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INTERVENTIONAL CLOSURE OF PERSISTENT FOETAL CARDIAC SHUNTS INCLUDING PDA AND PFO – STUDY OF OUTCOME, COMPLICATIONS AND NOVEL METHODS

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Interventional closure of persistent foetal cardiac shunts including PDA and PFO – study of outcome, complications and novel methods

Thesis for Doctoral Degree (Ph.D.)

By

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To my beloved family, Corinna, Morten and Elin

“Hur ska jag kunna veta det, när jag aldrig har försökt?” Astrid Lindgren, Pippi Långstrump, Pippi går i affärer

‘How am I supposed to know if I never have tried?’ Astrid Lindgren, Pippi Longstocking, Pippi goes shopping

Abstract

Background

Persistent foramen ovale (PFO) and persistent ductus arteriosus (PDA) are two of the most common congenital heart defects (CHD). The incidence of PFO is reported to be between 10% and 35% (1, 2). In term infants, a PDA is seen in around one in 2000 births, accounting for 5% to 10% of all congenital heart disease (3, 4). Transcatheter closure of these lesions has become standard procedure in children and adults and has largely replaced surgery for these congenital cardiac defects. Cardiac catheterisation techniques require ionising radiation and are generally classified as high-radiation dose procedures according to the European Directive 2013/59/Euratom (5).

New methods and materials have improved outcomes and safety, and have shortened periprocedural hospital stays for patients undergoing catheterisation.

Aim

This thesis aimed to study outcome and complications of new methods in patients undergoing heart catheterisation. The included studies aimed to evaluate new techniques, starting with vascular access and preclosure devices in the accessed vessel, to improve bleeding control and facilitate same-day discharge (SDD). A new method for surveillance of cancer risk during catheterisation procedures was introduced and can be used to alert the operator when the radiation has exceeded a certain cancer risk level. Lastly, several next-generation PDA devices were studied.

Methods

Four retrospective studies were conducted. In Study I, data from 238 paediatric patients were collected to estimate the risk of radiation-induced cancer death. Study II reviewed all patients undergoing PDA closure with an Amplatzer device over a fourteen-year period in a large centre in Tel Aviv.

Study III investigated same-day discharge (SDD) of adult patients undergoing PFO closure. All patients who underwent transcatheter closure of a PFO at the Karolinska University Hospital in Stockholm between March 2017 and June 2020 were included.

Study IV included all patients who underwent transcatheter PDA closure with a 5/7 Occlutech® duct occluder in three European centres in the UK, France and Sweden.

Results

More than 90% of the retrospective study cohort in Study I was within the range of very low (1–10 in 100,000) or low cancer risk level (1–10 in 10,000). No patient exceeded the high cancer risk level (> 1 in 100).

In addition, a new concept of age- and gender-specific risk reference values (RRVs) related to population cancer risk was introduced. The results showed that the RRV for males was a factor 2–3 higher than that for females.

In Study II, all Amplatzer devices demonstrated very good closure rates (> 99.5%) with a low rate of complications, such as device embolisation or left pulmonary artery (LPA) stenosis. A tendency toward less LPA stenosis with the Piccolo™ device was noted, and no aortic flow disturbance occurred in this study. The majority of complications (device embolisation and LPA stenosis) occurred in patients with a bodyweight < 15 kg.

Study III focused on SDD of patients undergoing percutaneous closure of PFO. A total of 246 of 262 patients (94%) had SDD. In 166 (63%) patients, a Perclose ProGlide™ system was used for femoral vein access closure. Post-interventional arrhythmias were noted in 17 (6%) of the patients, and vascular complications in nine patients (3%). There was no difference in SDD between patients who received ProGlide (n=159, 96%) and patients who did not receive ProGlide (n=87, 91%, p=0.10).

Eighteen paediatric patients with heart failure were included retrospectively in three study sites in Study IV. Eleven of them had a bodyweight below 12 kg, and pulmonary hypertension was noted in seven of the 18 patients.

All patients underwent successful PDA closure with no complications with a 5/7 Occlutech® duct occluder.

Conclusions

Various aspects of cardiac catheterisation, from radiation risks, device choice, SDD and access site closure, have been studied in this thesis.

Transcatheter closure of persistent foetal cardiac shunts is the standard treatment in full-term children and adults with low morbidity and mortality rates. New device development has improved PDA closure outcomes, even in small children with large PDAs. PFO closure has increased in the last five years due to several randomised controlled trials that have reported a lower risk of recurrent ischemic stroke after PFO closure compared with medical therapy. Cardiac catheterisations to treat CDH can be carried out with reasonably low radiation levels. Radiation-reducing tactics and the risk of radiation-induced cancer death must be taken into consideration, especially when treating younger patients.

List of scientific papers

The following articles are referred to by their Roman numerals throughout and are presented in full at the end of this thesis.

I. Karambatsakidou A, STEINER K, Fransson A, Poludniowski G. Age-specific and gender-specific radiation risks in paediatric angiography and interventional cardiology: conversion coefficients and risk reference values. Br J Radiol. 2020;93:1110
II. Bruckheimer E, STEINER K, Barak-Corren Y, Slanovic L, Levinzon M, Lowenthal A, Amir G, Dagan T, Birk E. The Amplatzer duct occluder (ADOII) and Piccolo™ devices for patent ductus arteriosus closure: a large single institution series. Front Cardiovasc Med. 2023 May 4;10:1158227.
III. STEINER K, Sjöberg G, Damlin A, Settergren M, Verouhis D. Same-day discharge after percutaneous closure of persistent foramen ovale. Submitted.
IV. STEINER K, Sjöberg G, Karsenty C, Bianco L, Bautista-Rodriguez C, Fraisse A. Mind the gap - Missing device on the shelf? A retrospective experience with the 5/7 Occlutech® Duct Occluder. Acta Paediatrica. Accepted for publication.

Contents

List of abbreviations

ADOII	Amplatzer® Duct Occluder II
ANOVA	analysis of variance
ASD	atrial septal defect
AVPII	Amplatzer® Vascular Plug II
BMI	body mass index
BW	bodyweight
CDO	conventional duct occluder
CHD	congenital heart defect
GSO	Gore® septal occluder
$Gycm^2$	Grays per square centimetre (unit for kerma-area product)
ICE	intracardiac echocardiography
LPA	left pulmonary artery
KAP	kerma-area product
ODO	Occlutech® duct occluder
PDA	persistent ductus arteriosus
PFO	persistent foramen ovale
PONV	postoperative nausea and vomiting
R	correlation (in statistical analyses)
REID	risk of exposure-induced cancer death
REIDHT	organ-specific risk of exposure-induced cancer death
SD	standard deviation
SDD	same-day discharge
VCD	vascular closure device

1 Introduction

1.1 The foetal circulation

The foetal circulation utilises three shunts: the intracardiac shunt at the atrial level (foramen ovale) between the right and left atrium, the extracardiac shunt between the pulmonary artery and the aorta (ductus arteriosus) and the ductus venous, which bypasses the liver (see Figure 1). This doctoral thesis studies the two former shunts when patent after birth, i.e., patent/persistent foramen ovale (PFO) and patent/persistent ductus arteriosus (PDA). During foetal life, the foramen ovale allows blood from the inferior vena cava to flow from the right to the left atrium so that oxygenated blood from the placenta can flow through the left ventricle to the developing brain. The less oxygenated blood from the superior vena cava flows mainly to the right ventricle and via the ductus arteriosus to the descending aorta; the majority goes to the placenta for oxygenation. This foetal circulation is programmed to change at birth when oxygenation is taken over by the lungs, inducing closure of the foetal shunts. However, this does not always occur, resulting in PDA, PFO or both.

1.2 Anatomy of the foetal circulation

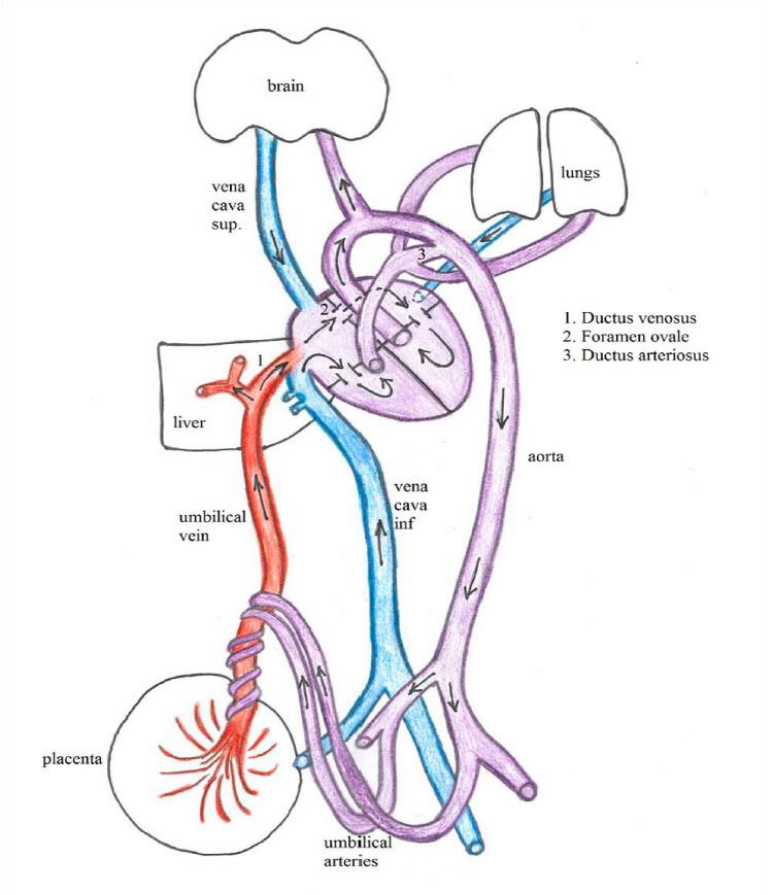

Figure 1. Anatomy of the foetal circulation. Courtesy Malin Holzmann.

