Pulmonary atresia with intact ventricular septum
epidemiology and outcome in children born in Sweden 1980-1999

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To the patients and their families

To understand Nature we seek Uniformity, but the rule of Nature is Variety

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Abstract

Aims: To describe children born with pulmonary atresia with intact ventricular septum (PA-IVS) in Sweden between 1980 and 1999, the incidence and outcome of PA-IVS, to examine cardio-pulmonary outcomes in survivors and to evaluate their quality of life.

Material and methods: Eighty-four subjects were identified. All available medical data were evaluated. Among 52 survivors, 29 underwent cardiopulmonary exercise testing and lung function tests at rest and 12 subjects underwent myocardial scintigraphy during exercise test and echocardiography at rest. A questionnaire concerning quality of life was completed by 42 subjects.

Results: The incidence was 4.2/100, 000 live births. Eight subjects had an Ebstein-like tricuspid ostium, 31 had a muscular pulmonary atresia and 40 had a membranous pulmonary atresia. Ventriculo coronary arterial communications (VCAC) were found in 36 subjects (43%). Follow-up time was 14 days to 20 years (median 6 years). Among 52 survivors 32 had biventricular repair and 20 univentricular palliation. The survival rate was 68% ten years after initial surgery. Exercise capacity was reduced, but subjects without VCAC and operated with biventricular repair had better exercise capacity than the others. Lung function was an independent predictor of exercise capacity. Nine of 12 subjects examined had myocardial perfusion defects during exercise, and these were associated with VCACs**.** Right ventricular function, as judged from echocardiography at rest, was impaired, while left ventricular function was normal or slightly impaired. Overall quality of life was similar to that of a healthy control group, but subjects with PA-IVS reported more psychosomatic symptoms.

Summary: PA-IVS is an unusual and heterogeneous congenital heart defect associated with high mortality during the first years of life. Membranous pulmonary atresia was associated with a better outcome than muscular pulmonary atresia with respect to survival, myocardial perfusion defects and exercise capacity. The majority of the survivors had biventricular repair. Overall quality of life was good.

Key words: pulmonary atresia with intact ventricular septum, ventriculo coronary arterial communications, biventricular repair, univentricular palliation, myocardial perfusion, myocardial function, cardiopulmonary exercise, lung function, quality of life, mortality, outcome

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List of publications

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

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II. Ekman-Joelsson B-M, Gustafsson PM, Sunnegårdh J. Exercise performance after surgery of pulmonary atresia and intact ventricular septum. In manuscript.

III. Ekman-Joelsson B-M, Berggren H, Boll A-B, Sixt R, Sunnegårdh J. Abnormalities in myocardial perfusion after surgical correction of pulmonary atresia with intact ventricular septum. Cardiol Young 2008; 18: 89-95.

IV. Ekman-Joelsson B-M, Berntsson L, Sunnegårdh J. Quality of life in children with pulmonary atresia and intact ventricular septum. Cardiol Young 2004; 14: 615-621.

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Abbreviations

PA-IVS	Pulmonary atresia with intact ventricular septum
RV	Right ventricle
LV	Left ventricle
VCAC	Ventriculo coronary arterial communications
TCPC	Total cavopulmonary connection
S-P shunt	Systemic to pulmonary shunt
SGA	Small for gestational age
Biv.rep	Biventricular repair
Univ.pall	Univentricular palliation
NYHA I-IV	Classification according to New York Heart Association, where I mean no limitation of activities and IV means that symptoms occur at rest, limitation of all activities

Glossary

Biventricular repair	Totally separated venous and arterial circulations in the heart
Univentricular palliation	The superior and inferior caval veins are connected directly to the pulmonary artery, bypassing the heart
S-P shunt	Insertion of a connection (for example an artificial vessel made of Gore-Tex®) between a systemic artery (a.subclavia/truncus brachiocephalica/aorta) and the pulmonary artery
Bidirectional Glenn	The superior vena cava is connected to the right or left pulmonary artery
One and a half ventricular repair	Bidirectional Glenn in combination with right ventricular outflow tract reconstruction
Homograft	Conduit, a valved formalin-prepared human vessel
Decompression of a ventricle	Opening of the atretic valve, relief of a high intraventricular pressure
Early death	Death within 30 days from surgery
Late death	Death occurring more than 30 days after surgery
Ventriculo coronary arterial communications	For description, see text page 10
Ebstein-like deformity of the tricuspid ostium	The septal leaflet of the tricuspid valve is partly bound down

Introduction

When I began my training in paediatric cardiology, I met a patient, a teenage girl, who regularly bicycled to school and lived an ordinary life, although she was born with pulmonary atresia with intact ventricular septum. When I searched for information about this heart defect, I encountered this statement: "it is worth emphasizing that survival to the age of one year does not imply that any of these babies will necessarily grow up having a normal existence" (Fyler et al. 1980). The statement conflicted with the condition of my patient and led me to undertake a survey about her heart defect. This survey turned into an investigation of the Swedish population of pulmonary atresia with intact ventricular septum born in the period 1980 - 1999.

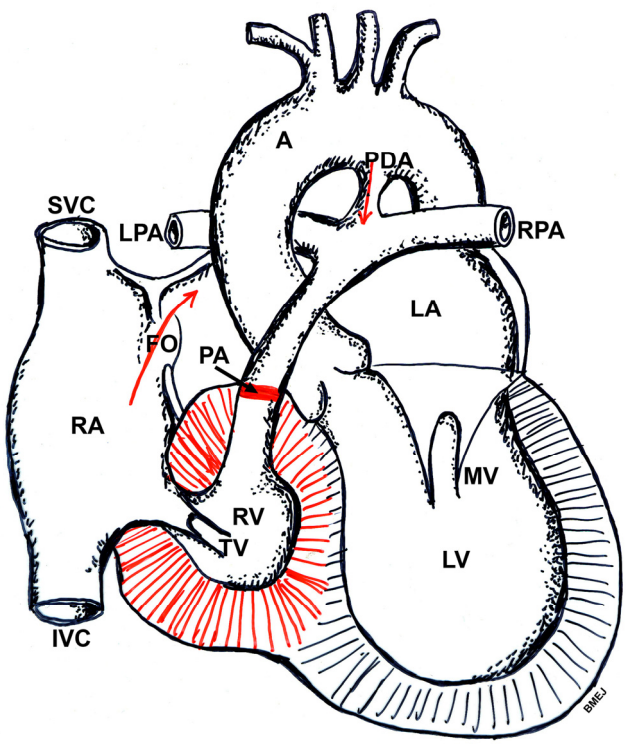

Figure 1. Pulmonary atresia with intact ventricular septum.
RA = right atrium, LA = left atrium, RV = right ventricle, LV = left ventricle, TV = tricuspid valve, MV = mitral valve, SVC = superior vena cava, IVC = inferior vena cava, PA = pulmonary atresia, LPA = left pulmonary artery, RPA = right pulmonary artery, PDA = patent ductus arteriosus, A = aorta, FO = foramen ovale.

Pulmonary atresia with intact ventricular septum (PA-IVS)

In PA-IVS (Figure 1), the valve between the right ventricle and the pulmonary artery is totally closed at birth (atretic) and there is no defect in the ventricular septum. The only communication between the heart and the pulmonary artery is the open ductus arteriosus. When the ductus arteriosus closes, usually during the first days of life, the baby will die unless there is an intervention. PA-IVS is characterised by a wide spectrum of malformations of the pulmonary valve and the right ventricle. In approximately 30-60 % of the cases there is the presence of malformed intracardiac vessels (ventriculo coronary arterial communications).

Pulmonary valve

The closed valve may be very thin and membranous with clearly identifiable valvular structures or it may be thick, overgrown with muscular tissue and without visible valvular structures.

Right ventricle

The cavity of the right ventricle may be dilated, normal sized, or diminutive, filled with muscular tissue and the myocardium usually present with various degrees of reduced contractility.

Ventriculo coronary arterial communications

In 30-60% of the cases there are malformed vessels between the right ventricular cavity and the coronary arteries, known as ventriculo coronary arterial communications (VCAC, see Figure 2). These malformed vessels may have an intraluminal narrowing, which often occurs at the point of connection between the VCAC and the coronary artery. There may even be an interruption between the coronary artery and the aortic root.

Right ventricular dependent coronary circulation

In PA-IVS, in the presence of a proximal stenosis in a coronary artery, some part of the myocardium may depend on the perfusion with the poorly oxygenated blood from the hypertensive right ventricle. The coronary circulation is then described as right ventricular dependent. A drop in the right ventricular pressure may then lead to myocardial infarction.

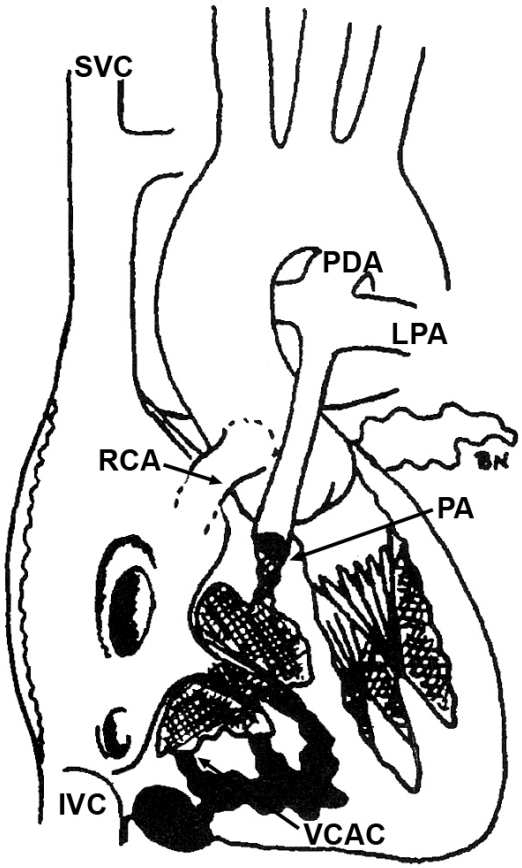

Figure 2. VCAC = Ventriculo coronary arterial communications RCA = right coronary artery, dilated from increased flow from the right ventricle, through the VCAC, PA = pulmonary atresia,, SVC = superior vena cava, IVC = inferior vena cava, PDA = patent ductus arteriosus, LPA = left pulmonary artery.

Background

A brief overview of history

PA-IVS has been recognised pathologically since 1783 (Peacock 1869). The natural history of subjects with pulmonary atresia with intact ventricular septum is bleak. Death occurs during the first days or weeks of life, when the ductus arteriosus closes. There are reports of survival into the third decade, thanks to a persistent ductus arteriosus, but such cases are extremely rare (Robicsek et al. 1966).

The history of congenital heart surgery

Cardiac surgery is an accomplishment of the twentieth century. The first reported successful case of cardiac surgery was the ligation of a patent ductus arteriosus in 1938 (Gross and Hubbard 1939). Another landmark for congenital heart surgery was in 1944 when A. Blalock performed the first subclavian-to-pulmonary artery shunt operation in a baby with inadequate pulmonary blood flow. Open heart surgery was first performed in a two-year-old boy by cross-circulation from the father in 1954. Since then, the technique of open heart surgery has had a tremendous development.

Development of surgery and intervention of the pulmonary valve

Successful surgery of the pulmonary valves started in 1946 when T. Sellors performed a valvotomy in a case of pulmonary stenosis, using a long tenotomy knife that passed through the right ventricle into the pulmonary artery (Sellors 1948). The transventricular approach became the standard approach until the development of open heart surgery. The technique of open heart surgery made it possible to approach the valve directly through the pulmonary artery. A landmark for treatment of the atretic pulmonary valve occurred when Ross and Somerville in 1966 described the insertion of an aortic homograft to bypass an atretic pulmonary valve. Since 1982 (Kan et al.), congenitally stenosed valves are treated by balloon catheter dilation, and since 1990 (Qureshi et al.1991) pulmonary atresia can be opened by radiofrequency perforation, using catheter technique.

Development of the technique of univentricular palliation

The development of the surgical technique for univentricular palliation began when W. Glenn in 1958 performed a cavopulmonary anastomosis, i.e. a con-

nection between the superior caval vein and the right pulmonary artery. In 1971, the French surgeons Fontan and Baudet (1971) described the atriopulmonary connection with the purpose of draining all the caval blood directly to the pulmonary circulation, without passing through the right ventricle. TCPC was described by de Leval et al. in 1988. The connection between the inferior caval vein and the pulmonary artery has been achieved using different techniques, for exampel. with an intracardiac tunnel consisting of pericardium or Gore-Tex®. This technique is still developing; and the extracardiac tunnel technique was introduced in Gothenburg by H. Berggren in 1998.

Development of imaging of congenital heart defects

One prerequisite for the development of heart surgery was the development of techniques for imaging of the heart. Before the era of imaging, the knowledge of cardiac anatomy and congenital heart defects was based on post-mortem examinations. The development of radiography opened the possibility of in vivo observations in early twentieth century, which began the era of heart catheterisation during the 1950s. However, heart catheterisation often required sedation and manipulation with catheters carries a definite risk, especially in the newborn. In the late 1960s I. Edler and N-R. Lundström introduced echocardiography for the evaluation of congenital heart disease, and this has provided a non-invasive, painless and risk free method for delineation of the structures in the heart (Lundström and Edler 1971). Today fetal echocardiography provides the possibility of performing serial examinations of the growing heart.

Development of pulmonary stenosis and atresia during and after pregnancy

Progression from a normal pulmonary valve to severe stenosis during fetal life, using echocardiography, was reported by Todros et al. 1988 and supported by observations reported from L.Allan 1988 and A. Galindo et al 2006. It is a well known fact that pulmonary stenosis can progress to pulmonary atresia after birth. (Sabiston et al. 1964). In 1989 D. Sahn, documented a case of acquired pulmonary atresia late in pregnancy, using fetal echocardiography (Freedom 1989). Since then there have been several observations of progression from pulmonary stenosis to pulmonary atresia in fetal life (Allan and Cook 1992, Daubeney et al. 1998, Sharland et al. 1991). In twin-to-twin transfusion during pregnancy, the recipient twin sometimes develops cardiac dysfunction and right ventricular outflow obstruction with no other signs of congenital heart defects. In an echocardiographic study of 73 pregnancies with the twin-to-twin transfusion syndrome, right ventricular outflow tract obstruction developed in six recipient subjects, among whom the pulmonary stenosis progressed to pulmonary atresia in four subjects (Lougheed et al. 2001). These findings show that pulmonary atresia can develop secondary to

a circulatory disorder during fetal life.

