt – ett hål mellan hjärtats förmak - är det vanligaste medfödda hjärtsviktet som upptäcks i vuxen ålder. Det beror på att det är symptomfattigt och inte ger så mycket väsen ifrån sig under barndomen och uppväxten. Vid förmakseptumdefekt passerar redan syratt blod genom hålet till höger förmak, det ”shuntas”, och pumpas helt i onödan ut i lungorna igen vilket leder till en övercirculation i lungorna. Mängden blod som går genom lungorna kan vara upp till 4-5 gånger större än normalt och det belastar hjärtat så att höger hjärthalva och vänster förmak förstoras. Med stigande ålder fär allt fler patienter symptom, i form av prestationssänkning, andfåddhet, svullnad och förmakssvämningar. Förmakssvämningar förekommer hos mer än hälften av dessa patienter när de kommit upp i medelåldern och det är en rytmstörning som kan bidra till proppbildning och stroke. Slutning av hålet mellan förmakken, antingen med hjärtkirurgi eller med s.k. kateterburen teknik (”paraplystängning”) då man når hjärtat via punktion av ett blodkärl, har visat sig ha god symptomlindrande effekt. Däremot tycks inte den framtidiga risken att utveckla förmakssvämningar påverkas om ingreppet sker i vuxen ålder.

Mer än 10% av alla medfödda hjärtsvikt utgörs av förmakseptumdefekt och det betyder att minst 100 barn per år föds med detta hjärtsvikt i Sverige. Eftersom de allra flesta överlever till vuxen ålder betyder det att antalet vuxna svenska med förmakseptumdefekt kan vara så många som 5000. Utifrån ett allmänt och djupt intresse för dessa medfödda hjärtsvikt har jag undersökt en rad aspekter som har betydelse för den vuxne med förmakseptumdefekt. Patienternas medelålder i arbetena II-IV var drygt 50 år.

Beräkning av mängden blod som passerar hålet i förmaket, och därmed belastar lungcirkulationen, har varit en viktig del i det kliniska beslutsunderlaget för att avgöra om förmakseptumdefekten behöver slutas eller ej. I det första arbetet jämfördes flödesmätning med magnetkamera (MR velocity mapping) mot en etablerad isotopmetod för beräkning av shuntens storlek. Beräkningarna med magnetkameran visade sig vara säkrare och pålitligare än med isotopmetoden. Magnetkameraundersökning har alla möjligheter att bli framtidens referensmetod i detta avseende.

Orsakerna och mekanismerna bakom den mycket höga förekomsten av förmakssvämningar hos patienter med förmakseptumdefekt är oklara. I andra sammanhang har förmakssvämningar förknippats med förlängsamt elektrisk överledning i förmak och det kan ses som en förlängning av P-vågen på EKG. I arbete II och III mättes P-vågens varaktighet (duration) med hjälp av ett medelvärdesbildat högupplöst EKG såväl före som efter slutning av förmakseptumdefekten. Samtidigt undersöktes med hjärtultraljud förmakens storlek hos patienterna. P-vågen var signifikant längre hos patienter med förmakseptumdefekt än hos ålders- och könsmatchade kontroller (148±16 vs. 128±15 ms, p<0.0001) och den påverkades ej av slutning av defekten (före;148±16 vs. efter;144±16 ms, p=0.07). P-vågens duration var inte heller på något tydligt sätt knuten till förmakens storlek. Man kan konstatera att vid förmakseptumdefekt förändras förmakens elektriska egenskaper på ett sådant sätt att uppkomsten av förmakssvämningar gynnas. I medelåldern tycks dessa förändringar ha blivit mer eller mindre bestående och låter sig ej påverkas av att defekten då sluts. För att motverka uppkomst av förmakssvämningar vid förmakseptumdefekt bör därför defekten slutas tidigt i livet.

ACKNOWLEDGEMENTS

I wish to express my sincere gratitude and appreciation to all those who have helped and supported me to complete this work. I will mention a few, others not forgotten:

Associate professor **Stig Persson** being my tutor for a long time and piloting me on the scientific sea. Our first route was directed to the “diastolic jungle” and someone named Doppler would join the crew. However, the closer we came that jungle, the more impenetrable the place seemed and we changed our plans. Now, redirecting, we headed towards the gate of the main artery of life, the aortic valve. Our purpose was to explore the obstructions and insufficient custody we knew existed there. However, soon after we had put out, the scientific winds slackened. Patiently we waited for windy weather, but from where would it blow? It started as breeze, just in a meteorological sense. It was a steady and pleasant wind, never stormy. We steered our ship to the middle of the heart, to find that there was a hole, a very intriguing one. Finally, that is today, we have reached our destination and unloaded our cargo. Let’s keep to sailor’s traditions and celebrate that.

Associate professor **Pyotr Platonov** being my tutor, for electric and scientific guidance. And I even know what ASD is in Russian. Дефект межпредсердной перегородки.

Professor **Nils Rune Lundström**, not only for bringing me into congenital heart disease and making it understandable but, particularly for making me a part of your “paediatric cardiology family”. I still recall the tea parties you and **Gudrun** gave, besides scones they were filled with clinical and scientific discussions.

Professor **Jane Somerville**, the head of the unicorns and the mother of GUCH. I am indebted to you for so much, you have always welcomed and supported me, and in one way you have made me to what I am. Your outstanding clinical experience and keen clinical judgement have been examples I have tried to reach. I also wish, I would have had your sharp tongue and your warm heart.

Professor **Bertil Olsson** for support and patience with my scientific bradycardia. You were the perfect “scientific pacemaker”; you read my activity and, in an “on demand” fashion, you triggered it when it failed, by encouraging and by providing me the time for scientific work.

Engineer and co-author **Jonas Carlson** for teaching a "cardiot" mathematical and technical matters.

**Monica Magnusson**, without your assistance in the labyrinths of the Academic Administration I would have gone crazy.

**Bibbi Smideberg**, being supportive and considerate. Knows that a cup of coffee can turn the world.

Colleague and friend **Thomas Higgins**, a great linguist, for the “make-up” of my English.
Associate professors Carl Meurling, Johan Holm and nurse Karin Paulsson, members of the GUCH group at Lund University hospital, for making everyday clinical work a pleasure.

“Microcardiologist” and co-author Katarina Hanséus. Have I ever heard a “no” from you? - which doesn’t mean you always say “yes”.

Håkan Arheden, the late Catarina Holmqvist, Olle Pahlm, Sven Laurin, Freddy Ståhlberg, Rasmus Havmøller, Sven Berlind and Ed Varnauskas, co-authors.

My dear parents, Astrid and Bo. The joy of work, the bent to debate, and an open mind have been important parental traits. Thank you, for transferring them and for your never-ending support.

Last but not least, my family, Britt, Maria and Johan, just because you are you.
REFERENCES


73. Tabery S DO. How classical are the clinical features of the "ostium secundum" atrial septal defect? Cardiol Young 1997;7:294-301.


APPENDIX: ORIGINAL PAPERS I – V