1.3 Heart catheterisation

The first heart catheterisation was performed by Werner Forssmann in 1929 in Berlin, when he inserted a urinary catheter into his antecubital vein before passing it into the right ventricle. Later, he was awarded the Nobel Prize in Medicine or Physiology with André Frédéric Cournand and Dickinson W. Richards 'for their discoveries concerning heart catheterisation and pathological changes in the circulatory system'.

Thirty-eight years later, the first transcatheter PDA closure was performed by Werner Porstmann in Berlin (6). The history of paediatric interventional catheter procedures was summarised by Mullins (7), with milestones including the first

pulmonic valve incision in 1953 (8), the first balloon atrial septostomy by Rashkind and Miller in 1966 (9), the first intracardiac correction of a congenital heart defect (CHD), the closure of an atrial septal defect (ASD) by King and Mills in 1974 (10), the development of 'Grüntzig balloons' for dilation of peripheral vessels in 1974 (11) and of coronary arteries in 1975 (12). A major breakthrough in paediatric interventional cardiology was seen in 2000 when Philip Bonhoeffer performed the first transcatheter implantation of a pulmonary valve in a 12-year-old patient (13).

The technique used in almost all these interventions to access the vein or artery leading to the desired localisation in the heart is called the 'Seldinger technique', developed by Sven Ivar Seldinger in Stockholm in 1952 (14).

1.4 Patent ductus arteriosus in full-term infants

CHDs occur in about 1 of 100 infants and are one of the most common congenital birth defects (15, 16). PDA is one of the most common CHDs, accounting for 5-11% of all CHDs in term infants (17, 18).

1.5 PDA in extremely premature-born children

The prevalence of PDA in extremely preterm-born children is much higher than in term infants (as the duct is programmed to be patent throughout pregnancy); the prevalence of PDA is reported in up to 66-80% in premature- and extremely premature-born children (19, 20). Dice et al. describe an inverse correlation between PDA and birthweight (as well as gestational age), with an incidence of 80% among children born with a bodyweight (BW) of less than 1,200 grams (18). Due to immaturity in preterm-born children, the normal physiological mechanisms that contribute to closure – oxygen tension and decreased prostaglandin levels – are altered, leading to delayed closure and patency of the ductus arteriosus (21-23).

A haemodynamically significant PDA can lead to increased morbidity and mortality in premature babies. Heart failure with dilation of left-sided heart structures, failure to thrive, need for ventilation assistance, necrotising enterocolitis, intraventricular haemorrhage and development of bronchopulmonary dysplasia are known complications of haemodynamically significant PDAs (18).

Treatment:

PDA can be treated with pharmaceuticals, such as indomethacin, ibuprofen or acetaminophen and respiratory treatment with positive airway pressure. Surgical ligation or interventional closure by catheterisation (24) may be needed if these actions do not affect the PDA.

Medical treatment:

In a meta-analysis, Olsson et al. concluded that medical treatment with paracetamol or acetaminophen was as effective as treatment with ibuprofen and more effective for duct closure than placebo or no intervention (25).

The non-steroidal anti-inflammatory drugs indomethacin and ibuprofen and the analgesic paracetamol/acetaminophen can be successful in reducing or closing the PDA in up to 67% of patients, according to a meta-analysis published by Mitra (26). Failure of medical treatment to close a PDA in 20-40% of patients has been described by Irmesi and Hammermann (27, 28).

Patients with heart failure or other complications due to the PDA who do not respond to medical treatment will be referred for either surgery or transcatheter closure of the PDA.

1.6 Transcatheter PDA closure

The first transcatheter closure of a PDA was performed in 1967 by Porstman et al. (35), with follow-up reports by Wierny and Rashkind in 1986 and 1987, respectively (29, 30). Large bore access was needed for these interventions due to the high profile of the PDA occluders used. The development of new low-profile devices has led to transcatheter PDA closure becoming the standard treatment option for isolated PDA, for patients without concomitant heart defects that require surgery, for children with BW over 6 kg and for adults (3, 21, 31).

The evolution of low-profile devices made PDA closure feasible even in extremely preterm-born children with BW of under 1,000 grams. The latest generation of the Amplatzer® Duct Occluder devices, the Amplatzer® Duct Occluder II Additional sizes (now named the Piccolo™ device), received approval from the American Food and Drug Administration in January 2019 and CE mark approval in September 2019 for PDA closure in children with BW over 700 grams.

The first studies reporting transcatheter PDA closure in extremely preterm children were published by Bentham 2011 (32) and Zahn (33, 34). Since then, numerous studies have been published in this field, demonstrating the procedure to be safe and effective in extremely low birthweight children (35-38).

Fraisse et al. showed a significantly shorter duration of mechanical ventilation after transcatheter PDA closure compared with surgery. Interestingly, this study also described that patients who underwent the procedure before four weeks of age were discharged home earlier than patients who underwent the procedure later in life (38).

Known complications related to transcatheter closure of PDA include device embolisation, left pulmonary artery (LPA) stenosis, aortic coarctation and vascular access-related injuries (39, 40).

1.7 Surgical closure

Surgical closure of the PDA can be performed in an operating room or bedside in a neonatal intensive care unit and is effective and safe but not free from complications. Significant numbers of extremely low birthweight patients are at risk of developing the so-called 'post-ligation syndrome' within 6-12 hours post-surgical PDA closure (41), (42). This complication has been studied extensively in the last decade.

El-Khuffash et al. reported that post-ligation syndrome occurred in up to 40-50% of preterm-born patients undergoing surgical PDA closure. The post-ligation syndrome is characterised by systemic hypotension, requiring inotropic drugs, and ventilation/oxygenation failure. It usually occurs in the first 6-12 hours after surgical ligation (43, 44). The syndrome is seldom, or to a much lesser extent, seen in patients undergoing transcatheter PDA closure (45).

Gudmundsdottir et al. showed a correlation between surgical PDA closure and neurodevelopmental impairment in a follow-up study of the EXPRESS cohort (46). The original EXPRESS study was conducted in Sweden between 2004 and 2007. Gudmundsdottir et al. demonstrated a higher risk of neurodevelopmental impairment if surgery was performed as the first treatment option without prior medical treatment. The risk of neurodevelopmental impairment was also higher in children who had PDA surgery during the first ten days of life compared with those who had surgery after the first 20 days of life (46).

Complications of surgical PDA closure seldom seen after transcatheter PDA closure are left vocal cord paralysis, occurring in around 9% to 32% of patients (47), scoliosis after posterolateral thoracotomy (48), chylothorax, pneumothorax and diaphragmatic paralysis (24).

1.8 Patent foramen ovale

Patency of the foramen ovale can occur after birth if the foramen ovale fails to close. Spontaneous closure occurs within days to weeks in about 75% of the population, and PFO is seen in approximately 25% of the adult population worldwide (49).

Blood that can shunt over a PFO does not get filtered from clots by the pulmonary capillary bed. Unfiltered small blood clots (venous thrombi) may paradoxically cross over from the venous system to the left atrium and travel via the left heart to the coronary arteries or the central nervous system, causing ischaemic damage.

The first clinical report of a paradoxical embolisation crossing a PFO leading to systemic embolisation in the fossa of Sylvius was written by Cohnheim in 1877 (50). The importance of PFO in patients with stroke was highlighted by Lechat (51), along with its importance in other clinical settings such as platypnea–orthodeoxia syndrome and decompression sickness (52).

Patients who have had a stroke will undergo clinical examination and investigations, including ultrasound imaging of the head and neck vessels, 24-hour electrocardiogram, echocardiography, and computed tomography or magnetic resonance imaging scans of the neck/brain, to look for a cause of the stroke. Common causes include atherosclerotic disease, carotid stenosis, atrial fibrillation, and intracerebral pathologies such as haemorrhage or space-occupying lesions. In around 40% of the patients with stroke, no clear cause can be found. In the presence of a PFO, a paradoxical embolus from the venous system across the PFO to the left heart is the presumed cause of stroke, a so-called 'cryptogenic' stroke (53, 54).

1.9 PFO closure

In the last two decades, there has been much discussion about whether or not to close the PFO in patients who have suffered from cryptogenic stroke, to prevent a second stroke episode (55). A comprehensive overview of this topic,

including anatomical considerations, diagnostic assessment, current data about PFO closure for secondary stroke prevention, and available devices, has been published by Alkhouli et al. (56).