Reports of VCAC during pregnancy

There have been several reports of VCAC in fetal life, diagnosed using echocardiography and verified at autopsy. They have been documented as early as week 15 (Chaoui et al. 1997, Sandor et al. 2002, Arabin et al.1996, Maeno et al. 1999).

Normal heart development

The embryonic period

Human structural development takes place during the first eight weeks after conception. In obstetrics, gestational weeks are counted from the first day of the last menstruation, which means that two weeks are added to the age of the embryo. In the present description, the age of the embryo is used. During weeks three to eight there is a rapid development from an embryonic disc with three layers to a human being with a complete set of organs. This period is called the embryonic period and then the embryo is most vulnerable to major birth defects. The cardiovascular system is the first system to function (days 21 – 22), in order to meet the embryo's metabolic needs during development.

Cell migration to the heart

Cells from different regions contribute to the structures in the heart. There are two main sources: 1. proepicardial cells from the coelomic wall, i.e. the septum transversum or the liver, 2. ectomesenchymal neural crest cells from the neural crest.

Proepicardial cells migrate to the heart tube from day 21, covering the surface of the heart, from the caudal pole, moving in the cranial direction and, finally covering the outflow tract. They form the epicardium and the coronary arteries, including the endothelial lining and smooth muscle inside the coronary vessels.

Neural crest cells migrate to the branchial arches 3, 4, and 6, where they proliferate, develop arteries corresponding to the branchial arches and then migrate to the heart. In the heart they contribute to the outflow tract, including the outflow cushions (future semilunar valves) and they also develop the innervation of the heart.

The development can be summarised in five steps (Table 1, Figure 3):

I. Fusion of the myocardium and the endocardium in the ventral midline to form a simple tubular heart and onset of peristaltic function, which is completed by the end of the third week (days 21-23). Blood flow is now established within the embryo and peristaltic waves of contractions are seen in the developing heart.

II. Looping to the right side. The simple heart tube is connected to the paired dorsal aortie passing through the embryo. During rapid growth of the embryo the tube rotates (forming an s-like structure) to the right side. This is completed by day 28.

III. Chamber specification and beginning of septation. The chambers are specified and the interventricular septum starts growing from the caudal end of the heart. At the same time, the complex development of the atrial wall begins. This takes place on days 27 to 42. Each branchial arch in the embryo is supplied by an artery, called an aortic arch. There are six such arteries and they are connected to the outflow tract in the heart. They appear by day 28, and continue to change and remodel until day 35. Parts of the future aorta, the pulmonary artery and the ductus arteriosus (the fourth aortic arch) develop from these structures. The development and function of the ductus arteriosus is crucial to the blood flow after septation, connecting the outflow from the right ventricle to the aortic arch. In the outflow channel, closest to the heart, a spiral-shaped wall starts to grow, dividing the shared vessel into two separate arteries (the future pulmonary artery and aorta). This takes place days 35-42.

IV. Development of coronary circulation, specialised conduction tissue and innervation. The coronary vessels develop relatively late in the embryological period, days 48-51. They develop from epicardial cells from the liver, which invade the muscle from the surface. The last step of development of the coronary vascular system is ingrowths of vessels from the aorta (sinus valsalva), and this is completed by the end of septation. Primitive nerve cells appear during week six, and maturation continues throughout pregnancy. The conduction system originates from myocardial cells close to vessels. Conduction tissue has been documented on day 35, and development continues throughout pregnancy.

V. Valves. A late step in the morphological heart development (day 42 and continuing throughout pregnancy) is sculpting of the valve leaflets at the atrioventricular and ventriculoarterial junctions. The atrioventricular valves are formed by cavitation of the mesenchyme at the atrio-ventricular junction. The semilunar valves grow from the walls of the vessels (endocardial cushions) when the spiral-formed wall has divided the shared canal into two arteries. The development of the semilunar valves starts just before septation is completed, and the histogenesis continues into the postnatal period. The growth of the valves is characterised by cell proliferation in the tissue lining

the walls in the vessel, in interaction with a continuous blood flow. Shear stress may play a role in the remodelling of the cusps, as interference with blood flow alters endothelial morphology and causes malformations of the aortic valve leaflets.

Septation completed. When the outflow tract has developed into two arteries at the proper places, the upper membranous part of the ventricular septum closes. This completes the septation at approximately day 53. The blood stream is now definitely divided into two flows: one through the right ventricle - the pulmonary artery - the lungs - the ductus arteriosus and to the lower part of the forming body and one through the left ventricle - the aorta - to the coronary arteries and to the upper part of the body.

(Kirby 2007, Sadler 2000, Moore-Persaud 1998, Gittenberger-de Groot A, Dept Anatomy and Embryology, Leiden University Medical Center, NL, personal communication, 2008).

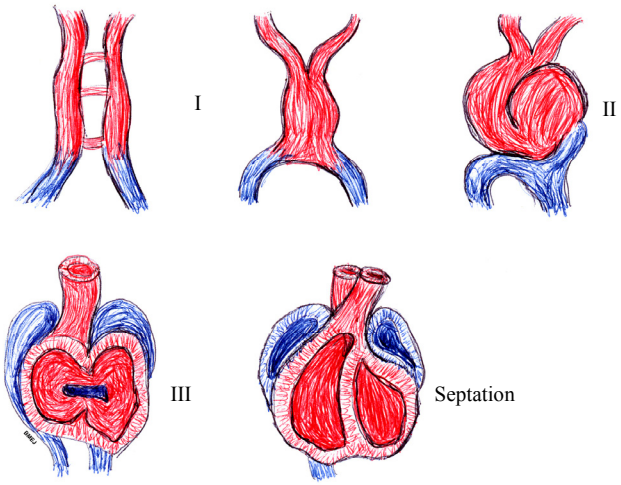

Figure 3. Normal heart development. Step I, II, III and septation completed.

Table 1. Normal heart development

Step		Mechanism	Cell origin	Time (day nr)
I	**Tubular heart**	Enclosure of enodocardium by myocardium, formation of cardiac jelly		17-22
		Onset of peristaltic function		23
II	**Looping to the right side**			23 - 28
III	**Chamber specification**			27 - 37
	Aortic arches appear and remodel		Neural crest and second heart field	28 - 35
	Muscular septum	Formation by outgrowth of ventricular cavities (ballooning)	Myocardium	27 - 37
	Atrial septum		Myocardium of second heart field mesenchyme	27 - 37
	Outflow tract septation	Spiral-formed wall	Neural crest, endocardial cushions, myocardium	35 - 42
IV	**Coronary circulation**	Ingrowth of epicardial cells, from surface	Proepicardial cells	48 - 51
	Innervation	Ingrowth	Neural crest cells	49 - birth
	Conduction tissue	Differentiation of myocardial cells, close to the vessels	Myocardium	35 - birth
V	**Intracardiac valves**			42 - postnatally
	Atrioventricular valves	Excavation and flow remodeling	Endocardium and epicardium derived cells	42 - week20
	Semilunar valves	Endocardial cushions are excavated and remodeled by flow vessel	Mesenchyme Endoderm, neural crest	44 - 72
	Septation completed	Closure of membranous interventricular septum that is fusion of atrioventricular and outflow tract cushions	Endocardial cushions and possibly epicardium derived cells	49 - 53

Sources: Kirby 2007, Sadler 2000, Moore-Persaud 1998, Gittenberger-de Groot 2008.

The morphological insult in PA-IVS

The structural development of the heart follows a strict order. The normal development at a certain point in time is crucial for the subsequent normal development to continue. Experiences from other structural defects, e.g. malformations from thalidomide taken by mothers during pregnancy, show that the time of the injury is crucial to the outcome (the same agents can cause different defects at different points in time). In PA-IVS, all major structures in the heart are fully developed and in the majority of cases the pulmonary valve consists of three fused cusps, the pulmonary trunk has a normal size and the morphology of the ductus arteriosus is normal (Kutsche et al.1983). In a study of the morphology of the ductus arteriosus in newborns with PA-IVS compared to the ductus arteriosus in newborns with pulmonary atresia *with ventricular septal defect*, the inferior angle of the ductus arteriosus was normal in all but one subject with PA-IVS (suggesting a forward flow in fetal life) but acute in all with a pulmonary atresia with a ventricular septal defect (suggesting a retrograde flow in fetal life) (Santos et al. 1980). In the single subject with PA-IVS and VCACs with a small right ventricle the angle was acute. The authors concluded that the atresia in subjects with PA-IVS occurred later than in the subjects also having a ventricular septal defect, and that there had been a forward flow from the right ventricle to the pulmonary artery at some time duringfetal life. The authors also suggested that there is earlier closure of the valve in the case of coexistence of VCACs, and a small right ventricle (Santos et al.1980). The conclusion that the pulmonary atresia in PA-IVS is an acquired, secondary process, occurring at variable times during pregnancy was suggested as early as in 1908, and this notion has been supported by several authors and reports (Abott 1908, Santos et al. 1980, Kutsche et al. 1983, Freedom 1989, Lougheed et al. 2001, Sandor et al. 2002). Most of these authors speculated on an *inflammatory process* as the primary disorder, although there were no histopathological signs of any panmyocardial process (Abbott 1908, Freedom 1989, Kutsche et al. 1983). An inflammatory process occurring relatively late did not explain the coexistence of ventriculocoronary arterial communications (Freedom 1989).

Reduced blood flow through the pulmonary valve has been observed during the development of atresia, both during and after fetal life. Reduced blood flow across the pulmonary valve may be a result of diminished forward flow from the right ventricle or of impeded flow from the pulmonary trunk to the aorta via the ductus arteriosus. Theoretically, reduced forward flow can be attributable to severe tricuspid malformation causing regurgitation, to cardiomyopathy or to a competing outflow path. Severe malformation of the tricuspid valve leading to severe regurgitation has been reported in subjects with pulmonary atresia with intact ventricular septum (Anderson et al.1990, Daubeney et al. 2002). The development of right ventricular outflow tract obstruction in twin-to-twin transfusion is considered secondary to cardio-

myopathy (Lougheed et al. 2001). Gittenberger-de Groot has suggested that the development of pulmonary atresia was secondary to a reduced flow through the valves due to a competing pathway through VCACs from the right ventricle (Gittenberger-de Groot et al. 2001). Diminished ductal flow would also reduce the blood flow through the pulmonary valve, and there have been reports of stenoses of the pulmonary arteries at the site of the ductal insertion (Kutsche et al. 1983, Moon-Grady et al. 2007, Elzenga and Gittenberger-de Groot 1986). The mechanism is thought to be constriction of ductal tissue within the pulmonary artery, i.e. as in coarctation of the aorta.

Theories about development of VCAC

The traditional explanation to the presence of VCAC is the abnormal persistence of the ventriculo-coronary communications normally found in avian embryonic hearts. It is thought that the high pressure in the right ventricle, due to the pulmonary atresia would keep these communications patent (Bull et al 1982, Dusek and Duskova 1975). Some studies of human embryonic hearts show that communications between the right ventricle and the coronary arteries are not seen normally (Hutchins et al 1977). There is evidence of two different vascular abnormalities in the right ventricle in pulmonary artesia and intact ventricular septum: VCAC consisting of coronary vasculature that connects abnormally to the ventricular lumen, and myocardial sinusoids consisting of dilated intramyocardial spaces due to high pressure (Gittenberger-de Groot et al 2001). The origin of the coronary arteries is the epicardium and not, as previously thought intertrabecular spaces (Poelmann et al 1993, Gittenberger-de Groot et al 2001, Kirby 2007). The presence of VCAC has been suggested to be due to abnormal migration of the coronary arteries, leading to a blood flow through the malformed vessels, thus reducing the blood flow through the pulmonary valve.The reduced flow itself causes a stenosis of the pulmonary valve and this progress to atresia. (Gittenberger-de Groot et al 2001). There is a case report of VCACs in a newborn baby with critical pulmonary valve stenosis, which suggests that the malformed vessels may appear before the pulmonary atresia (Bonnet et al 1998).

Aetiology of the pulmonary atresia with intact ventricular septum

There is no evidence that any specific genetic defect or any specific environmental influences are the causes of PA-IVS. It has been said that “Heart development is an interaction of genes, environment and chance” (Rose and Clark 1992). “Most congenital heart abnormalities fall within the category of a multifactor background, implying involvement of both genetic and environmental factors. This explains the variable expression of the severity of the malformations encountered within families with the same genetic background. In order to understand the pathogenesis of congenital heart disease, it is convenient to group the malformations in clusters that might involve com-

mon mechanism" (Gittenberger-de Groot A, Dept Anatomy and Embryology, Leiden University Medical Centre, NL, personal communication, 2008).

Treatment strategies in PA-IVS

At birth, the only communicating vessel for the blood flow to the pulmonary circulation is the ductus ateriosus, and when ductal closure occurs some sort of intervention is necessary for survival. There are three ways to secure the pulmonary circulation: to temporary keep the ductus arteriosus open by infusion of alprostadil (Prostivas®), to connect the aortic artery to the pulmonary artery with a shunt (an artificial vessel made of Gore-Tex®) known as a systemic-to-pulmonary shunt, or to open the pulmonary valve by surgery or catheter intervention (radiofrequency perforation). The choice of surgical approach varies among heart centres, but there are two principal possibilities; to plan for biventricular repair or to plan for univentricular palliation.

Biventricular repair

When the aim is biventricular repair the pulmonary valve is opened. This can be achieved by radiofrequency perforation using catheter technique or by surgical valvotomy. Biventricular repair provides a pulsatile blood flow through the lungs. The function of the right ventricle is often compromised at birth. When the pulmonary valve is opened, the right ventricle is not always able to provide the pulmonary circulation with enough blood. In this case the valvotomy initially has to be combined with a persistent opened ductus arteriosus or insertion of a systemic-to-pulmonary shunt. After relief of the high pressure, the right ventricle will gradually perform better and the ductus arteriosus or the shunt can be closed. Blood flow through a hypoplastic right ventricle can lead to an increase in its size. The pulmonary valve has a tendency to restenose or not to grow. Repeated surgery is then often necessary. This may include outflow tract reconstruction with or without insertion of a homograft.

Univentricular palliation

In univentricular palliation (total cavopulmonary connection or Fontan circulation, see Figure 4) in subjects with PA-IVS, the right ventricle is not incorporated into the circulatory system. The venous blood passes directly to the pulmonary artery, through the superior and inferior venae cavae, without passing through the pumping heart. This is usually accomplished with three different procedures at different ages; first insertion of a S-P shunt (the first days of life), second a bidirectional Glenn procedure (usually at 6 months of age) connecting the superior vena cava to the right pulmonary artery and third connecting the inferior vena cava to the pulmonary artery with a tunnel

made of Gore-Tex® (usually at three to five years of age). The Gore-Tex® tunnel can be situated intra- or extracardially. In univentricular palliation the lungs are provided with a continuous non-pulsatile blood flow, in part dependent on the intrathoracic pressure variations during breathing.

One and a half ventricular repair

In some cases, sometimes after biventricular repair, it might become apparent that the right ventricle is unable to support the entire pulmonary circulation. Then a one and a half ventricular repair may be an alternative to univentricular palliation. The superior vena cava is then connected to the right pulmonary artery in a bidirectional fashion, and the lungs continue to be provided with a pulsatile blood flow through the open right ventricular outflow tract.

VCAC

The VCACs can be left without treatment, closed using a catheter technique or surgically ligated, depending on size and occurrence of coronary artery stenosis.

Considerations of surgical approaches

As there is a wide spectrum and various combinations of these three malformed structures (the pulmonary valve, the right ventricle and VCACs) the choice of surgery is not always self-evident and combinations of surgical procedures may be required. The treatment strategies vary in different institutions. In most centres the choice of surgery is based on the size of the right ventricle and/or the dimensions of the tricuspid valve, the anatomy of the pulmonary valve, and the presence and delineation of VCACs (Bull et al 1982, de Leval et al 1982, Giglia et al 1992, Rychik et al 1998, Syamasundar 2002,). Some centres, however, report successful outcome after insertion of a right ventricular outflow patch even if the right ventricle is very hypoplatsic (Steinberger et al 1992).

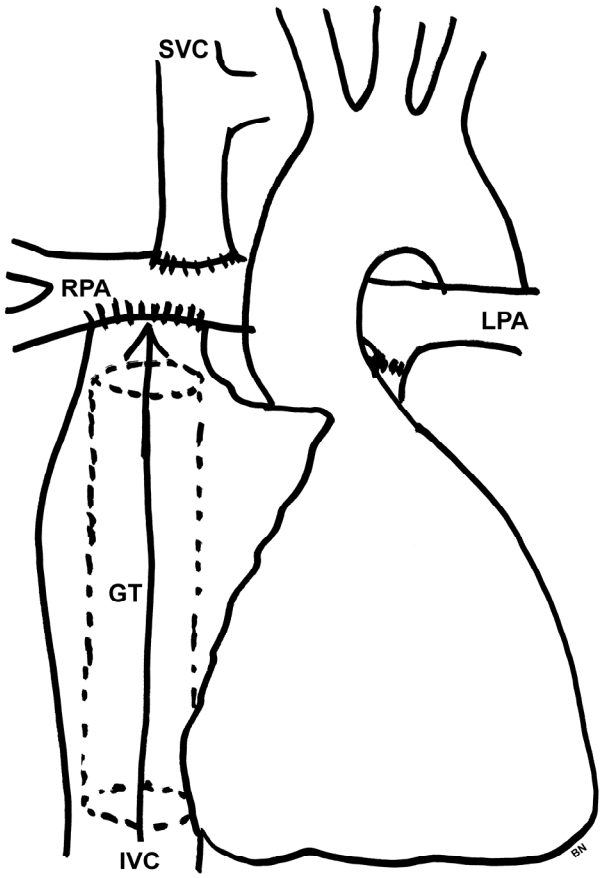

Figure 4. Total cavopulmonary connection (TCPC). RPA = right pulmonary artery, LPA = left pulmonary artery, SVC = superior vena cava, IVC = inferior vena cava, GT = Gore-Tex® tunnel.

Study

Aims of the study

The overall aim was to describe all the children born with pulmonary atresia with intact ventricular septum in Sweden between 1980 and 1999.

The specific aims were:

To study the incidence of PA-IVS during this period, the anatomical variations at birth, the choice of surgery performed, the mortality, and the long-term outcome. (Paper I)

To determine the exercise capacity as compared with healthy children, its relationship to surgical management, in terms of biventricular repair or univentricular palliation, and to study the pulmonary function. (Paper II)

To study myocardial perfusion at exercise, to see if perfusion defects relates to anatomical defects and/or choice of surgery and to study myocardial function at rest. (Paper III)

To assess the quality of life as compared with a healthy group of children from the general Swedish population. (Paper IV)

Material

Study population

(See Table 2)

Epidemiology (Paper I)

A total of 84 children (37 females) with PA-IVS were born in Sweden from 1980 (January 1) to 1999 (December 31), giving an incidence of 4.2/100,000 live births. The patients were identified using the Swedish National Registry of Congenital Malformations and the local registries at paediatric cardiac centres. The identified population forms the basis for this thesis and is analyzed in paper I.

Cardiopulmonary exercise test (Paper II)

A total of 66 children (30 females) with PA-IVS were born in Sweden between 1980 (January 1) and 1995 (December 31). Children born during this time period were older than nine years of age, and were therefore considered old enough to complete the study. Thirty-nine of 66 subjects were still alive and of them 35 were asked to participate. Four subjects were not asked to participate: one was pregnant, one had leukaemia, one had psychological problems, and one was mentally retarded. Another eight subjects declined participation for non-medical reasons, they were all doing well according to the classification of NYHA and the morphology and outcomes were similar to the participants of the study. The results of exercise tests in the 27 index subjects were compared with those of 28 age- and sex-matched healthy volunteers.

Myocardial function and perfusion (Paper III)

Eighteen subjects (8 females) with PA-IVS were born in the western part of Sweden between 1980 and 1994, and they constituted the initial cohort of the study in paper II. We asked all 13 surviving subjects to participate. Of them, one boy with biventricular repair without presence of VCAC declined participation for non-medical reasons. Thus, 12 accepted the invitation (7 females). The time since the last operation varied from 4 to 15 years, with a median of 5.5 years.

Quality of life (Paper IV)

All 52 subjects still alive in December 1999 were asked to participate in a study on quality of life. The respondents consisted of 42 subjects (23 females), aged 1-20 years (median 8.5). A total of 29 subjects were reported to live according to NYHA I, six NYHA II and two NYHA III (five unclassified). The group of non-respondents consisted of 10 subjects (1 female), aged 1-16 years of age (median 5.5). The morphology of the heart defects and the outcomes were similar to those of the group of respondents.

The healthy group consisted of 1856 subjects and was a random sample of subjects aged 2-18 years, drawn from the population register in Sweden in 1996. (Berntsson, 2000).

Table 2. Subjects. Papers I - IV

The cohorts of all studies are derived from the cohort of Paper I. Number of subjects, demographic data, of particpants, surgical outcome of participants.

Paper	Initial cohort n	Deaths n		Participants n	Age at study years (median;range)		Biv. rep. n	% of survivors with biv. rep.		Univ. pall. n
I	84	32	VCAC	84 36 (43%)	5 (0 -20)	VCAC	32 5 (16%)	62	VCAC	20 14(70%)
II	66	27	VCAC	27 9 (33%)	13 (9-24)*	VCAC	16 2 (12%)	59	VCAC	11 7(64%)
III	18	5	VCAC	12 4 (33%)	11 (6-18)*		5	42	VCAC	7 4(57%)
IV	84	32	VCAC	42 15 (36%)	8.5 (1-20)		26	62		26

Biv. rep. = biventricular repair, Univ. pall. = univentricular palliation, VCAC = ventriculo coronary arterial communications. * Subjects younger than 6, respectively 9 years of age were excluded.

Methods

Epidemiology (Paper I)

Study design

Medical records were studied, with a focus on perinatal conditions, diagnostic procedures, type of surgery, mortality, and physical condition at follow-up. Forty-one of the 48 preoperative angiocardiographic examinations and 68 of the 79 preoperative echocardiographic examinations were available for review.

Classification of the morphology

The cardiac morphology at presentation was described using all available information from angiocardiograms, echocardiograms, surgical records, and autopsy findings. The size of the right ventricle, tricuspid ostium, pulmonary ostium, pulmonary trunk and pulmonary arteries were estimated as dilated, normal, hypoplastic, or severely hypoplastic. In the echocardiographic examinations, the length (from the apex to the medial junction of the atrioventricular valve), the width (the largest diameter) of the right ventricle in apical and subcostal views, and the diameters of the tricuspid and pulmonary valve rings at the short axis were measured in late diastole and reported as a mean of three to five consecutive beats. The size was considered normal if the right ventricle was greater than 15 x 15 mm, hypoplastic if it was smaller than 15 x 15 mm, or severely hypoplastic if it was smaller than 10 x 10 mm. The pulmonary ostium was judged to be small if the diameter was less than 8 mm, the pulmonary trunk if the diameter was smaller than 10 mm, and the pulmonary arteries if the diameter was less than 4 mm. The size of the tricuspid ostium was reported as z-scores, as described by Hanley et al. 1993. The right ventricle was considered tripartite if there was an inflow tract, a trabecular part, and an infundibulum, bipartite if two of these components were present and monopartite if the inflow tract was the only part of the ventricle present. The pulmonary atresia was described as membranous when it consisted of a thin imperforate membrane, and as muscular when there were varying degrees of muscular overgrowth in the infundibular part, as described by Anderson et al. 1991.

Fistulous communications between the right ventricle and the coronary arteries were classified as VCAC. The coronary circulation was considered right-ventricular dependent if:

1. autopsy showed stenosis of the proximal part of the coronary arteries and

myocardial infarction,
2. VCAC were present in combination with high pressure in the right ventricle and the child died when the right ventricle was decompressed without any other obvious cause of death,
3. if myocardial infarction occurred after ligation or coiling of VCAC (Coles et al. 1989).

Possible risk factor for death
Factors considered possible risk factors associated with death were birth weight, body surface area, sex, size of the pulmonary valve, tricuspid ostium, right ventricle and the pulmonary trunk in mm, occurrence of membranous or muscular pulmonary valve, subjective estimation of size of the right ventricle, composition of the right ventricle, presence of VCAC, the different surgical procedures and age at surgery.

Cardiopulmonary exercise test (Paper II)

Study design
All subjects were interviewed about their current health status by the same investigator, who also performed the physical examinations (B-M Ekman-Joelsson). All subjects performed spirometry before the exercise test, and the index subjects also underwent more extensive lung function tests.

Exercise test
Exercise testing was performed in the upright position using a calibrated cycle ergometer (Sensor Medics ergometrics 800S, SensorMedics, Bilthoven, The Netherlands). The starting workload was one watt per kilogram body weight. The test began with a two-minute baseline recording, with the subject sitting on the cycle ergometer. The workload was then increased continuously at a rate of 10 W/min. The subject wore a nose clip and breathed through a flow meter to which a sample line for gas analysis was connected. O_2 and CO_2 were measured continuously for breath-by-breath analysis of oxygen uptake ($V'O_2$) and carbon dioxide production ($V'CO_2$) (V-max 229, Sensor Medics, Bilthoven, The Netherlands). A 12-lead electrocardiogram was obtained at rest and monitored throughout exercise and until four min after exercise. Blood pressure was measured every 2-4 minutes, using a standard blood pressure cuff on the left arm unless a left sided Blalock-Taussig anastomosis had been performed. Arterial blood oxygen saturation was measured continuously using a pulse oximeter with the probe on a finger (Oximeter®, Radiometer, Copenhagen, Denmark). Transcutaneous measurements of PO_2 ($tcPO_2$) and PCO_2 ($tc\ PCO_2$) were recorded on the volar aspect of the fore-

arm. All subjects were encouraged to exercise until exhaustion.

Lung function tests

Spirometry and static lung volumes were measured with the Master Screen Body System (Eric Jaeger, Würzburg, Germany). The diffusion capacity for carbon monoxide (D_{LCO}) was assessed using the single-breath technique, with the same system. The tests were undertaken in accordance with the ERS/ATS standards (MacIntyre et al. 2005, Miller et al. 2005, Wanger et al. 2005). The single-breath vital capacity N_2 washout test (P.K. Morgan Kent, UK) was used to determine ventilation distribution from the phase III slope of N_2.

Transcutaneous (Tc) blood gases

$TcPO_2$ and $tcPCO_2$ were monitored using a TCM3® (Radiometer, Copenhagen, Denmark). The electrodes were placed on the volar aspect of one forearm. The temperature of the $tcPO_2$ electrode was 45^{o} C, and the instrument was calibrated by one-point calibration in air. The temperature of the $tcPCO_2$ electrode was 43^{o} C, and the instrument was calibrated by one-point calibration against 5% CO_2. All values were corrected to 37^{o} C and for ambient pressure. At least 20 min were allowed to stabilise $tcPO_2$ and $tcPCO_2$. This method has previously been validated in our laboratory, both in healthy subjects and subjects with chronic disease. (Holmgren and Sixt 1992, Lagerkvist et al. 2003, Strömvall-Larsson et al. 2004). In further calculations, arterial PO_2 (PaO_2) was assumed to be $tcPO_2$ plus 1.3 kPa and $PaCO_2$ was calculated as $tcPCO_2$ minus 0.6 kPa (Holmgren and Sixt 1992).