The enthusiasm for PFO closure has grown in the last five years, as several randomised controlled trials and meta-analyses have reported a lower risk of recurrent ischemic stroke after transcatheter PFO closure compared with after medical therapy (48-52).

Traditionally, patients undergoing interventional heart catheterisation with device implantation were discharged on day one after the procedure, after echocardiographic or radiological control. Discharging a patient on the same day, within hours after the procedure, is a relatively new occurrence, seen only in the last 10–15 years and first performed in adult heart catheterisation, in patients undergoing arrhythmia ablation (57-59).

Same-day discharge (SDD) has gained increasing attention after being used for numerous and complex transcatheter procedures, such as transcatheter aortic valve implantation, percutaneous coronary interventions, and mitral valve procedures. Patient selection and postprocedural follow-up are highly important (60-63).

PFO closure is always performed as right heart catheterisation from the venous side with considerably smaller delivery catheters than transcatheter aortic valve implantation or mitral valve procedures, making the intervention suitable for early discharge.

Intracardiac echocardiography:

Intracardiac echocardiography (ICE) has gained more acceptance as an imaging tool in the last 20 years and has partially replaced transoesophageal echocardiography. A phased-array intracardiac echocardiography probe is inserted into the femoral vein through a sheath, often the same vein used for access to the right heart. Visualisation of the atrial septum with ICE eliminates the need for transoesophageal echo and, thus, the need for general anaesthesia.

In 2014, Alqahtani reported use of ICE in more than 50% of the patients undergoing ASD/PFO closure in the US, compared with 9.7% in 2003 (64). An overview of the advantages and disadvantages of ICE for PFO closure was published by Assenza (65).

1.10 Vascular access closure

Vascular closure devices (VCDs) have gained increasing attention for transcatheter procedures during recent years and can be used for both arterial and venous access closure, even after use of large sheaths (66, 67). The Perclose ProGlide device has been shown to reduce vascular complications, time to discharge and patient discomfort (68). The device is inserted over the guidewire at the beginning of the procedure.

1.11 Ionising radiation

The main part of all interventional cardiac interventions requires x-ray/fluoroscopic guidance. Reducing radiation during the intervention is of utmost importance to improve patient safety and avoid acute or chronic damage from ionising radiation, especially in paediatric patients (69, 70).

Cardiac magnetic resonance imaging, computed tomography and ultrasound are essential in diagnosis and follow-up management in paediatric cardiology. However, the catheterisation laboratory has unique abilities that have yet to be matched by other modalities.

The concept of keeping radiation 'as low as reasonably achievable' in the paediatric catheterisation laboratory has been described by Justino, highlighting the importance of radiation reduction in paediatric patients as they often undergo multiple procedures, contributing to an increased amount of total lifetime radiation (71).

In general, there are two types of radiation effects: deterministic (acute) and stochastic (long-term). Deterministic effects are based on a harmful tissue reaction that can occur if the radiation dose exceeds threshold levels. Stochastic effects, or the risk of developing cancer, are considered to increase with the dose and do not have any threshold. One important aspect that needs to be considered is the radiation sensitivity to these two effects in each specific organ, which can differ between children and adults (72).

The skin, brain, eye lens (cataract) and heart are organs potentially affected by deterministic effects. The paediatric brain, eye lens and heart appear to be more radiation-sensitive than in adults, according to the UNSCEAR Report 2013. On the other hand, the skin seems less sensitive to radiation in children, possibly due to faster skin repair mechanisms in younger individuals (73).

Data on the long-term or stochastic effects of radiation are based on epidemiological data from the Japanese population surviving the atomic bombs in Hiroshima and Nagasaki in 1945 (74-79). The dose-effect relationship for these effects can be linear, linear-quadratic or quadratic (80).

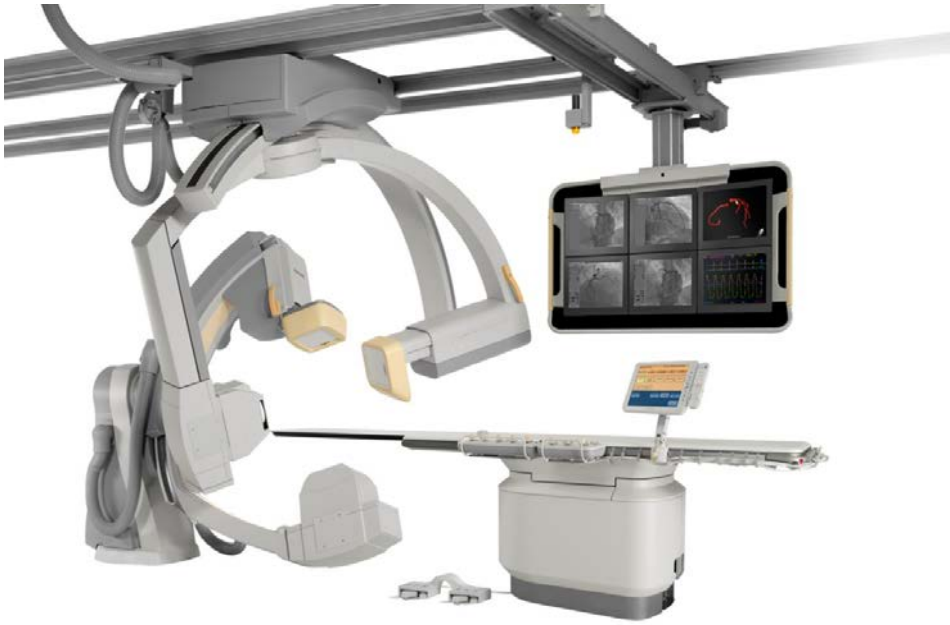

Figure 2. Biplane catheterisation laboratory. Courtesy Philips.

Technical modifications of the catheterisation laboratory can achieve this, optimising angiographic techniques to reduce the amount of emitted and absorbed x-rays and using other non-radiation-based techniques such as transthoracic, transoesophageal or intravascular ultrasound for guidance during the procedure. Justino published an extensive overview of possible radiation-reducing and imaging-improving tactics (71).

Exposure to radiation leads to increased cancer risk in paediatric patients. Only a few studies have addressed the increased cancer risk from cardiac interventions. (81, 82) The fact that the use of x-ray-based intervention is

becoming more widespread calls for consistent data on the doses delivered, together with reliable estimates of the risks of late effects (83, 84).

This thesis includes four retrospective studies on paediatric interventional cardiology, aiming to study the outcomes and safety of patients when using new techniques and materials in the catheterisation laboratory.

2 Research aims

2.1 General aims

The general objectives of this thesis were to study novel methods and devices for closure of persistent foetal cardiac shuts in various patient groups. A PDA is usually treated in infancy or early childhood due to the haemodynamic effects and compromise of a significant left-to-right shunt with pulmonary overcirculation. In contrast, this procedure is rarely carried out in adults. However, treatment of cryptogenic stroke due to PFO is usually performed in younger or middle-aged adults, but rarely in children.

An aim was to describe the complications and outcomes of interventional closure. This was done in three retrospective studies. Studies II and IV described the outcome of transcatheter PDA closure with modern commercially available devices in a paediatric population. In Study III, the aim was to study patients with cryptogenic stroke undergoing PFO closure, and to examine the outcomes for patients who were discharged on the same day and describe the contributing effect of a VCD, used in more than 60% of patients.

In Study I, we aimed to describe the stochastic effect risk from cardiac catheterisation procedures in a paediatric cohort, and the contributing risks of different organs to the total risk. Conversion coefficients for the risk of radiation-induced cancer death and a novel risk surveillance tool – the risk reference value (RRV) – were described.

2.2 Specific aims

2.2.1 Study I

In this study, we aimed to estimate the risk of exposure-induced cancer death (REID) and organ-specific risks of exposure-induced cancer death ($REID_{HT}$) in a cohort of paediatric patients undergoing cardiac catheterisation.

2.2.2 Study II

This study aimed to describe the outcome of transcatheter PDA closure in a large single-centre study. The second- and third-generation Amplatzer® devices (Amplatzer® Duct Occluder II (ADOII), Piccolo™) and the off-label used Amplatzer® Vascular Plug II (AVPII) were compared in an all-comer paediatric cohort. The primary outcome was successful PDA closure and the secondary

outcome was complications such as device embolisation, LPA stenosis and coarctation.

2.2.3 Study III

This study aimed to describe periprocedural and postinterventional outcomes in patients undergoing transcatheter PFO closure with a Gore® septal occluder (GSO) device. Complications that were studied included bleeding, arrhythmia and the need for hospital readmission. In this study, SDD after PFO closure was studied as an effect of VCD.

2.2.4 Study IV

In this study, a single size (5/7 mm) of a relatively new Occlutech® device was studied in a cohort of paediatric patients with clinical evidence of heart failure and/or dilated left-sided cardiac cavities on echocardiography.

The primary outcome – successful PDA closure – was similar to that in Study II, as was the secondary outcome, including complications such as device embolisation, LPA stenosis or coarctation.

3 Materials and methods

3.1 Populations

3.1.1 Study I

This study included 238 paediatric patients (130 females and 108 males). All patients underwent heart catheterisation at the Karolinska University Hospital between November 2013 and November 2016. Eighty percent of the patients underwent interventional procedures such as PDA or ASD closure, balloon pulmonary valvuloplasty/angioplasty, stenting of pulmonary arteries or coarctation, or heart muscle biopsies following heart transplantation. The remaining 20% underwent diagnostic heart catheterisation.

The patients were divided into five age groups for organ dose calculations based on paediatric phantom sizes:

- 42 children (18 female, 24 male) in the phantom size 0 (0–0.5) years.
- 60 children (33 female, 27 male) in the phantom size 1 (0.5–2.5) years.
- 81 children (51 female, 30 male) in the phantom size 5 (2.5–7.5) years.
- 34 children (18 female, 16 male) in the phantom size 10 (7.5–12.5) years.
- 21 children (10 female, 11 male) in the phantom size 15 (12.5–18) years (85).

3.1.2 Study II

This retrospective study included all consecutive patients who underwent PDA closure at the Schneider Children's Medical Center in Tel Aviv, Israel. In total, 762 patients underwent PDA closure between January 2008 and April 2022, with a median age of 2.6 years (range 0-46.7) and a median weight of 13 kg (range 3.5-92). A total of 296 (38.8%) patients were treated with ADOII devices, 418 (54.8%) with Piccolo™ devices and 44 (5.8%) with AVPII devices.

3.1.3 Study III

This retrospective, single-centre, register-based study included patients from the Swedish registry of congenital heart disease (SWEDCON) (86). Patients with cryptogenic stroke who underwent PFO closure between March 2017 and June 2020 were eligible for inclusion. In total, 262 (98 female, 164 male) patients were included, with a mean age of 46.3 years (standard deviation (SD) ±10.4) and a mean body mass index (BMI) of 25.5 kg/m^2 (SD ±4.2).

3.1.4 Study IV

Eighteen patients from three study sites were included and their median BW was 13.6 kg (range 4–63.2). Eleven (61%) patients had a BW between 4 and 12 kg. Pulmonary hypertension was noted in seven patients (38.8%), and mean pulmonary artery pressure was 22.6 mmHg (SD ±8.3). Three (17%) of eighteen patients were treated off-label due to a BW below 6 kg. The indication for PDA closure was clinical evidence of heart failure and/or dilated left-sided cardiac cavities on echocardiography.

3.2 Statistical analyses

Descriptive statistical methods were used when appropriate: medians (with interquartile ranges in the 25th to 75th percentile), means (with standard deviations), and numbers (with proportions).

3.2.1 Study I

A non-linear parametric model was used to determine conversion coefficients to fit the ratio between REID and kerma-area product (KAP) ($CC_{REID:KAP}$) with patient age for each gender.

The structure of this model was not specified a priori; the parameters were flexible and not fixed in advance. A MATLAB curve-fitting toolbox was used to perform the fitting. The goodness-of-fit was tested using the coefficients of determination.

3.2.2 Study II

Statistical analysis was performed using the Kruskal-Wallis nonparametric analysis of variance (ANOVA) test to determine a statistically significant difference between the medians of the three groups. Dunn's multiple comparison was subsequently used to determine the difference between groups.

3.2.3 Study III

Categorical variables were analysed using logistic regression models and described as proportions (percentages). Continuous variables were analysed using linear regression models and expressed as mean values with SDs. In all analyses, P values < 0.05 were considered statistically significant.

3.2.4 Study IV

Patient and device characteristics were described using descriptive statistical methods due to the non-comparative design of the study.

3.3 Devices and methods

3.3.1 Study I

All procedures were performed with a biplane Philips AlluraClarity X-ray system (Philips, Best, The Netherlands) as shown in Figure 2. A KAP meter (Diamentor; PTW-Freiburg, Germany) was fitted on each X-ray-tube housing, and the KAP meter was checked and calibrated. The air kerma rate settings at the entrance surface of the flat panel detector were 0.08, 0.06 and 0.05 µGy per frame in fluoroscopy mode and 0.018, 0.014 and 0.1 µGy/s in radioscopy mode. For cardiac procedures, the tube is programmed to a total filtration of 4.5 mm aluminium + 0.4 mm copper in radiography and fluoroscopy mode. The frame rate for image acquisition is 7.5, 15 or 25 frames per second. The system uses automatic dose rate control, which adjusts the beam quality depending on patient size and type of examination.

Equivalent organ dose

A commercially available program, the Monte Carlo PCXMC v2.0, was used to estimate equivalent organ doses (H_T). A mathematical hermaphrodite model was used to simulate humans of different ages and genders (the five phantom sizes described in 3.1.1). H_T is calculated based on the input parameters: peak tube kilovoltage, thickness of total filtration, KAP value, collimated beam size, beam position, focus-to-skin distance, irradiation geometry and the height, weight and age of the patient. The program reports the mean absorbed dose averaged over the organ volume.

3.3.2 Study II

This study used three different Amplatzer® devices: the second-generation ADOII and the third-generation Piccolo™ (previously called ADOII Additional Sizes or ADOIIAS). All devices are depicted below in Figures 3–5.

The Piccolo™ device, seen in Figure 4, was introduced in 2011 and became the most frequently used device at the study site in the following year. The Piccolo™ has been used in about 75-80% of all PDA closures in the last few years, as seen

in Figure 6. This study demonstrated a shift from the second-generation ADOII towards the newer Piccolo™. The AVPII device has been used more constantly in about 8% of all PDA closures due to the excellent occluding properties of this device in type C, E and F PDAs (87-90).

Figure 3. Amplatzer® Duct Occluder II. Courtesy Abbott.

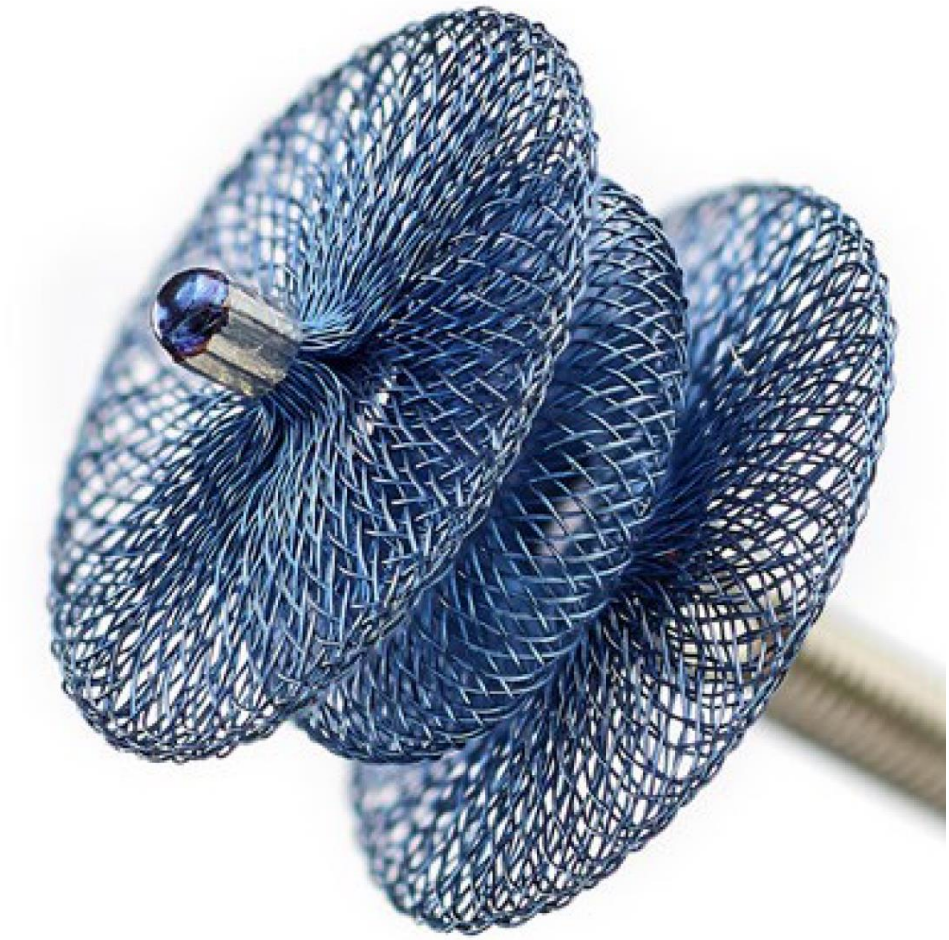

Figure 4. Amplatzer® Piccolo™ Occluder. Courtesy Abbott.

Figure 5. Amplatzer® Vascular Plug II. Courtesy Abbott.