Data analysis

The results from the cardiopulmonary exercise test were compared with those from the healthy control group using regression analysis taking height, sex and age into consideration (Wasserman 2005, Jones et al. 1989, Davis et al. 2002). Maximal work load was defined as the oxygen uptake when the respiratory exchange ratio (RER) was above 1.0, the V′E/V′O2 was above 30 and the respiratory rate was more than 40 breaths/min.

Spirometry, lung volumes and N_2 phase III slope values in subjects up to 20 years of age were related to previously published reference equations from our laboratory (Solymar et al. 1980). For D_{LCO}-analysis, the reference equations of Paoletti et al. 1985 were used for comparison. In the adult patients, Swedish reference values were used for lung volumes and spirometry (Hedenström et al. 1985, Hedenström et al. 1986). For D_{LCO} analysis, the reference equation of Salorinne (1976) was used, and for the N_2-slope we used the reference equation of Sixt et al. 1984. Lung function was expressed as z-scores, which were calculated as ([measured value-predicted value]/RSD), where RSD is residual standard deviation for the reference population, and

the resulting z-scores were used in the statistical analyses.

The anatomical dead space (2.5 ml/kg body weight/breath) and the dead space of the equipment were subtracted from each breath before calculation of the physiological dead space. The alveolar PCO_2 was assumed to be equal to the $tcPCO_2$, minus 0.6 kPa. As the correlation between the true arterial PCO_2 and $tcPCO_2$ is less reliable at rest, only peak values were included (Strömvall-Larsson et al. 2004). The physiological dead-space-to-tidal-volume ratio (V_D/V_T) was calculated using the following equation:

$$V_D/V_T = (Pa\ CO_2 - P_ECO_2)/Pa\ CO_2,$$

where V_D denotes dead space volume, V_T denotes tidal volume, and P_ECO_2 denotes the CO_2 partial pressure in mixed expired gas. Alveolar ventilation ($V'A$) was calculated using the equation:

$$V'A = V'E - V'D,$$

where $V'E$ is minute ventilation and $V'D$ is dead space ventilation.

Possible predictors of peak oxygen consumption in the patient group

Demographic variables, functional class according to the NYHA, actual myocardial function age at surgery, time since surgery, type of surgery, complications, cardiac anatomy at birth, variables from the cardiopulmonary exercise test and pulmonary function were all evaluated for the prediction model. Clinical history, neonatal echocardiographic and angiocardiograhpic data were derived from a previous study (Paper I). Updated information on cardiac function was derived from medical records.

Myocardial function and perfusion (Paper III)

Study design

All children underwent a thorough clinical examination, electrocardiography, transthoracic echocardiography at rest, exercise test and myocardial perfusion scintigraphy at exercise test. The medical records were studied, focusing on anatomical defects and surgical methods.

Exercise test and myocardial scintigraphy

All children performed cycle ergometer tests on two consecutive days. The workload was increased in a stepwise manner by 10 watts per minute. A standard 12-lead electrocardiogram was recorded at rest and during exercise. The first exercise test was used to identify performance ability. The exercise test was interrupted at the work load where it was impossible to push the child further. During the second exercise test, technetium Tc-99m tetrofosmin

at a dose of 120-190 MBq per m^2 body surface area was injected at a sub-maximal work load, 10 watts lower than the maximum work load obtained the day before. The exercise test was then continued for at least another minute after injection. The child was given ice cream right after the exercise in an attempt to reduce the uptake of radioactivity in the liver, while waiting for the imaging to take place. The time period between the injection and the imaging was at least 30 minutes.

For acquisition, a triple-head gamma camera (Picker Prism 3000) was used, fitted with low energy high resolution or low energy ultra high resolution parallel hole collimators. The machine was running in a continuous mode over 360 degrees, with 3 degrees per projection, and a total acquisition time of 20 minutes. Data were reconstructed with correction for attenuation using the standard 3-dimensional post filtering algorithm.

Data analysis

Myocardial scintigraphy

The scintigrams were analysed for perfusion defects in a semi-quantitative manner, classifying the perfusion as normal, scored zero, and slightly, moderately, or severely reduced, scores as 1 to 3. The perfusion defects were described as located in the apical or basilar parts of the ventricular septum or left ventricular free wall. As there are limitations to studying the right ventricular wall with perfusion scintigraphy, and as the right ventricle is often small and has a bizarre shape in this particular group of patients, it was not included in the analysis.

Echocardiography

All patients were examined with transthoracic and Doppler echocardiography in the supine position by one investigator (B-M Ekman-Joelsson). The studies were performed using an Accuson 128XP with 3.5 MHz and 5 MHz transducers. Global systolic function was evaluated using two methods; LVEF was calculated from the algorithm of the biplane method of discs or modified Simpson's rule and at a visual estimation. For measuring the ejection fraction according to the biplanar method, images were acquired from the apical four chambers and apical two chamber views, tracing the endocardial borders, excluding the papillary muscles and moderator band. The calculated ejection fraction was classified as normal if it was more than 50% (scored 4), slightly reduced 49-35 % (scored 3), moderately reduced 34-21 % (scored 2) and severely reduced if below 20% (scored 1).

A visual estimate of the function, from four standard planes (parasternal, long and short axis, apical four-chamber view and apical two-chamber view) was performed according to accepted clinical standards, classifying the function in four degrees: normal (4), slightly reduced (3), moderately reduced (2) and

severely reduced (1) (Mueller et a.l 1991, Helbing et al. 1994, Nishimura et al. 1993). In patients with biventricular repair the global right ventricular function was studied using calculations according to the biplanar method and a visual estimation as described above. The calculated ejection fraction was classified as normal if it was more than 45% (scored 4), slightly reduced 44-30 % (scored 3), moderately reduced 29-20 % (scored 2) and severely reduced if ejection fraction was below 20% (scored 1). Wall motion was analysed on two-dimensional images of the apical four chambers, apical two chambers, parasternal long axis and parasternal short axis views, at echocardiography. The left ventricular wall was divided into 16 segments and the mural motion was scored according to a six point scale, from 1 for normokinesia, through hypokinesia, akinesia, dyskinesia, aneurysm, and 6 for paradoxical movements, according to the recommendations by the American Society of Echocardiography (Schiller et al. 1989). The results were analysed blinded by two additional independent investigators with experience from echocardiography performed on adults and children. When the observers were in disagreement, a mean value was reported.

Quality of life (Paper IV)

The results are based on the reports given by the 42 subjects who completed the questionnaire.

Quality of life model and measures

Information on medical follow up was obtained from Paper I. Quality of life was measured according to the model of Lindström, taking into consideration the three life spheres: external, interpersonal and personal (Lindström). Objective conditions (factual measures) and perceived subjective satisfaction are included in all dimensions. The model has been validated in large population studies (Berntsson 2000, Lindström 1994, Möyen Laane 2000). Quality of life is defined as the essence of existence of the individual, which presupposes necessary internal and external resources for a good life (Lindström 1994). Every child has a personal sphere which is experienced in a context of social relationships and support. This, in turn, has a socio-economic context and beyond this is a macro level, society. Since the family forms the contextual framework for the child's quality of life, reports on both the family and the child are included.

Data analysis

A combined set of variables was used to study the quality of life of children. Every variable had a defined base level, which was specified to meet the

needs of children in Sweden. For the analysis, all variables were dichotomised with values one and zero. The value one corresponds to being above the base level, zero to being below. The external sphere represented the socio-economic status of the family and included three dimensions: work, economic situation and housing conditions. The interpersonal spheres represented the structure and function of the child's networks and included three dimensions: family, intimate relationship and social support. The personal sphere represented the child's psychological well being and included three dimensions: activities, self-esteem and basic mood. The psychosomatic symptoms were defined as: sensation of stomach complaints, sleeplessness, dizziness, back ache, lack of appetite and psychological problems.

Overview of the study

To facilitate for the reader, an overview of the study designs and the methods used is presented below. Table 3.

Table 3. Methods Papers I - IV

Paper	Type of study	Control group	Method
I	Retrospective review	no	Medical charts, initial echocardiography and angiocardiography.
II	Prospective examination	yes	Physical exam, lung function tests, ergospirometry.
III	Prospective examination	no	Physical exam, echocardiography, exercise test, myocardial scintigraphy.
IV	Prospective evaluation	yes	Evaluation of reported quality of life.

Statistical analysis

Paper I (Epidemiology)

The observations were stored into a database (while maintaining confidentiality) and analysed using the Statistical Analysis System (SAS). Cox proportional hazards model was used to identify factors related to a higher probability of death.

Paper II (Cardiopulmonary exercise test)

Data are expressed as median and range. For comparisons between groups, multiple linear regression analysis and Fisher's exact test were used. A p-value of < 0.05 was regarded as statistically significant. Variables in prediction models were selected using stepwise regression techniques. Statistical analysis was performed with SPSS version 15.0 for Windows.

Paper III (Myocardial function and perfusion)

No statistical analysis was performed, owing to the small number of patients.

Paper IV (Quality of life)

The statistical analyses were all performed with the SPSS/PC software package. Proportions based on simple variables exceeding base level and means of such proportions within a sphere were used in the analysis. In the comparison of proportions, the χ^2-test with a 5% significance level was used.

Ethics

The study was approved by the Human Research Committee of the Medical Faculty of Gothenburg University and informed consent was obtained from each participant and/or the parents.

Results

Perinatal conditions and diagnostics

Six of the children were born prematurely, with gestational age ranging between 31 and 36 weeks. The birth weight varied between 1463g and 4380g, mean birth weight for boys was 3380g and for girls 2998g. Twelve children (14%) were small for gestational age (SGA). All children but two presented with cyanosis with or without heart murmur within 72 hours of birth. Fifteen children had respiratory symptoms and were put on a ventilator before surgery. A total of 80 children (95%) were referred to a surgical centre within 72 hours of birth, and two were referred within 2 weeks of birth. One death in a local hospital was reported and one presented at three weeks of age with heart failure. A total of 71 children (84%) were treated with prostaglandin infusion prior to surgery. The diagnosis was confirmed by angiocardiography and echocardiography in combination for 51 children (41 available for review) and by echocardiography alone for 33 children. An atrial septostomy was performed on 13 children. Three children were initially falsely diagnosed as having tricuspid atresia, two by angiocardiography and one by echocardiography. This delayed the diagnosis of VCACs in two of them.

Morphology

In the majority of children, the right ventricle was considered tripartite and hypoplastic or severely hypoplastic. The tricuspid ostium was dysplastic and hypoplastic in the majority of cases, in eight subjects the septal leaflet was described as Ebstein-like. In all cases, there was some degree of tricuspid regurgitation. The pulmonary atresia was membranous in 46 children and muscular in 31 children (data missing for seven). The pulmonary arteries and the pulmonary trunk were of normal size in most children. VCAC were found in 36 (43%) patients: before the first operation in 19, by angiocardiography after the initial surgery in nine, at surgery in two, at section in four, and from the initial echocardiography in two. Ten patients had VCAC to the right and left coronary artery systems; eight had VCAC to the right coronary artery only; and four had VCAC to the left coronary artery system only (insufficient data in 14 subjects). Stenosis in the left coronary artery was diagnosed in two children, and three children had a single coronary artery. Eight children were considered to have right ventricular-dependent coronary circulation.

Surgery

Seven children died before reaching treatment. One child with a single coronary artery and VCAC was considered inoperable but survived and was accepted for surgery at 6 weeks of age. A total of 76 patients underwent surgery within three weeks of birth (0-21 days, median 4 days). The different surgical procedures undertaken are delineated in Figures 4-7. *Early death* occurred in 17 children, with 13 deaths after the initial operation and four after subsequent operations. Seven of the 13 children dying after the initial operation had VCACs, and in five of those the cause of early death was related to right ventricular-dependent coronary circulation. In two of those children, the presence of VCAC was unknown before surgery as angiocardiography was not performed. Two of the four children dying after subsequent operations had VCACs, one died after right ventricular decompression, the other after total cavopulmonary connection.

Late death occurred in eight children; six of them were completely dependent on an S-P shunt. Six children with VCAC died suddenly at home at 3 to 24 months of age. In four of those, the coronary circulation was right-ventricular dependent.

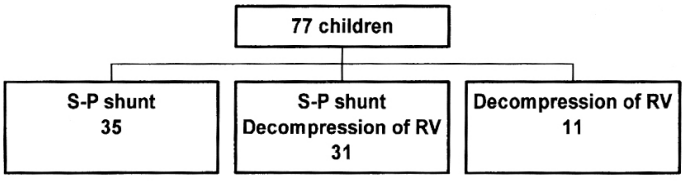

Figure 5. Type of initial surgery.

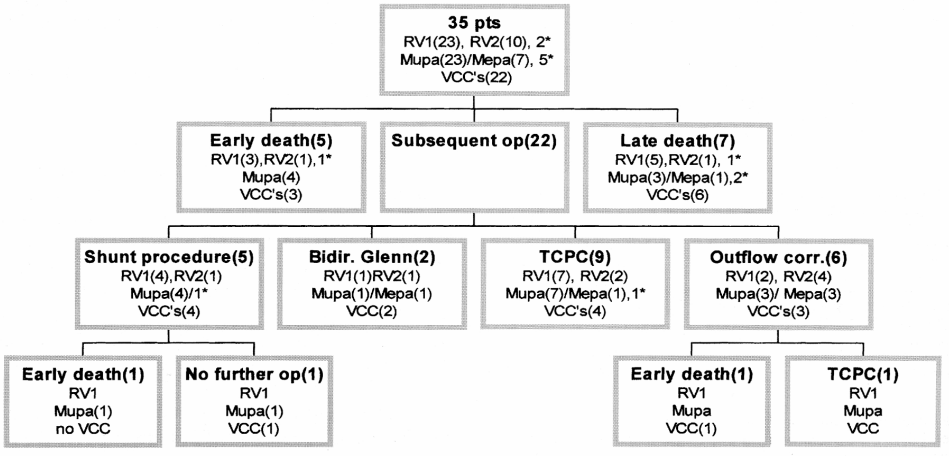

Figure 6. Outcome in relation to initial morphology for 35 children who received a systemic-pulmonary shunt as initial intervention. RV1 = severely hypoplastic right ventricle, RV2 = hypoplastic right ventricle, RV3 = normal-sized right ventricle, Mupa = muscular pulmonary atresia, Mepa = membranous pulmonary atresia, VCC = ventriculo coronary communications. * classification not possible.

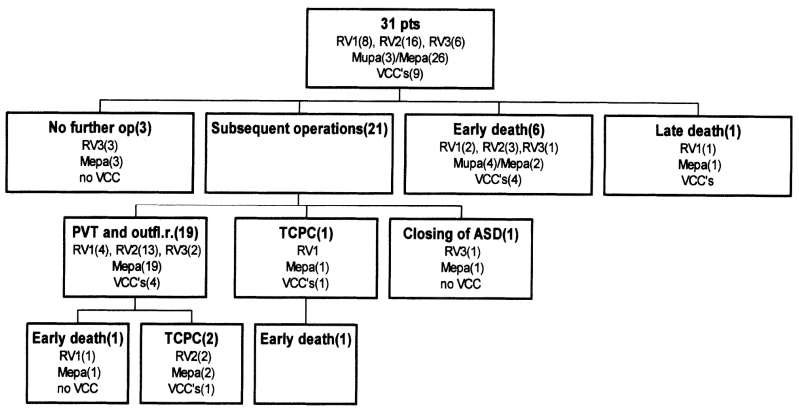

Figure 7. Outcome in relation to initial morphology for 31 children who received a systemic-pulmonary shunt and right ventricular decompression as initial procedure. For abbreviations, see legends figure 6.

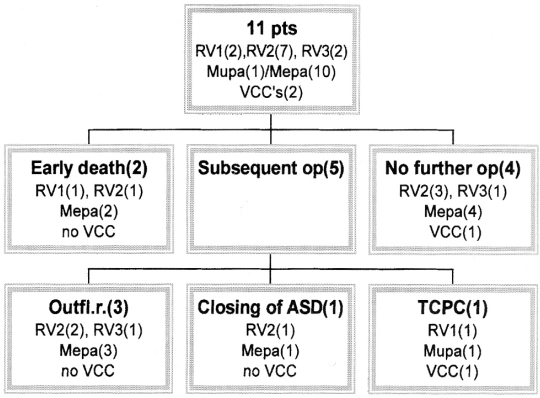

Figure 8. Outcome in relation to initial morphology for 11 children in whom the right ventricle was decompressed as initial procedure. For abbreviations, see legends figure 6.

Follow up

The cumulative survival at ten years after surgery is given in Figure 9. Follow-up time was 14 days-20 years (median 6 years). At the end of the study period, 32 of the 52 surviving children (62%) had undergone biventricular repair, and 20 univentricular palliation. According to the medical records, 26 were doing well and living a normal life (NYHA I), and three were reported to have reduced working capacity but were otherwise living normal lives (NYHA II). Statistically significant risk factors for death are given in Table 4.

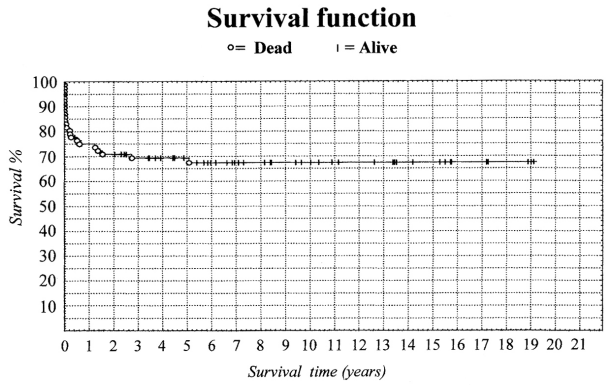

Figure 9. Cumulative survival.

Table 4. Risk factors for death

Variables	Risk ratio	p-value	Risk Ratio 95% Confidence Limits
Male gender	4.573	0.0078	1.493 - 14.004
Birth weight(kg)	0.147	0.0001	0.066 - 0.330
Muscular pulmonary atresia	6.637	0.0098	1.578 - 27.919
No initial RV-decompression	3.376	0.0385	1.067 - 10.684

Parameter estimates in the Cox proportional hazards model. The parameters are estimated using the method of maximum likelihood. RV = right ventricle, male = 1, female = 0, membranous pulmonary atresia = 0, muscular pulmonary atresia = 1, decompression of RV = 1, no decompression of RV = 2.

Cardiopulmonary exercise test

Twenty-seven subjects, 16 with biventricular repair / 11 with univentricular palliation and 28 age and sex matched healthy controls completed the cardiopulmonary exercise test. All subjects in the index group had a respiratory exchange ratio above 1.0, a ventilatory equivalent for oxygen ($V'E/V'O_2$) above 30 and all but four male subjects had a respiratory rate above 40/min. In the control group, all but two had respiratory exchange ratios above 1.0, all but one had $V'E/V'O_2$ above 30 and all but four had respiratory rate above 40/min.

The index group had significantly lower peak $V'O_2$ as compared with the control group. The index group also showed a significantly higher respiratory exchange ratio, lower peak heart rate and oxygen pulse (mL O_2 uptake/heart beat). Analysis of the peak ventilatory response showed that the index group had significantly smaller tidal volume, and higher respiratory rate. Gas exchange response showed significantly higher $V'E/V'O_2$, and lower end-tidal CO_2 in the PA-IVS group.

Physiological dead space during exercise was 0.37 (median), 0.05; 0.51 (range); which was higher than the predicted values (0.16 [0.04]) (mean [SD]) (Wasserman K 2005), and D_{LCO} was lower than predicted in the index group.

After controlling for the effect of height and sex there was no statistically difference in peak $V'O_2$ between subjects with biventricular repair and subjects with univentricular palliation ($p = 0.100$). The 14 subjects with biventricular repair and no VCACs had significantly higher peak $V'O_2$ and lower end tidal carbon dioxide than the remaining 13 index subjects. There was no statistically significant difference in peak $V'O_2$ between the subgroup with biventricular repair and no VCAC as compared with the healthy controls.

Peak heart rate was lower in the subgroup with univentricular palliation and VCACs than in the remaining index subjects ($p < 0.005$). All subjects but one had sinus rhythm.

Lung function

Forced expiratory volume in one second (FEV_1), functional residual capacity (FRC) and total lung capacity (TLC) were on average below the predicted values in the index group. There was no significant difference between subjects with univentricular palliation and those with biventricular repair. Subjects with VCACs had similar lung function values as the rest of the subjects. See Table 5.

Table 5. Lung function, given as z-scores (median and range are given)

	Subjects n=27	
Total lung capacity (TLC) *(n = 22)*	- 0.7	(-3.0 ; 1.8)
Vital capacity (VC) *(n = 22)*	- 1.6	(-7.0 ; 0.7)
Residual volume (RV) *(n = 22)*	1.2	(0.0 ; 1.1)
Forced expiratory volume (FEV_1)	-1.2	(-5.5 ; 1.1)
Forced vital capacity (FVC)	-1.2	(-5.7 ; 0.5)
FEV_1/FVC	1.3	(0.6 ; 3.6)
D_{LCO} (diffusion capacity for carbon monoxide) *(n = 17)*	- 2.1	(-7.6 ; 0.5)
N_2-slope (single-breath N_2 phase III slope)	0.45	(-4.5 ; 5.5)
V_D/V_T ratio (peak exercise)	0.37	(0.05 ; 0.51)

V_D = dead space volume, V_T = tidal volume

Predictors of peak oxygen consumption in the patient group

Stepwise multiple linear regression was used to establish prediction models for peak $V'O_2$. Only variables that provided a statistically significant contribution were included in the model. The resulting model with three predictor variables: volume expired gas ($V'E$) ($p < 0.001$), physiological dead space-tidal volume ratio (V_D/V_T) at peak exercise ($p < 0.001$), and total lung capacity ($p < 0.05$) explained 97% of the variation in peak $V'O_2$.

By controlling for height and sex using multiple linear regression analysis the group was split into two subgroups; subjects performing below and above the expected value for an index subject. Fourteen of 27 subjects performed below the expected value and they were characterised by a severely hypoplastic right ventricle, muscular pulmonary atresia, VCACs, decompressed right ventricle, univentricular palliation, treatment of the VCACs, complication of

the pulmonary arteries related to surgery and an Ebstein-like tricuspid ostium.

Myocardial function

Myocardial perfusion defects, presence of VCAC and findings on echocardiography and electrocardiography are presented in Table 6. Results of measurement of myocardial function in relation to anatomy and surgical outcome are presented in Table 7. In conclusion, all but one had ejection fraction of the left ventricular function above 50% and three of five had an ejection fraction of the right ventricular function above 47%. At visual estimation, 6/12 subjects had left ventricular function estimated as normal and 6/12 subjects had slightly reduced function. At visual estimation of the right ventricle, all were estimated as reduced: in 2/5 subjects slightly reduced and in 3/5 subjects moderately reduced.

Table 6. Myocardial perfusion defects

Patients		VCAC			Perfusion defects location and degree			Echocardiography wall motion abnormalities			
no.	Years since last surgery	rca	lcx	lad	septum	LV	degree*	septum	LV base	LV mid part, apex	TR degree
1	15				0	0	0	dyskinesia (base)	no		1-2
2	10				0	0	0	paradox (entire wall)	no		3
3	6				base	0	1	hypokinesia (base)	no		1
4	5				base	0	2	paradox (base, mid wall)	dyskinesia	dyskinesia	1
5	4				all	0	3	paradox (entire wall)	hypokinesia	hypokinesia	1
6	5				apex	apex	3	hypokinesia (base)	hypkinesia		
7	6				0	apex	3	no	no	hypokinesia**	
8	7.5				0	0	0	no	no		
9	5		yes	yes	apex	apex	2	no	no		
10	10		yes		apex	apex	1	hypokinesia (base)	hypokinesia		
11	5	yes		yes	apex	apex	3	no	no		
12	4	yes	yes	yes	all	all	2	no	no		

Patients 1 through 5 had biventricular repairs, while those numbered 6 through 12 had univentricular palliations. Those numbered 9 through 12 also have ventriculo-coronary arterial communications. Age = age at examination. Perfusion defects, location, septum = interventricular septum, LV = left ventricular free wall. VCAC = ventriculocoronary arterial communications, rca = right coronary artery, lcx = left circumflex coronary artery, lad = left anterior descending coronary artery. TR = tricuspid regurgutation. * 0 = normal perfusion, 1 = slightly reduced perfusion, 2 = moderately reduced perfusion, 3 = severely reduced perfusion. **Incomplete examination, no 2-chamber-view.

Table 7. Ventricular function in relation to anatomy and surgery

Patient	Anatomy		Surgery	Echocardiography							
nr	*Pulmonary valve* membranous/ muscular	*VCAC*	*Biv.rep/Univ.pall*	*Wall motion abnormalities*			*Left ventricular function*		*Right ventricular function*		
				septum	LV base	LV mid-apex	EF(bps) %	V.E.	EF(bps) %	V.E.	T.R.
1	membranous	no	Biv.rep.	dyskinesia	no	no	50	3	50	3	1-2
2	membranous	no	Biv.rep.	paradox	no	no	60	4	62	2	3
3	membranous	no	Biv.rep.	hypokinesi	no	no	44	3	43	3	1
4	membranous	no	Biv.rep.	paradox	dyskinesia	dyskinesia	64	3	56	2	1
5	membranous	no	Biv.rep.	paradox	hypokinesia	hypokinesia	53	3	42	2	1
6	muscular	no	Univ.pall.	hypokinesia	hypokinesia	no	63	4			
7	muscular	no	Univ.pall.	no	no	hyopinesia	56	4			
8	muscular	no	Univ.pall.	no	no	no	51	3			
9	muscular	yes	Univ.pal.	no	no	no	64	4			
10	muscular	yes	Univ.pall.	hypokinesia	hypokinesia	no	57	3			
11	muscular	yes	Univ.pall.	no	no	no	64	4			
12	muscular	yes	Univ.pall.	no	no	no	59	4			

The patients are listed as in Table 6. VCAC = ventriculo coronary arterial communications, Biv.rep. = Biventricular repair, Univ.pall. = univentricular palliation, LV = left ventricle, RV = right ventricle, EF (bps) = ejection fraction measured in biplane according to Simpson, VE = visual estimation, scored scale were 4 = normal, 3 = slightly reduced, 2 = moderately reduced, 1 = severy reduced, T.R. = tricuspid regurgitation scored scale were 0 = no, 1 = slight, 2 = moderate, 3 = severe regurgitation.

Morphology - Surgery - Outcome

With access to all the summarised data obtained in studies I, II, III it seemed necessary to re-evaluate the morphology in relation to surgery and outcome. In this evaluation three different groups became distinct: Group 1. Subjects with an Ebstein-like tricuspid ostium, Group 2. Subjects with muscular pulmonary atresia and Group 3. Subjects with membranous pulmonary atresia. The summarised results will be reported with respect to these groups. See Figure 10 and Table 8.