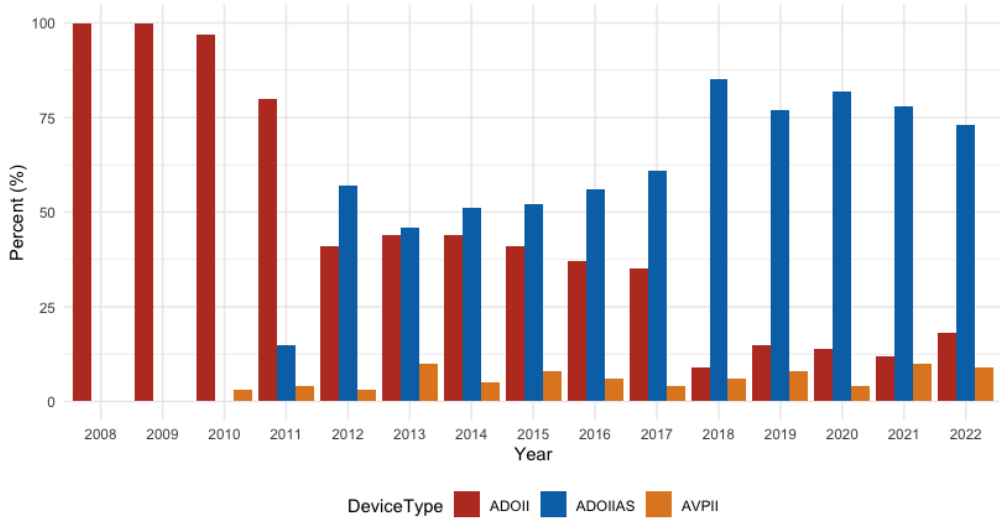

Figure 6. Device use over time in 2008–2022. Reused with permission from the publisher. Front. Cardiovasc. Med., May 2023.

3.3.3 Study III

Two types of devices were used in this study: one to close the defect in the atrial septum and the other to close the vascular access. All PFO closures were performed with the GSO device. It consists of five platinum-filled nickel-titanium (Nitinol) wires and a polytetrafluoroethylene-covered frame and was CE-marked in 2011. Three sizes were used in this study: 20, 25 and 30 mm.

The other device was the Perclose ProGlide™ system, used to close the access site in 166 out of 262 patients (63%). The device is depicted below in Figure 7. Use of VCD or figure-of-eight suture was at the sole discretion of the interventionist.

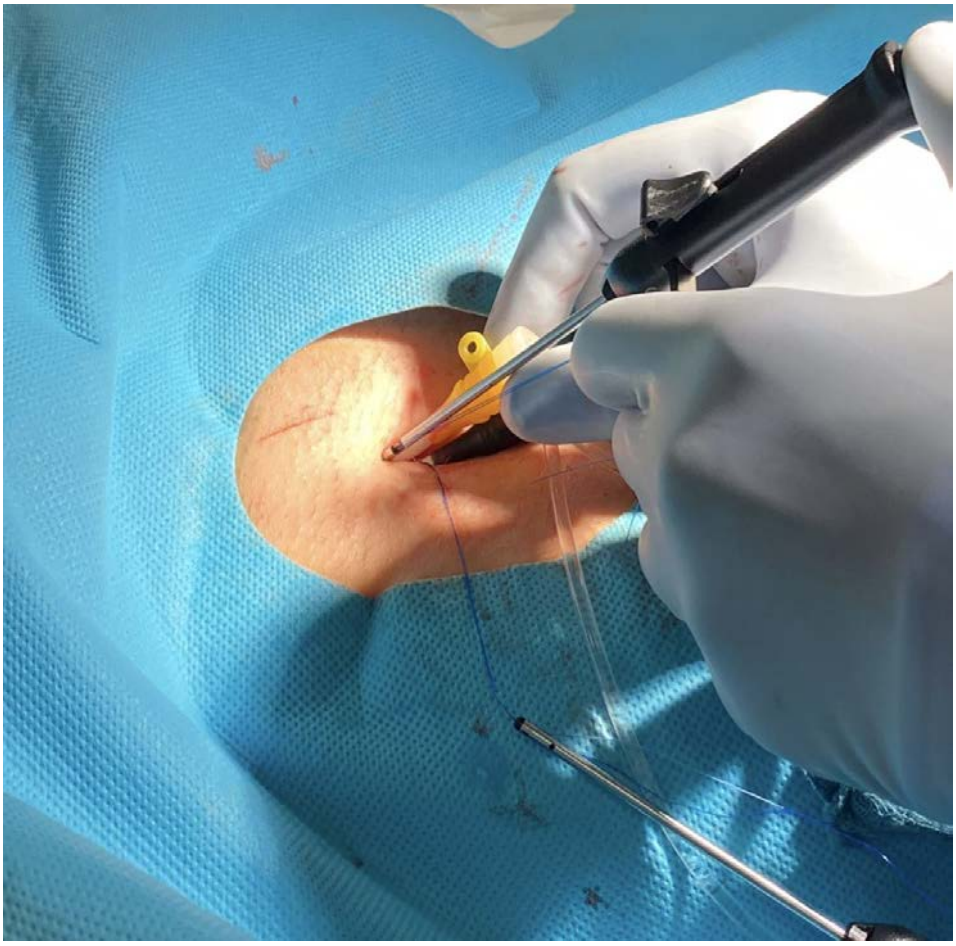

Figure 7. Perclose ProGlide™ system. Courtesy Magnus Settergren.

3.3.4 Study IV

In this study, a single size (5/7 mm) of the new Occlutech® PDA occluder was studied. The PDA occluder consists of a flexible nitinol-braiding with a shape reminiscent of a champagne cork. It has a flat distal disk connected to the shank. Depending on the size of the PDA, polyethylene terephthalate threads and patches may be integrated into the shank and the disc to ensure a better closure of the defect. The PDA occluder is selected based on the smallest measured diameter of the PDA. An implant at least 2 mm larger than the minimum ductal diameter is recommended. The used 5/7 mm size is not available as a conventional duct occluder (CDO) from other companies. The device has demonstrated safe and effective closure of PDAs in previous studies (91-95).

The size of the retention skirt at the aortic ampulla is slightly smaller than that of a CDO, which may facilitate implantation in younger patients with less space to accommodate the aortic disc. An ODO device is depicted below, in Figure 8.

Figure 8. Occlutech® PDA occluder. Courtesy Occlutech®.

3.4 Ethical considerations

Ethical approval was obtained from local authorities for all studies. Informed consent was retrieved from the patients (Study III) or their caregivers (Studies I, II and IV). The treating physicians made the decisions on all interventions based on clinical indications. All data were stored and analysed anonymously.

4 Results and discussion

4.1 Study I

4.1.1 Conversion coefficients for cancer risk

Paediatric patients undergoing cardiac catheterisation procedures are often exposed to relatively high doses of ionising radiation. As children are more radiation-sensitive than adults, they have an increased risk of developing cancer. Figure 9 shows how the conversion coefficient for cancer risk ($CC_{REID:KAP}$=REID/KAP) varies as a function of age and gender. The $CC_{REID:KAP}$ decreases with increasing age and is always higher for female patients.

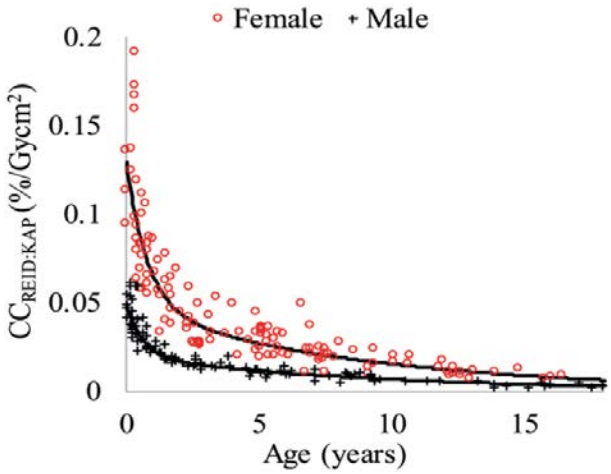

Figure 9. Conversion coefficients for cancer risk ($CC_{REID:KAP}$) together with the non-linear fit. Reused with permission from the publisher. Br J Radiol June 2020.

4.1.2 Organ-specific risks

The organ-specific risks $REID_{HT}$ (normalised to total REID for age and gender) contributing to the total REID for children are presented in Figure 10. The radiation field was the chest in all patients, as all patients in this study had undergone cardiac catheterisation. The highest risk-contributing organ across all age groups was the lung. The second highest contributing organ was the breast (15-30%).