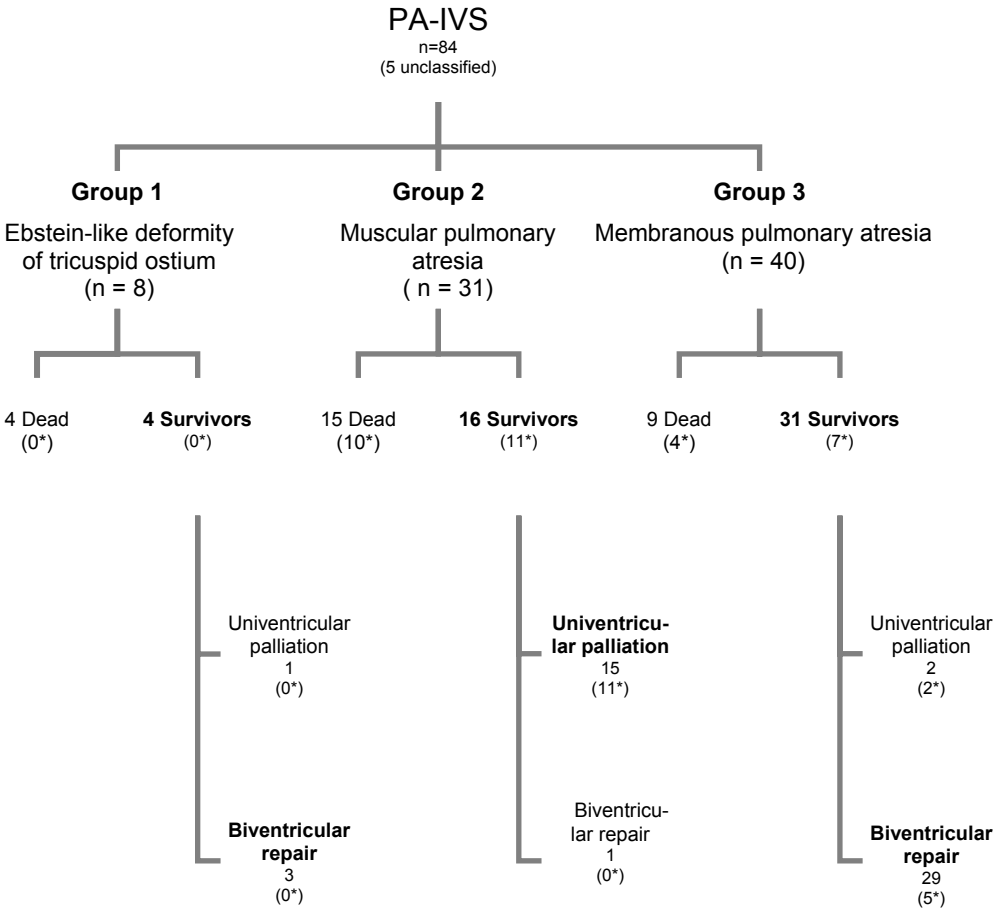

Fig. 10. Summarised results. * Numbers in parenthesis are numbers of subjects with VCAC.

Table 8. Morphology - Surgery - Outcome

		Group 1			Group 2			Group 3		
Paper I	n (missing data for 5 subjects)	8			31			40		
	Anatomy									
	VCAC	0			21			11		
	RV-size (median;range)	2 (2;4)			1.5 (1;2)			2 (1;3)		
	mortality (n%)(vcac)	4 (50%)			15 (48%)(10)			9 (22%)(4)		
	Follow-up									
	n	4			16			31		
	Surgery		*Biv r*	*Univ p*		*Biv r*	*Univ p*		*Biv r*	*Univ p*
			3	1		1	15 (11)*		29 (5)*	3 (2)*
Paper II	*Surgery*		*Biv r*	*Univ p*		*Biv r*	*Univ p*		*Biv r*	*Univ p*
	n		2	1			8 (5)*		14 (2)*	2 (2)*
	Ergospirometry									
	lower performance		2				8		2 (1)*	1 (1)*
	higher performance			1			0		12 (1)*	1 (1)*
Paper III	*Surgery*		*Biv r*	*Univ p*		*Biv r*	*Univ p*		*Biv r*	*Univ p*
	n		1				7		4	
	Myocardial function									
	LVEF% (bps) (median;range)		60				59 (51;64)		53 (44;64)	
	VE LV (median;range)		4				4 (3;4)		3 (3;3)	
	RVEF% (bps) (median;range)		62						46 (42;62)	
	VE RV (median;range)		2						2.5 (2;3)	
	Perfusion defects		septum				septum and LV free wall		septum	

Group 1: Ebstein-like deformity of the tricuspid ostium. Group 2: Muscular pulmonary atresia. Group 3 : Membranous pulmonary atresia. VCAC = ventriculo coronary arterial communications, RV = right ventricle, RV-size: scored scale: 1 =severely hypoplastic, 2 = moderately hypoplastic, 3 = normal, 4 = dilated, LV = left ventricle, EF = ejection fraction, VE = visual estimation, Biv rep = biventricular repair, Univ pall = univentricular palliation. * number in parenthesis are number of subjects with VCACs.

Group 1. Ebstein-like deformity of the tricuspid ostium

Eight subjects were identified, four died, all within the first two weeks of life and three died before surgery was performed.

In study II there were three subjects with Ebstein-like abnormality of the tricuspid ostium. Two of them had biventricular repair and were the only ones with severe tricuspid regurgitation. Both had severely reduced exercise performance. The one with univentricular palliation had better exercise performance. Although the number of subjects in this group was very small, the variable "Ebstein-like tricuspid ostium" turned out to be a significant predictor for poor exercise performance in the regression analysis. One subject with Ebstein-like tricuspid ostium participated in study number III. He had normal function of the left ventricle, moderately reduced function of the right ventricle, but the most severe tricuspid regurgitation and perfusion defects in the entire interventricular septum.

Group 2. Muscular pulmonary atresia

In Paper I, the total cohort comprised 31 subjects with muscular pulmonary atresia. The mortality rate among subjects with muscular pulmonary atresia was high (48%) and the muscular atresia was a significant risk factor for death. Of the sixteen survivors, 15 had univentricular palliation. In seven subjects a right ventricular decompression was performed, but at the follow up only one had biventricular repair.

Eight subjects from this subgroup participated in study II, all with univentricular palliation. All had lower exercise performance than the subjects with membranous PA-IVS.

In study III there were seven participants from this group, all had univentricular palliation. Six had perfusion defects in the left ventricular free wall, while none of the subjects with biventricular repair had perfusion defects in this location. All four subjects with VCACs had perfusion defects in all locations. By visual estimation, the left ventricular function was considered normal in four subjects and slightly reduced in three. None had ejection fraction below 50%, measured according to biplane Simpson's rule.

Group 3. Membranous pulmonary atresia

In the whole group of subjects with PA-IVS (Paper I) there were 40 subjects with membranous pulmonary atresia, of who nine died. At follow up all but three had biventricular repair See summarised results Table 8.

Membranous pulmonary atresia was associated with increased survival rates. In the majority of the subjects in this group the right ventricle was moderately hypoplastic and without VCAC. Among the 29 survivors with biventricular repair (Figure 9) 21 had homografts, three had right ventricular outflow patch and in five pulmonary valvotomy was sufficient.

There were 16 subjects with membranous pulmonary atresia in study II, and when the group was divided into groups with higher respectively lower exercise performance, all subjects in the group with higher performance had membranous pulmonary atresia. There were three with lower exercise performance and membranous pulmonary atresia, two of whom had VCACs.

In Paper III there were five subjects with membranous pulmonary atresia none had VCACs, and three had perfusion defects in the interventricular septum, none in the left ventricular free wall. Left ventricular function was considered normal in one subject and slightly reduced in the remainders, mainly due to hypokinesia, dyskinesia or paradoxical movements in the interventricular septum. A correlation between perfusion defects and abnormal septal motion was seen in three of the five children with biventricular repair (Table 7). The left ventricular function at rest, measured as ejection fraction according to biplane Simpsons rule at echocardiography was above 50% in all but one subject. There was no correlation between ejection fraction at rest and exercise performance.

The right ventricular function was considered subnormal in all five subjects by visual estimation and ejection fraction was above 47 % in all but two subjects. The tricuspid regurgitation was considered grade 1-2 in all but one (grade 3). There was a considerable degree of pulmonary regurgitation in all subjects and all but one were operated with insertion of a homograft.

Quality of life

When the results in this study were re-evaluated and organised into the groups 1.Ebstein-like tricuspid ostium, 2. muscular and 3. membranous pulmonary atresia, group 2 had generally lower values than the two other groups. The only statistically significant difference was, however, a lower school-satisfaction ($p < 0.05$).

The external and interpersonal quality of life

The total outcome of the external and inter-personal quality of life was almost the same for the index group (PA-IVS group) and the healthy group. Income level and satisfaction with one's financial situation was slightly higher in PA-IVS families than in the healthy group. Parents in the PA-IVS group spent more time with their children than those in the group with healthy children. Major negative life events (separation, divorce or death) were as frequent in the PA-IVS group as in the healthy group**.**

Personal quality of life (Table 9)

The PA-IVS children had a higher independent activity level and they were more active with their parents than the other group, but satisfaction with activities was lowest among the PA-IVS families ($p< 0.05$). Self-esteem was

almost equal between the PA-IVS children and children in the healthy group. There were more psychosomatic problems (sensation of stomach complaints, sleeplessness, dizziness, back ache, lack of appetite and psychological problems) in the PA-IVS group than in the healthy group. Peer acceptance was equal between the groups. The total outcome of the personal quality of life was almost the same for the groups.

Overall quality of life (Table 10)

The PA-IVS children rated well within the external and inter-personal spheres, but lower within the personal sphere. The objective conditions and the subjective perceptions were on the same level in the PA-IVS and the healthy group. The overall quality of life did not differ between healthy children and PA-IVS- children, or between children with biventricular or univentricular palliation.

Table 9. The personal sphere

	Healthy (n = 1856)	PA-IVS (n = 42)	Biv. repair (n = 26)	TCPC (n = 16)
Activity				
Child activity	83	88	85	94
Child-parent activity	89	90	89	94
Satisfaction	69*	54	56	50
Self-esteem	54	57	58	56
Basic mood				
Psychosomatics	83***	56	60	50
Peer acceptance	94	90	88	93
Satisfaction at school	95	94	100	86
Personal sphere total mean	81	76	77	75

PA-IVS = pulmonary atresia and intact ventricular septum, Biv repair = biventricular repair, TCPC = total cavo-pulmonary connection. * $p < 0.05$; *** $p < 0.001$, statistically significant difference compared with the healthy group.

Table 10. Overall quality of life

	Healthy (n = 1856)	PA-IVS (n = 42)	Biv. repair (n = 26)	TCPC (n = 16)
External	71	74	76	72
Interpersonal	73	74	74	75
Personal	81	76	77	75
Mean all spheres	75	75	76	74
Average subjective variables	70	68	70	67
Average objective variables	77	79	79	79

PA-IVS = pulmonary atresia and intact ventricular septum, Biv repair = biventricular repair, TCPC = total cavopulmonary connection. No statistically significant differences between those with cardiac anomaly and the healthy group, nor between subjects undergoing biventricular repair as opposed to univentricular palliation.

Discussion

The aim of these studies was to describe all children born with PA-IVS in Sweden between 1980 and 1999, the epidemiology of PA-IVS and survival (Paper I), cardiopulmonary exercise capacity (Paper II), myocardial perfusion and function (Paper III) as well as quality of life (Paper IV). The different aspects, with special focus on the morphology in relation to outcome, methodology and future are discussed (Papers I, II, III).

The summarised results point out a group of individuals with an unusual, once fatal heart defect for whom the achievements of surgery during the last 50 years have meant survival and so far, for the majority, survival to an independent life.

Epidemiology

The incidence of PA-IVS was 4.2 per 100 000 live births in Sweden, with a total population of 9 million. The incidence and range of morphology was similar to those described in the United Kingdom and Ireland Collaborative Study of PA-IVS, a large epidemiological study of an unselected population (Daubeney et al. 2002). The survival rates after the initial operation, i.e. 81% after one month, 69% after four years, and 68% after 10 years, are also comparable with previous reports (Hanley et al. 1993, Leung et al. 1993, Ashburn et al. 2004, Fenton et al. 2004, Dyamenahalli et al. 2004). Mortality was high during the first years of life and declined after infancy. There was no statistically significant improvement of survival rates during the time of the present study. PA-IVS is, however, an unusual heart defect, and therefore surgical progress in this size of study population, will not be recognisable until after a considerable number of years**.** Recent reports show improvements, but the management of PA-IVS still presents a challenge (Powel et al. 2000, Asburn et al. 2004, Dyamenahalli et al. 2004, Fenton et al. 2004).

Morphology - Surgery - Outcome

Three different groups with different outcomes are described in Papers I, II and III: one group with an Ebstein-like tricuspid ostium, a second group with muscular pulmonary atresia and a third group with membranous pulmonary atresia. In the present study these groups overlap to some extent. Similar groups were identified by R. Anderson et al. (1991) in a post-mortem study of 43 hearts with PA-IVS. He focused on the pulmonary ostium and sug-

gested that the distinction between valvar and muscular atresia is of critical importance for the outcome. He also stated that the valvar (membranous) atresia was acquired later during fetal life than muscular atresia (Anderson et al. 1991).

Group 1. PA-IVS with an Ebstein-like tricuspid ostium

These subjects have previously been identified as a group of PA-IVS with very high mortality, particularly during fetal life (Anderson et al. 1991, Allan and Cook 1992, Daubeney et al. 2005, Freedom 2006). In the present study these subjects had special characteristics that made them clearly identifiable through all studies. They were particularly vulnerable early in life, and later, these subjects were those with the most severe tricuspid regurgitation and severely reduced exercise capacity. There was, however, one subject in study II with univentricular palliation and better exercise performance than the others with an Ebstein-like deformity of the tricuspid ostium. In the subjects with PA-IVS, severe tricuspid regurgitation has a crucial impact on the already compromised right ventricular function. In a previous study of exercise capacity in subjects with PA-IVS, the main predictor of peak V′O2 in the group with biventricular repair was severe tricuspid regurgitation (Sanghavi et al. 2006).

Group 2. PA-IVS with muscular pulmonary atresia

In this group the mortality and morbidity were significantly higher than among subjects with membranous pulmonary atresia. Although there were many attempts to correct to biventricular repair this was only successful in one subject. Exercise performance was significantly lower than in the group with membranous pulmonary atresia. The findings in the subjects with univentricular palliation were similar to those in other reports; reduced peak heart rate, small lungs, uneven pulmonary perfusion with a large amount of dead space ventilation and below normal aerobic capacity. The subjects in the present study had, however, better exercise capacity than those with univentricular palliation in previous reports (Table 11). This can be explained by the fact that all subjects in the present study had the left ventricle as the systemic chamber, none had a ventricular septal defect, and all but one had sinus rhythm. There is only one previous study reporting on aerobic capacity in subjects with univentricular palliation, including only subjects with PA-IVS. This study (Sanghavi et al. 2006) reported an aerobic capacity of 76 % of the predicted value, which is close to the findings in the present study (see Table 11).