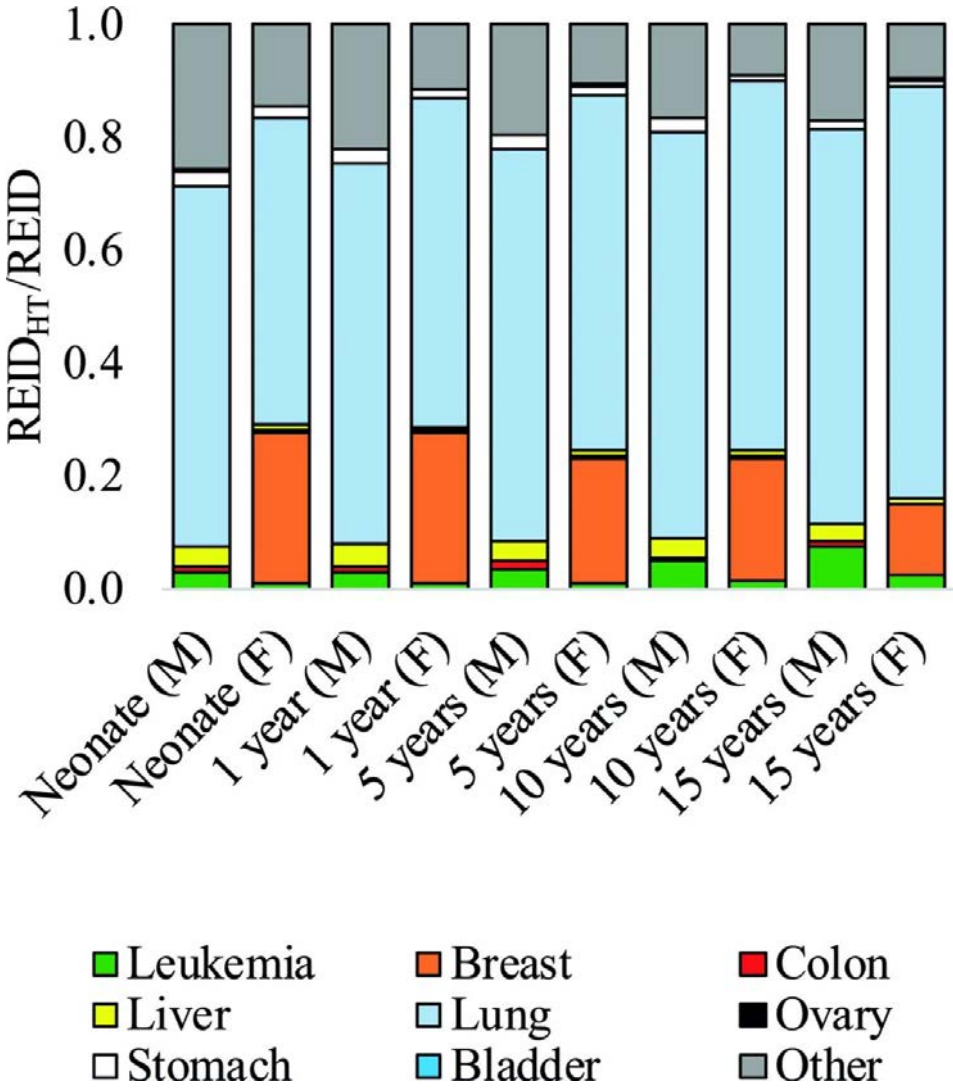

Figure 10. The contribution to the total risk of exposure-induced cancer death (REID) for different organs ($REID_{HT}$). Female (F); Male (M). Reused with permission from the publisher. Br J Radiol June 2020.

4.1.3 Risk reference values

In daily clinical work, it is not possible to determine if the risk to the patient is high or low based only on the KAP value monitored by the x-ray equipment. However, the novel concept presented in this thesis – risk reference values (RRVs) related to population cancer risk – provides the cardiologist with an indication of if the cancer risk of 0.1% is exceeded.

Age (y)	RRV* (Gycm^2)	RRV* (Gycm^2)
0	0.77	2.1
1	1.5	4.3
5	3.7	8.7
10	6.5	15
15	11	25

Table 1. RRVs (in Gycm^2) corresponding to a 0.1% increase in the population REID for females (pink) and males (blue). Reused with permission from the publisher. Br J Radiol June 2020.

As shown in Table 1, there is an increase in RRVs with age, and the RRVs leading to a 0.1% increase in REID were higher for males than females by a factor of 2.2-2.8.

Age- and gender-specific RRVs should not be used as accurate values for any one patient, nor as maximum thresholds. Rather, these values should be seen as a supporting and guiding tool for interventional cardiologists.

4.2 Study II

Three types of PDA occluders were used in this retrospective study. Successful PDA closure (primary outcome) was seen in 99.6-100% across all devices. Patients treated with ADOII devices were significantly younger and smaller and had larger PDAs than patients in the Piccolo™ group. Patient demographics and device characteristics can be seen in Table 2 below. As the mean device diameter was similar for both groups, the device:PDA ratio was significantly greater for patients in the Piccolo™ group.

There were no cases of aortic coarctation related to the device or any venous or arterial complications related to the procedure.

The rate of complications was low in all groups; device embolisation occurred in two patients with ADOII devices (0.7%), two patients with Piccolo™ devices (0.4%) and none with AVPII devices. LPA stenosis occurred in only one patient in the Piccolo™ group (0.02%), in four patients (1.3%) with ADOII devices and in one patient (2.3%) with an AVPII device. Most complications occurred in younger patients with BW below 15 kg, as shown in Table 3.

AVPII devices were used predominantly in tubular ducts Krichenko type C, E and F with a minimal diameter of 3 mm or more. LPA stenosis was noted in only one patient with an AVPII device; this rather bulky device with three similarly sized disks is theoretically superior for reducing LPA stenosis than ADOII devices with larger disks. In a study by Tomasulo et al., LPA stenosis was associated with younger procedural age, larger PDA diameter and closure with a device other than AVPII (96).

More than 90% of the ADOII devices were implanted in Krichenko type A ducts., The ADOII device was used in two patients with very short, window-like type B ducts. These short and broad window-like ducts are very difficult to treat interventionally due to the high risk of device embolisation. AVPII devices were used for all types of ducts in a large multi-centre study by VanLoozen et al. The study reported closure rates similar to our study, with a slightly higher incidence of LPA stenosis (4.5%) (97).

The modified Krichenko classification described by Philip et al. is depicted below in Figure 11 (90).

Piccolo™ devices were implanted in all other PDA types. Devices were implanted with a retrograde approach from the aortic side through a 4 French delivery catheter. The device size should be chosen so that the device size:PDA ratio is 2:1. In conical PDAs, the shortest length device is 'wedged' deep in the ampulla to fill the peak of the cone. The extensive use of Piccolo™ occluders may have contributed to the low rate of LPA stenosis. Kenny et al. published excellent ductal closure rates in an early study on Piccolo™ devices, with device deployment both from the arterial and venous side (98).

Piccolo™ devices can be delivered easily from the aortic side through a 4 French delivery catheter, which was the favourite approach in our study. PDA closure with occluders offers improved immediate closure, whereas unfavourable outcomes, such as residual shunt, embolisation and haemolysis can be seen

more often after coil closure (99-101). The availability of the Piccolo™ device had led to complete abandonment of coils for PDA closure at the study site.

The Piccolo™ device has been used successfully in extremely premature-born children since 2015 (35-37, 102). To our knowledge, this study is the most extensive single-centre study on Piccolo™ devices in a non-premature cohort. The Piccolo™ device was used with high success rates and low complication rates in both smaller and larger patients.

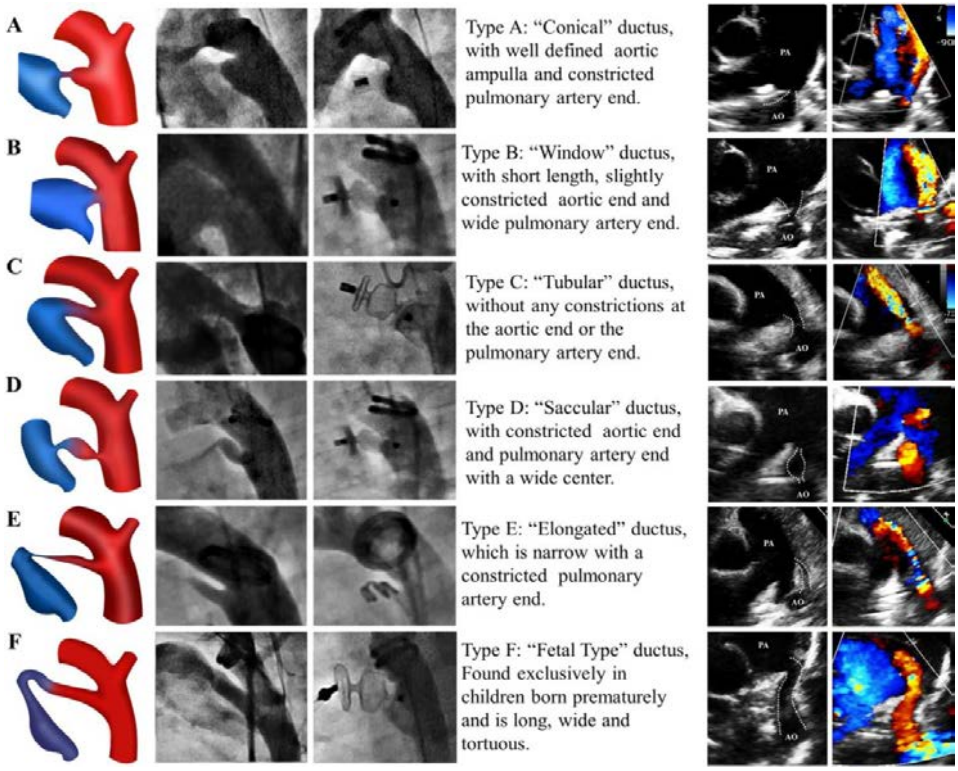

Figure 11. Angiographic classification of PDA according to Philip et al. (90)

	ADOII (N=298)	Piccolo (N=420)	AVPII (N=44)	Overall (N=762)
Sex				
Female	206 (69.1%)	270 (64.3%)	33 (75.0%)	509 (66.8%)
Male	92 (30.9%)	150 (35.7%)	11 (25.0%)	253 (33.2%)
Age (years)				
Mean (SD)	3.46 (4.07)	5.03 (4.53)	3.09 (7.74)	4.31 (4.66)
Median [Min, Max]	1.90 [0, 31.8]	3.50 [0, 24.9]	1.00 [0, 46.8]	2.60 [0, 46.8]
Missing	1 (0.3%)	0 (0%)	1 (2.3%)	2 (0.3%)
Weight (kg)				
Mean (SD)	15.8 (13.7)	20.5 (15.8)	11.4 (12.5)	18.1 (15.1)
Median [Min, Max]	11.4 [1.80, 84.0]	14.5 [1.20, 92.0]	8.00 [3.50, 67.0]	13.0 [1.20, 92.0]
Min. Diameter (mm)				
Mean (SD)	2.32 (0.479)	1.89 (0.378)	3.07 (0.663)	2.12 (0.538)
Median [Min, Max]	2.25 [1.30, 4.20]	1.80 [1.20, 3.50]	2.90 [2.00, 5.30]	2.00 [1.20, 5.30]
Length (mm)				
Mean (SD)	6.16 (1.43)	7.03 (2.42)	9.08 (2.98)	6.81 (2.24)
Median [Min, Max]	6.00 [3.20, 11.2]	6.50 [2.00, 15.2]	8.60 [4.50, 18.5]	6.30 [2.00, 18.5]
PDA Type (Krichenko)				
a	273 (91.6%)	238 (56.7%)	13 (29.5%)	524 (68.8%)
b	2 (0.7%)	0 (0%)	0 (0%)	2 (0.3%)
c	19 (6.4%)	158 (37.6%)	16 (36.4%)	193 (25.3%)
d	3 (1.0%)	7 (1.7%)	0 (0%)	10 (1.3%)
e	1 (0.3%)	13 (3.1%)	1 (2.3%)	15 (2.0%)
f	0 (0%)	4 (1.0%)	14 (31.8%)	18 (2.4%)
Complications				
embolized	2 (0.7%)	2 (0.4%)	0 (0%)	4 (0.5%)
LPA stenosis	4 (1.3%)	1 (0.2%)	1 (2.3%)	6 (0.8%)
None	292 (98.0%)	418 (99.5%)	42 (95.5%)	752 (98.7%)

Table 2. Patient demographics, PDA device characteristics and complications. Reused with permission from the publisher. Front. Cardiovasc. Med., May 2023.

Weight (kg)	Total count	Embolised	LPA stenosis
0–4	5	1 (20%)	0 (0%)
5–10	244	2 (0.8%)	2 (0.8%)
11–15	233	1 (0.4%)	1 (0.4%)
16–20	105	0 (0%)	1 (1%)
21–25	50	0 (0%)	0 (0%)
25–30	30	0 (0%)	1 (3.3%)
31–40	25	0 (0%)	0 (0%)
>40	70	0 (0%)	1 (1.4%)

Table 3. Complications by weight (in kg). Reused with permission from the publisher. Front. Cardiovasc. Med., May 2023.

4.3 Study III

A total of 261 GSO devices were implanted; one procedure had to be stopped due to an intraprocedural complication. Three device sizes were used: GSO 20 mm in four patients (3%), GSO 25 mm in 164 patients (62%) and GSO 30 mm in 93 patients (35%). In our study, all patients were treated with a GSO device, in contrast to the only two previously published studies on SDD after PFO closure, which used either the now discontinued Gore Helex occluder, the Amplatzer occluder (103) or the Amplatzer PFO occluder (104).

One hundred sixty-six patients were treated with VCD. Of these, 159 (96%) underwent SDD. Of the remaining 96 patients who were treated with figure-of-eight sutures, 87 patients (91%) underwent SDD. There was no statistically significant difference between these groups (p=0.1).

Seventeen patients (6%) developed atrial tachycardia (16 atrial fibrillation, one atrial flutter). No other arrhythmia complications were seen on follow-up. Nine vascular complications (eight minor bleeding and 1 arteriovenous fistula) occurred in nine patients (four ProGlide and five non-ProGlide), and there was no statistically significant difference between VCD and non-VCD (p=0.24).

There was no statistically significant difference in SDD rate between patients who received VCD and patients who did not.

A sub-analysis showed that patients > 40 years of age who received VCD had higher SDD rates. The reason for this could not be explored in the present study design; notably, this sub-group analysis should be interpreted cautiously as we had not designed it a priori.

While younger patients are generally healthier and have fewer comorbidities, age > 40 years may define a higher risk population for vascular complications, possibly getting greater benefit of VCD.

All patients in our study underwent PFO closure with conscious sedation and local anaesthesia. Postoperative nausea and vomiting (PONV) is a common adverse effect of general anaesthesia, affecting up to 80% of patients (105), and may prolong hospital stay. The major risk factor for PONV is the use of volatile anaesthetics. Performing an intervention with conscious sedation and local anaesthesia can possibly facilitate SDD by reducing the rate of PONV. An argued advantage of general anaesthesia with intubation is the possibility to perform transoesophageal echocardiography. In our study, ICE was used for imaging of the atrial septum in all cases, enabling procedures without transoesophageal echocardiography and general anaesthesia.

4.4 Study IV

All patients had successful device implantation. At a median follow-up of 18 (1–52) months, there were no complications related to the procedure. There were no cases of device embolisation, LPA stenosis, haemolysis or access-related complications. A significant residual shunt was seen in one patient initially and was not seen on follow-up nine months post-implantation. Initial residual shunting on early follow-up with Occlutech® duct occluder (ODO) devices has been seen in several past studies (93, 94, 106).

The study by Subramanian et al. described, in great detail, different ways of implanting the device closer to either the aorta or the pulmonary end, and how the ODO devices could be 'downsized' one or two sizes, compared with CDO devices. (94) The potential for downsizing of an ODO in combination with the slightly smaller retention disk compared with a CDO can argue for implantation of these devices even in small children, where space is limited. Patient and PDA characteristics in Study IV can be seen in Table 4. The median minimal PDA diameter was 3.6 mm. According to the instructions for use, 33% of these patients would have required an 8/6 or even 10/8 CDO with a retention disk of 12 or 16 mm, respectively. The smaller ODO retention disk of 11 mm can facilitate implantation in younger patients with a potentially smaller risk of aortic coarctation. The findings of this study are limited by the small sample size. However, the initial results indicate very good outcomes. These findings were consistent even in challenging settings, such as patients below 10 kg of BW or patients with very large ducts and pulmonary hypertension.

Sex	Age at cath (months)	Weight (kg)	PDA type	Minimal PDA diameter (mm)	Aortic Ampulla diameter (mm)	PA press mean (mmHg)
m	185	63,2	conical	4	14	15
m	9	6,5	conical	3	9.8	32
f	160	43,3	conical	3.8	11.6	11
m	11	6,9	conical	2.8	10.2	19
m	4	5,4	tubular	4.5	9.3	28
f	52.8	30	conical	3	13	20
m	10.5	6,3	saccular	3	8.7	23
f	18	8.6	conical	4.5	10.3	17
f	17	7.6	conical	4.5	9.5	18
m	32	17	saccular	2	8.5	15
f	153	36	conical	3.4	10.2	19
m	88	20	conical	3	10.8	18
f	41	15.2	conical	4	10.9	16
m	16	12	conical	3.5	9.5	14
f	6	4	conical	3.7	8.8	36
m	7	7.1	conical	4	10.4	40
f	4	4.5	conical	4	9.7	39
f	10	7.6	conical	3.7	10.1	28

Table 4. Patient, PDA and haemodynamic characteristics.

5 Conclusions

The risk that ionising radiation poses for young patients must not be ignored. In children, the risk of radiation-induced cancer is more relevant than the risk of skin lesions. Radiation surveillance and, subsequently, radiation reduction are critical topics in interventional cardiology.

The usage of ionising radiation has recently become the subject of more research. A European-funded project, Harmonic, has been set up to better understand the long-term health effects of medical exposure to ionising radiation in children.

Communication of this risk with patients and parents must not be overlooked.

Heart catheterisation techniques have developed substantially during recent decades and now play an essential role in paediatric and adult cardiology, both as diagnostic and –in particular – as therapeutic options. Interventional treatment has replaced cardiothoracic surgery for many different congenital heart defects, and ongoing improvement of devices and materials may enable use for additional indications or patient groups.

The development of new low-profile devices, such as the Piccolo™, has opened up the field of potentially transcatheter-amenable CHD and contributed to potential catheter-based interventions in patients as small as 700 grams. Due to the high variation in BW, from tiny newborns to adult-size patients, and anatomical variability, access to different device types and sizes is crucial for successful outcomes and to reduce complications.

Unfortunately, paediatric interventionists and their patients are currently struggling with the ongoing transition from the Medical Devices Directive to the Medical Device Regulation. During this transition, several devices and materials that have been available for decades have been taken off the European market.