VCACs were common (68%) and myocardial perfusion defects more extensive in this group. Subjects with VCAC and univentricular palliation had perfusion defects in the interventricular septum and in the left ventricular free

wall. There are few studies of myocardial perfusion defects in PA-IVS (Björkhem et al. 1990), but there are several post-mortem studies reporting myocardial pathology and myocardial infarction in the presence of VCACs (Bulkely et al.1977, Freedom et al. 1983, Fyfe et al. 1986, O'Connor et al. 1988, Oosthoek et al. 1995). There are also reports of ongoing changes in the coronary arteries, development of sclerosis and stenosis with ischemia in the myocardium, leading to a risk for late death (Coles et al. 1989, Akagi et al.1993, Gittenberger-de Groot et al. 1988). One of the patients in the present study experienced symptomatic relief when the VCACs were embolized, and there was no progress of perfusion defects seen on myocardial scintigraphy performed after this procedure.

Group 3. PA-IVS with membranous pulmonary atresia

This group was the largest, and associated with higher survival and better outcome. Most of the subjects in this group had biventricular repair. Exercise capacity was superior to that of the group with muscular pulmonary atresia, but reduced compared with a healthy control group. Sanghavi et al (2006) found no statistically significant difference between subjects with biventricular repair and univentricular palliation. This is in agreement with the findings in the present study, but when excluding the two subjects in the group with biventricular repair with VCACs, biventricular repair was found to be associated with significantly higher peak $V'O_2$. Studies of exercise capacity in subjects corrected for congenital heart defects resulting in biventricular circulation show exercise capacity ranging from normal to reduced, depending on the type of congenital heart defect and the type of surgery (Table 12).

In the present study, 11 subjects were identified with the combination of membranous pulmonary atresia and VCACs. This did not preclude biventricular repair in five subjects. In the present study there was no correlation between left ventricular function at rest evaluated by echocardiography and the presence of VCACs, but such a correlation has been described previously (Hausdorf et al. 1987, Akagi et al. 1993). The presence of VCAC most probably influenced ventricular performance during exercise, as shown in Paper II, where the two subjects with VCACs and biventricular repair had lower exercise capacity than the others with biventricular repair. By visual estimation, the myocardial function of the left ventricle tended to be more normal in univentricular palliation than in biventricular repair, mainly owing to the findings of abnormal septal movements in biventricular repair. Abnormal septal movements have previously been reported in PA-IVS and in some studies they appeared after right ventricular decompression (Gentles et al. 1993, Mi and Cheung 2006). The abnormal septal motion may be attributable to the reduced function of the right ventricle. As early as during pregnancy, the developing right ventricle is exposed to a considerable amount of stress, contracting against an obliterated outflow tract. After birth, and after decom-

pression of the right ventricle, the pressure is reduced, but almost all subjects continue to have impaired right ventricular function (Freedom 1983, Mishima et al. 2000, Mi and Cheung 2005), (see Table 7).

Treatment considerations

Although there are many suggestions for treatment strategies, the heterogeneity of the morphology, still presents a challenge and the treatment strategy is not always self-evident in the individual case. (de Leval et al. 1982, Freedom et al.1983, Anderson et al.1991, Hanley et al. 1993, Rychik et al.1998, Syamasundar 2002)**.** Most treatment strategies are based on the morphology and size of the right ventricle, although some authors focus mainly on the morphology of the infundibular part (Pawade A et al. 1993, Sano et al. 2000). The findings in the present study support the treatment strategy based on the morphology of the infundibular part of the right ventricle. Classification in terms of Ebstein-like tricuspid ostium, muscular and membranous pulmonary atresia may facilitate the choice of surgery.

In Ebstein-like tricuspid ostium with severe tricuspid regurgitation, the right ventricular performance is more compromised and many of these patients may end up with univentricular palliation**.** It is, however, also necessary to take into consideration that the pulmonary function and vascular development in the lungs seem to be dependent on at least a period of pulsatile blood flow. Therefore, the treatment strategy of first choice may be biventricular repair. But if the right ventricular performance is deteriorating owing to severe tricuspid regurgitation, then univentricular palliation may be the treatment of choice.

In muscular pulmonary atresia there is no outflow tract and VCACs are very common. Concerning treatment strategy, most authors agree that for subjects lacking the outflow tract, univentricular palliation is the treatment of choice (Hanley et al. 1993, Pawade et al. 1993, Syamasundar 2002, Sano et al. 2000). In the present study, VCACs appeared in 68% in this group. In previous reports the number was even higher (Anderson et al.1991) and as right ventricular dependent coronary circulation represent a high risk of death, exact delineation of the VCACs before surgery is important (Hanley 1993, Giglia 1992, Coles 1989, Akagi 1993, Freedom1983). In conclusion, it might be favourable to ligate the VCACs as early as possible.

When the pulmonary atresia is membranous biventricular repair is usually considered, and right ventricular decompression is advocated as the primary procedure (de Leval et al.1982, Pawade et al. 1993). In cases where the right ventricle is more hypoplastic in combination with membranous pulmonary atresia, there are several reports of increased growth after decompression of the ventricle (Graham et al.1974, Patel et al. 1980, de Leval et al.1982, Hanséus et al.1991). In the present study, membranous pulmonary atresia did not preclude the presence of VCAC and exact delineation of the morphology is

recommended, although according to some authors, the VCACs in subjects with membranous muscular atresia are most often small (Pawade et al. 1993). There are also reports that VCACs can disappear after decompression (Giannico 1998), and some authors suggest providing early relief of the high pressure in the right ventricle to enable the coronary blood flow to become antegrade and to provide the myocardium with highly oxygenated blood (Freedom et al.1983, Bull et al. 1982, Giglia et al. 1992).

When the right ventricle continues to be very small after otflow tract reconstruction, a one and a half ventricular repair may be an alternative treatment to univentricular palliation. The pulmonary circulation is then provided with pulsatile blood and this may reduce the risk of development of pulmonary arteriovenous fistulae (Gentles et al 1994, Miyaji et al 1995). The long term results, however, are not always reported to be satisfactory (Numata et al. 2003) and as this treatment strategy was not used in Sweden during the time of the present study, it is not evaluated.

Since 1991 radiofrequency assisted perforation of the atretic pulmonary valve has successively become the primary treatment when the anatomy is favourable (Syamasundar 2002, Humpl et al. 2003, Agnoletti et al. 2003). In some cases the right ventricle is initially incapable of providing enough blood to the pulmonary circulation and an S-P shunt is also necessary (Hawkins et al. 1990, Humpl et al. 2003, Syamasundar 2002). During the time of the present study the technique of radiofrequency assisted perforation was not available in Sweden, but to date six patients have now been successfully treated with this technique in Gothenburg.

Biventricular repair versus univentricular palliation

When comparing biventricular repair with univentricular palliation in the present study, there were no significant differences in exercise capacity, lung function or quality of life. The absence of differences may be attributable to the small size of each group. The underlying cardiac morphology had more influence on exercise capacity than the choice of surgical approach. Biventricular repair is, of course, the treatment of choice whenever possible, owing to the unphysiological circulation and potential complications of univentricular palliation (atrial arrhythmias, progressive cyanosis due to right-to-left shunts, thromboembolic events, and protein-losing enteropathy) But if univentricular palliation is the only possibility, then the cardiac morphology in PA-IVS seems to be favourable, especially as compared with subjects receiving this treatment for a number of other complex congenital heart defects.

Lung function

Exercise capacity was generally reduced in subjects with PA-IVS, but there were marked inter-individual differences. The reduced lung function and the

increased dead space ventilation explained more than 90 % of the variations in exercise capacity. The group with membranous pulmonary atresia had less restrictive lung function than the group with muscular pulmonary atresia. Restrictive lung function was reported as early as 1972 in patients corrected for tetralogy of Fallot (Bjarke 1972), but there are very few published results from more extensive lung function examinations (Wessel and Paul 1999). Thoracic surgery *per se* may affect lung mechanics, but lung compliance was found to be affected in a recent study, depending on pulmonary blood flow prior to surgery (Stayer et al. 2004). The reported reduction in lung function after open heart surgery does not involve an increase in physiological dead space ventilation (Rosenthal et al. 1999).

There are reports emphasizing that pulmonary blood flow is necessary for the development of the acini, which starts in week 17 of gestation (Hislop and Pierce 2000). Interestingly, there are several reports from post-mortem studies of newborns with PA-IVS showing pulmonary vascular changes, including thrombosis and underdeveloped arteries in the intra-acinar region present at birth (Haworth and Reid 1977, Tanaka et al 1996, Thomas 1964, Wagenvoort et al. 1961, Best and Heath 1958). In some report the pulmonary vessels were described as normal and even dilated to a very specific point, where the acinar vessels are connected (Haworth and Reid 1977, Haworth et al 1980). In the present study, there were several findings from the lung function tests supporting the view that the PA-IVS subjects may suffer from poor alveolarisation or poor peripheral lung vascularisation. For example, eleven index subjects had a low N_2 phase III slope, which is consistent with less complex acinar airway architecture, i.e. underdevelopment of the gas exchange region (Paiva and Engel 1989). The type of surgery in the present study also influenced exercise capacity, as decompression of the right ventricle and biventricular repair were associated with higher aerobic capacity. In the group with higher aerobic capacity there were two subjects with univentricular palliation. Interestingly, both had undergone right ventricular decompression before one year of age, providing the pulmonary artery and the lungs with pulsatile blood flow. There are studies emphasizing the importance of pulsatile pulmonary blood flow for the lung development and in addition, pulsatile blood flow is believed to improve the endocrine function of the lung and to prevent development of pulmonary arteriovenous fistulae (Cloutier et al. 1985, Miyaji et al. 1995, Kurotobi et al. 2001). This makes it of great importance to provide the pulmonary circulation with pulsatile flow as early as possible, ideally within the first two to three years of life, when alveolarisation still occurs. See Figure 11.

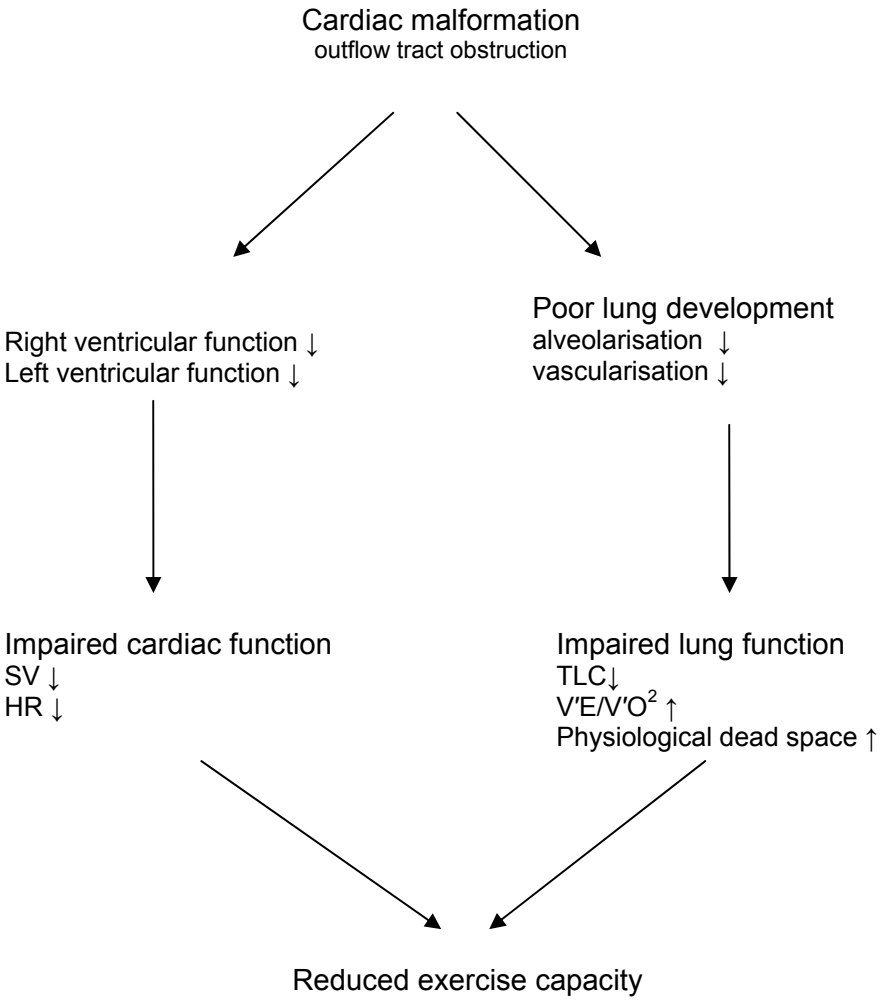

Figure 11. Schematic illustration of possible relationships between cardiac malformation, lung development, lung function and overall cardio-pulmonary performance. SV = stroke volume, HR = heart rate, TLC = total lung capacity, $V'E/V'O^2$ = ventilatory equivalent for oxygen

Table 11. Studies of aerobic capacity after Fontan Surgery

Congenital heart defect	Reference	N	age	VO_2 - peak	
			mean(SD)/ range	ml/kg/min mean (SD)	% predicted mean (SD)
Various conditions	Zellers 1989	20	15.3 (7.9)	27 (6)	59 (15)
Various conditions	Nir 1993	25	6 - 44	25.0 (4.3)	57 (17)
	Driscoll 1986	29	6 - 36	24 (4.5)	
Tricuspid atresia		16			48 (16)
Various conditions		13			56 (15)
Various conditions	Giannico 2006	127	11 - 22		59 (5)
Various conditions	Harrison 1995	30	25.7 (6.3)	14.8 (4.5)	
Various conditions	Durongpistikul 1998	59			60
Various conditions	Strömvall-Larsson 2002	20	11 - 30	21.1	65
Pulmonary atresia and intact ventricular septum	Sanghavi 2006	10	12.7 (5)		76 (17.5)
Pulmonary atresia and intact ventricular septum	Ekman-Joelsson 2008	11	13 (4)	32 (8)	

Table 12. Studies of aerobic capacity after operation for congenital heart defects (biventricular repair)

Congenital heart defect	Reference		N	age	VO_2 - peak		VAT
					ml/kg/min	% predicted	% predicted
				mean (SD)	mean (SD)	mean (SD)	mean (SD)
Excessive pulmonary blood flow before surgery							
Atrial septal defect	Mejbom 1993		104	14.5 (2.8)		104 (17)	
	Rosenthal 1997		22	8 - 50			100
Ventricular septal defect	Perrault 1989		7	15.1 (1.5)	34 (10)		
	Driscoll 1993		97	27 (8)	35.2 (9.76)		
Reduced pulmonary blood flow before surgery							
Pulminary stenosis	Driscoll 1993		62 males	29 (7)	33.3 (8.79)		
Fallot	Wessel 1999		45*	17.1 (7.4)	36 (5.5)	84 (8)	
Pulmonary atresia and intact ventricular septum	Sanghavi 2006	(biventricular repair)	19	16.5 (6.5)		83.5 (21.1)	
Pulmonary atresia and intact ventricular septum	Ekman-Joelsson 2008	(biventricular repair)	16	14 (4)	34 (8)		
Variable pulmonary blood flow before surgery							
Transposition great arteries	Paul 1987	(Mustard)	38	14 (3.4)	27 (8.4)		
	Reybrouk 2001	(arterial switch)	15	8.5 (9)			91 (7.8)
		(Mustard/Senning)	32	9.2 (1.8)			75 (13.1)
Aortic stenosis	Driscoll 1993		25	31 (6)	35.7 (1.64)		
Total anomalous pulmonary venous return	McBride 2007		27	11 (4)	36 (6.9)	88 (16)	

*number of studies. VAT = ventilatory anaerobic threshold

Quality of life

The overall differences between children with PA-IVS and healthy children are small. When comparing children subjected to uni- or biventricular repair, there were no statistically significant differences. To the author's knowledge, this kind of comparison of children with the same sort of congenital heart defect has not been made before. In follow-up studies of adults with univentricular hearts, the majority of the patients were in NYHA classes I or II, living normal lives (Mair et al.1997, Gentles et al. 1997). In a recently published study of quality of life in children with hypoplastic left heart syndrome, using exactly the same questionnaire, there were more marked differences compared with a healthy control group, both in the interpersonal and personal sphere. The affected children had lower psychological well being than that of the healthy group (Mellander et al. 2007). The differences may be explained to some extent by the fact that hypoplastic left heart syndrome represents one of the most severe forms of congenital heart defects. (Mellander et al. 2007, Mahle et al. 2000).

The most significant difference in the present study, comparing healthy children and children with PA-IVS, was found at the personal level, the degree of psychosomatic complaints and the satisfaction with activities. This is in line with some reports (Möyen Lane 2000), but there are studies that report the opposite (Favarato and Romano 1994, Spijkerboer et al. 2007). In a recently reported qualitative interview study, adolescents with chronic illness (also including congenital heart defects) experienced well-being when they were allowed to prepare for living a normal life integrated in society (Berntsson et al 2007). Long term studies in adults treated for congenital heart defects report a group of people successful in society but with significantly more psychological problems than in the general population (Saliba et al. 2001, Ternestedt et al. 2001, Bromberg et al. 2003). These studies reflect, however, the conditions several years ago and the treatments of congenital heart disease as well as the knowledge about the outcomes are evolving and changing rapidly. Concerning the symptoms that are classified as psychosomatic in the present study, there could also, to some extent, be a physiological explanation, especially in children with univentricular palliation. There were, however, no statistically significant differences between subjects with biventricular repair and univentricular palliation.

Methodological considerations

Epidemiology

Data on all subjects born with PA-IVS in Sweden between 1980 and 1999 were obtained. All available data were reviewed by one person, which makes the evaluation uniform. The classification of the morphology is retrospective, but it is based on medical charts, angiocardiographies and echocardiographies, with high concordance. If centres from other countries had been included, it would have been more difficult to obtain uniform data and to have a high inclusion rate.

Exercise capacity

This study included 27 of 35 conceivable participants. The eight subjects who declined to participate had similar surgical procedures and outcomes as the study group, which implies that the study group consists of a representative sample of the survivors with PA-IVS. Invasive data, such as arterial blood gases and measurement of cardiac output were not recorded during the exercise test, owing to ethical constraints in this respect. Moreover, although the data in the present study is not as reliable as it might have been, transcutaneous blood gases were obtained. The method of measuring cardiac output non-invasively during exercise was not available in our laboratory at the time of the study.

Myocardial perfusion

All 13 subjects born in the Western part of Sweden were asked to participate in the study and the participation rate was high (12/13). The range of morphology and outcomes in the study group was similar to that in the whole population of survivors and is therefore likely to be a representative sample. Limitations are the relatively small number of children, the absence of a control group, and the small number of investigations in each child, owing to ethical constraints concerning radiation exposure in children. From an ethical standpoint, recruitment of age-matched control groups for any radionuclide study on children is difficult.

Quality of life (Paper IV)

The quality of life questionnaire was chosen because it has been validated in a large population study in Sweden and scrutinised in two Swedish PhD dissertations (Lindström 1994, Berntsson 2000). Furthermore, it includes data from a large healthy Swedish control group (Berntsson 2000). Another advantage of this instrument is that it captures most relevant aspects of chil-

dren's life, including physical, social and mental components, objective parameters such as housing, parental education and finances. The quality of life instrument is also general, which means that it can be applied to any disease. The method used in the present study was included in a review of 70 articles covering the subject quality of life assessment in congenital heart disease and, it ranked very high (Moon P et al. 2004).

Qualitative studies with interviews of fewer subjects would give a different kind of information about the individual's relation to life; and the present study does not include this aspect of feelings.

Future

The development of interventional catheterisation may lead to a better outcome for the patients with PA-IVS, with possibilities to insert a stent in the ductus arteriosus as an alternative to surgical insertion of an S-P shunt and insertion of biological valves in the pulmonary position (Boshoff et al. 2007, Nordmeyer et al. 2007).

Knowledge is evolving in the field of genetics and embryological development. Many authors have speculated on the development of pulmonary atresia, and come to the conclusion that muscular pulmonary atresia is acquired earlier in pregnancy than membranous pulmonary atresia (Anderson et al. 1991, Freedom 1989, Daubeney et al. 1998). Still, taken the rules of embryology into account, the pulmonary atresia must develop late in cardio genesis, after septation is completed. If the development of some cases of muscular atresia is secondary to a disorder in the coronary arteries, as described previously (Gittenberger-de Groot et al 2001), this type of congenital heart disease might be a disorder of the blood vessels, and not primarily a cardiac disorder. The consequence of this is that there could be defects in the blood vessels in other parts of the body, with the same embryological origin as the coronary arteries. An increased knowledge about the mechanisms of this sort of defects could lead to development of other kinds of treatment.

Membranous pulmonary atresia probably develops later in pregnancy. There have been some attempts to treat PA-IVS before birth with prenatal cardiac intervention. Daubeney reported two cases: one by transventricular puncture (unsuccessful) and one by radiofrequency perforation of the pulmonary valve (successful) at 26 gestational weeks. In the latter case, the valve had almost become atretic again at birth (Daubeney et al. 1998,). If the development to atresia is secondary to some condition during pregnancy, for example moderate stenosis in proximity to the ductus arteriosus, the treatment of choice may be to induce birth earlier, for example in gestational week 32, when the fetal risks regarding extrauterine life are very low.

If the peripheral vascular bed in the lungs is underdeveloped in PA-IVS, it

would create a high resistance for the right ventricle. The pressure in the right ventricle in subjects with right ventricular outflow obstruction is reported to be high during exercise (Finnegan et al. 1974, Krabill et al. 1985). High pressure on the pulmonary valve may result in a continuous damage to the already compromised valve, with an increasing need for reoperations. A complementary way of treating this condition would be to stimulate the growth of the peripheral pulmonary vasculature. In animal experiments, it has been shown that the growing, immature lung is capable of developing the alveolar and vascular dimensions (Hsia et al. 1992, Takeda et al. 1999). In human beings, such stimulation probably has to be started early, presumably during the first years of life when the lungs are still developing.

Summary and Conclusions

- The incidence of PA-IVS was 4.2/100 000 live births.
- The cumulative survival rate was 68% ten years after surgery.
- At the end of the study period, 32 of 52 survivors had biventricular repair.
- Three main groups with different mortality and outcome have been delineated:
  - Ebstein-like deformity of the tricuspid ostium with high mortality (50%) and reduced exercise capacity.
  - Muscular pulmonary atresia with high mortality (48%), high rate of VCACs and myocardial perfusion defects, reduced exercise capacity, and univentricular palliation in the majority of subjects.
  - Membranous pulmonary atresia with a lower mortality (22%), better exercise capacity, and biventricular repair palliation in the majority of subjects.
- Reduced lung function was the major determinant of impaired exercise capacity.
- Overall quality of life was good.

Final reflexions

The development of imaging methods and surgery has opened the door to survival for this group of individuals. Although the mortality is still high during early life, the survivors live normal lives with respect to school and daily activities. Upon examination, the subjects were found to have reduced myocardial function, lung function and exercise capacity, and to be physically limited compared with a healthy population, but they perceive themselves as living ordinary lives. As concerns the families, there were no differences in income or frequency of divorces or number of children, as compared with a healthy Swedish population. In conclusion, the majority of the survivors, born with PA-IVS have not turned out to be severely disabled. With the continuous and rapid progress of paediatric cardiac treatment the outcomes will continue to improve.

The teenage girl, who inspired me to start my work with this thesis participated in all the studies and continued to be a source of inspiration. She had

muscular pulmonary atresia, without VCACs, and underwent univentricular palliation. Although she underwent several operations and was not successfully palliated until the age of fourteen, the final results of surgery were good and the myocardial function was good. Despite the seriousness of her heart malformation she graduated from upper secondary high school, got a driving licence, had an apartment of her own, earned her own living, and had a boy friend. She even participated in a cooking competition and was one of the winners. Very sadly, she died in liver cancer due to Hepatitis C a few years ago. This was a consequence of having received infected blood during one of the heart operations in her early life. She is sorely missed, and my future research will continue to be inspired by her memory.

Populärvetenskaplig sammanfattning

Det övergripande syftet med den här studien var att beskriva barn som fötts med ett ovanligt järtfel, pulmonalisatresi med intakt ventrikelseptum (stängd klaff till lungpulsådern utan samtidigt hål i hjärtskiljeväggen) i Sverige under 20 år (1980 – 1999). Detta är ett dödligt hjärtfel om man inte opererar barnet under de första levnadsdagarna.

De specifika frågeställningarna i studien var: incidens, hjärtfelets variation, operationsmetoder, operationsresultat, överlevnad, samt barnens nuvarande hälsa, fysiska prestationsförmåga och livskvalitet.

Material och metod: För att besvara frågeställningarna identifierades barnen utifrån olika register. Data från sjukvården granskades. Vidare undersöktes lungfunktionen och arbetsprov gjordes med samtidig mätning av syreupptag och koldioxidproduktion. Den grupp barn som fötts i Västsverige genomgick en detaljerad undersökning av hjärtmuskeln både i vila och under arbete. De undersöktes med ultraljud och en radioisotopundersökning av hjärtmuskeln i samband med arbetsprov. Livskvaliteten värderades med hjälp av en enkät, framtagen vid Nordiska Hälsovårdshögskolan i Göteborg

Resultat: Kartläggningen visade att det fötts 84 barn med detta hjärtfel under tidsperioden. Sjuttiosju opererades, med en ettårsöverlevnad på 75 % och en kumulativ 10-årsöverlevnad på 68 %. Vid slutet av perioden levde 52 barn, 32 med normal cirkulation genom lungorna och 19 med s.k. en-kammarcirkulation. Statistisk analys visade att följande faktorer var oberoende riskfaktorer för död; låg födelsevikt, manligt kön, muskulär pulmonalisatresi (avsaknad av höger kammares utflödesdel) och enbart aorto-pulmonell shunt som första operationsingrepp.

Tjugosju av 35 tillgängliga personer från hela landet med det här hjärtfelet undersöktes med arbetsprov. Resultaten jämfördes med en frisk ålders- och köns-matchad kontrollgrupp. Gruppen med hjärtfel hade lägre syreupptagningsförmåga än kontrollgruppen. Inom gruppen med hjärtfel hade individer med normal blodcirkulation genom lungorna (tvåkammarsystem) och utan förekomst av onormala blodkärl mellan höger kammare och kranskärlen bättre syreupptagningsförmåga än resten av gruppen. Inom hela patientgruppen var lungfunktionen i vila under det normala och effektiviteten i gasutbytet under ansträngning sämre än normalt.

Den detaljerade hjärtmuskelundersökningen av individer i Västsverige visade att hjärtfunktionen var normal eller strax under det normala hos alla undersökta, medan isotopundersökningen visade att det fanns ärr i hjärtmuskeln,

vilka var mer uttalade vid svårare grad av hjärtfel. Livskvalitetundersökningen jämfördes med svar från 1856 friska svenska barn. Den visade ingen statistisk säkerställd skillnad mellan grupperna som helhet, men vid detaljanalys fanns fler psykosomatiska symptom hos barnen med hjärtfel

Slutsatser: Incidensen av PA-IVS var 4,2/100 000 levande födda barn. Hjärtfelet var förknippat med en hög tidig mortalitet, men majoriteten av dem som överlevt de första åren mådde bra vid uppföljningen. 32 av de 52 överlevande hade normal cirkulation genom lungorna och trots att det fanns ärr i hjärtmuskeln var hjärtfunktionen god hos de flesta. Prestationsförmågan mätt med arbetsprov var god, men inte likvärdig med en grupp friska individer. Lungfunktionen begränsade och den var sannolikt nedsatt på grund av otillräcklig lungutveckling redan under fosterlivet. Livskvalitetsundersökningen visade att familjerna fungerade väl men att barnen med hjärtfel oftare rapporterade psykosomatiska symptom.

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