Transcatheter interventions are high-tech, high-stake interventions, especially in smaller children, aiming to cure or palliate CHDs. Matching the patient's unique anatomy with a suitable device is of utmost importance. Close collaboration with the industry is necessary to have access to various devices – in contrast to our current situation, where we are losing devices and materials due to new regulations.

Randomised controlled trials are the gold standard for evaluating new interventions, using predefined protocols to minimise bias. However, such trials are rare and difficult to conduct in interventional paediatric cardiology.

A randomised controlled trial on PFO closure and VCDs would have been helpful to clarify the benefits of VCD further and reduce the risk of selection bias or confounding factors.

The use of VCD also needs to be studied further in paediatric populations. SDD is a concept that is probably highly appreciated by our small patients and their parents. Larger randomised controlled trials will be needed to study safety and efficacy in younger patients.

6 Points of perspective

6.1 Implication for clinical practice

The studies in this thesis suggest that transcatheter closure of persistent foetal cardiac shunts can be carried out with high success rates, low complication rates and reasonably low radiation doses. Further research will be needed to study, for example, VCD and SDD in paediatric patients.

6.2 Implication for future studies

Current ongoing research projects:

- Long-term neurodevelopmental follow-up of extremely premature-born children who underwent transcatheter PDA closure <3 kg of BW. Study site: Karolinska University Hospital, Solna.
- Validation of a novel method for non-invasive mixed venous oxygen saturation monitoring in anaesthetised children. Study site: Karolinska University Hospital, Solna.
- Outcome of coarctation-stenting with Bentley BeGraft aortic covered stents. Study site: Schneider Children's Medical Center, Tel Aviv.
- Participation in a study on three-dimensional aortic arch geometry and blood flow in neonates after surgical repair for Aortic Coarctation. Study site: Skåne University Hospital, Lund.
- Participation in a multicentre, international, prospective and retrospective study on PDA closure with ODO.

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9 Deutsche Zusammenfassung

Hintergrund

Das persistierende Foramen Ovale (PFO) und der persistierende Ductus Arteriosus (PDA) sind zwei der häufigsten angeborenen Herzfehler. Die Inzidenz des PFO liegt Studien zufolge zwischen 10 und 35 % (1, 2). Bei reifgeborenen Kindern wird ein PDA bei etwa 1 von 2000 Fällen diagnostiziert (3, 4). Der katheterinterventionelle Verschluss dieser angeborenen Herzfehler ist bei Kindern und Erwachsenen zum Standardverfahren geworden und hat die Operation dieser Herzfehler weitgehend ersetzt. Herzkatheteruntersuchungen erfordern ionisierende Strahlung und werden im Allgemeinen als Verfahren mit hoher Strahlendosis gemäß der europäischen Richtlinie 2013/59/Euratom (5) eingestuft.

Neue Methoden und Materialien haben die Ergebnisse und Sicherheit von Katheteruntersuchungen und Interventionen verbessert und die Krankenhausaufenthaltsdauer von Patienten, die sich dieser Verfahren unterziehen müssen, verkürzt. Bei der interventionellen Behandlung angeborener Herzfehler wird versucht die Strahlenbelastung so gering wie möglich zu halten, der Erfolg der Intervention ist trotzdem das oberste Ziel.

Zielsetzung

Ziel dieser Arbeit war es, die Ergebnisse und Komplikationen neuer Methoden bei Patienten zu untersuchen, die sich einer Herzkatheterisierung unterzogen hatten. Die eingeschlossenen Studien zielten darauf ab, neue Techniken zu evaluieren.

In Studie I wurde eine neue Methode zur Überwachung des Krebsrisikos bei Katheterisierungsverfahren eingeführt. Hierbei wird der Untersucher gewarnt, wenn die Strahlung ein bestimmtes Risikoniveau überschreitet.

In den Studien II und IV wurden die Ergebnisse und Komplikationen neuer Generationen von PDA Okkludern untersucht.

In Studie III wurden die Ergebnisse und Komplikationen von Patienten untersucht, die sich einem PFO-Verschluss mit dem Gore®Cardioform Septal Okkluder (GSO) unterzogen hatten. Weiterhin sollte evaluiert werden, ob die Entlassung des Patienten am selben Tag möglich war und ob eingriffsbedingte Komplikationen auftraten.

Methoden

Es wurden vier retrospektive Studien durchgeführt. In der ersten Studie wurden Daten von 238 pädiatrischen Patienten gesammelt und untersucht, wie hoch das Risiko ist, an strahlenindiziertem Krebs zu sterben.

In Studie II wurden die Daten alle Patienten analysiert, die sich über einen Zeitraum von vierzehn Jahren in einem großen medizinischen Herzzentrum in Tel Aviv einem PDA-Verschluss mit einem Amplatzer-Okkluder unterzogen hatten.

Studie III untersuchte alle Patienten, die sich zwischen März 2017 und Juni 2020 am Karolinska Universitätskrankenhaus in Stockholm einem katheterinterventionellen Verschluss eines PFO unterzogen hatten.

Studie IV umfasste alle Patienten, die sich in insgesamt drei europäischen Zentren im England, Frankreich und Schweden einem Transkatheter-PDA-Verschluss mit einem 5/7 Occlutech® Ductus Okkluder unterzogen hatten.

Ergebnisse

Mehr als 90 % der retrospektiven Studienkohorte in Studie I lagen im Bereich eines sehr niedrigen (1–10 von 100.000) oder niedrigen Krebsrisikoniveaus (1–10 von 10.000). Kein Patient überschritt das hohe Krebsrisikoniveau (> 1 von 100).

Darüber hinaus wurde ein neues Konzept alters- und geschlechtsspezifischer Risikoreferenzwerte im Zusammenhang mit dem Krebsrisiko der Bevölkerung eingeführt. Die Ergebnisse zeigten, dass die Risikoreferenzwerte für Jungen um den Faktor 2-3 höher war als die für Mädchen.

In Studie II zeigten alle Amplatzer-Okkluder sehr hohe Verschlussraten (>99,5 %) mit sehr wenigen Komplikationen wie Embolisierung des Okkluders oder Stenose der linken Pulmonalarterie (LPA). Mit dem Piccolo™-Okkluder wurde eine Tendenz zu noch geringeren Raten von LPA-Stenosen festgestellt. In dieser Studie trat keine Stenose im Bereich der Hauptschlagader auf. Die meisten Komplikationen (Deviceembolisierung und LPA-Stenose) traten bei Patienten mit einem Körpergewicht < 15 kg auf.

Studie III untersuchte die Entlassung von Patienten am Eingriffstag nach perkutanem PFO-Verschluss. 246 von 262 Patienten (94 %) konnten am selben Tag entlassen werden. Bei 166 (63 %) der Patienten wurde ein Perclose ProGlide™-System zum Verschluss des Leistenvenenzugangs eingesetzt.

Postinterventionelle Herzrhythmusstörungen wurden bei 17 (6 %) der Patienten und vaskuläre Komplikationen bei 9 Patienten (3 %) festgestellt. Es konnte kein statistisch signifikanter Unterschied zwischen Patienten, die Proglide erhielten (n = 159, 96 %) und Patienten, die kein Proglide erhielten (n = 87, 91 %, p = 0,10) festgestellt werden.

Achtzehn pädiatrische Patienten mit Herzinsuffizienz aufgrund eines PDA wurden retrospektiv aus drei Studienzentren in die Studie IV eingeschlossen. Elf der Patienten hatten ein Körpergewicht unter 12 kg und bei sieben der 18 Patienten wurde eine pulmonale Hypertonie festgestellt.

Alle diese Patienten konnten erfolgreich mit einem 5/7 Occlutech® Ductus Occluder behandelt werden. In dieser Studie konnten keine postinterventionellen Komplikationen gesehen werden.

Schlussfolgerungen

Verschiedene Aspekte der Herzkatheterisierung wurden in dieser Arbeit untersucht, Augenmerk lag dabei auf dem Strahlenrisiko, der Okkluderauswahl, Möglichkeit der Entlassung am Eingriffstag und den Verschlusstechniken der Leistenvene.

Der katheterinterventionelle Verschluss persistierender fetaler Shunts ist die Standardbehandlung bei reifen Kindern und Erwachsenen mit niedrigen Morbiditäts- und Mortalitätsraten. Die Entwicklung neuer Okkluder hat die PDA-Verschlussergebnisse verbessert, selbst bei kleinen Kindern mit großen PDAs.

Der PFO-Verschluss hat in den letzten fünf Jahren zugenommen, was auf mehrere randomisierte kontrollierte Studien zurückzuführen ist, die ein geringeres Risiko eines erneuten ischämischen Schlaganfalls nach einem PFO-Verschluss im Vergleich zur medikamentösen Therapie zeigten.

Herzkatheteruntersuchungen zur Behandlung von angeborenen Herzfehlern können mit akzeptabel niedrigen Strahlenbelastungen durchgeführt werden. Insbesondere bei der Behandlung jüngerer Patienten müssen das Risiko einer strahleninduzierten Krebserkrankung als auch strahlenreduzierende Maßnahmen berücksichtigt werden.

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