Valvular aortic stenosis in children

Outcome, physical activity and health-related quality of life

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To my family with all my love!

Abstract

Introduction: Isolated valvular aortic stenosis (VAS) accounts for 3–5% of congenital heart disease and presents with a wide spectrum of severity. Critical VAS in the neonate is the most severe form, fatal in the absence of treatment. Physical activity is essential for normal development and is a prerequisite for long-term cardiovascular health. Health-related quality of life (HRQoL) and life satisfaction are important subjective outcome factors.

Aim: To investigate survival and treatment outcome in neonates, children and adolescents treated for isolated VAS and also, in the children and adolescents, to study physical activity, HRQoL and life satisfaction.

Methods: All patients were treated for VAS with surgical valvotomy as the preferred primary intervention. Patients were identified in surgical registries at the two Swedish paediatric surgical heart centres. A distinction was made between neonatal critical VAS with duct-dependent systemic circulation and/or depressed left ventricular function, and neonatal non-critical VAS. Data were collected from patient files and echocardiograms, with survival data from the Swedish Population Registry for long-term follow-up. Physical activity was measured objectively with accelerometry. HRQoL was measured with KIDSCREEN-52 and life satisfaction was measured with the Satisfaction With Life Scale. Patients were matched with controls from the Swedish Population Registry.

Results and conclusions: Mortality after treatment for VAS in neonates and children was low. Transplant-free survival was 96% in the paediatric cohort (n=113), 91% in neonates with critical VAS (n=65) and 98% in neonates with non-critical VAS (n=42) with median follow-up between 11 and 14 years. Reinterventions were common and performed in 38% of the paediatric patients, 58% of neonates with critical VAS and 33% of neonates with non-critical VAS (p=0.008). Patients and controls fulfilled the WHO recommendations for physical activity to a high degree. Accelerometry revealed a different physical activity pattern in patients compared to controls. Patients rated their HRQoL and life satisfaction as similar to healthy controls. An unexpected finding was a negative association between high-intensity physical activity and psychological well-being and life satisfaction in adolescent patients.

Keywords: Valvular aortic stenosis, critical aortic stenosis, neonate, child, outcome, surgical valvotomy, physical activity, heatlh-related quality of life, life satisfaction

Sammanfattning på svenska

Bakgrund

Valvulär aortastenos hos barn är en medfödd förträngning av klaffen mellan utflödet från vänster kammare och stora kroppspulsådern. Medfött hjärtfel förekommer hos 8–10 per 1000 levande födda barn. Av dessa föds i sin tur 3–5% med förträngning av aortaklaffen. Det finns en tydlig könsskillnad där valvulär aortastenos drabbar pojkar i 75–80% av fallen. Aortaklaffen är en fick-klaff uppbyggd av tre klaffblad. Vid aortastenos är klaffbladen helt eller delvis sammanväxta och ofta förtjockade och missbildade. Svårighetsgraden av hjärtfelet varierar från kritisk aortastenos hos det nyfödda barnet, som då behöver akut behandling för att överleva, till ett tillstånd där behandling blir aktuell senare under barndomen, i vuxenlivet eller i vissa lindriga fall inte alls. Sjukdomen kan också presentera sig redan under fostertiden i svåra fall vilket påverkar hela hjärtats utveckling.

Historiskt sett har svår aortastenos hos barn varit förenad med hög dödlighet. Möjlighet till behandling blev tillgänglig mot slutet av 1960-talet. Initialt var behandlingen dock förknippad med hög dödlighet, speciellt hos nyfödda och små barn. Behandlingsmetoderna och det medicinska omhändertagandet har succesivt utvecklats vilket radikalt förbättrat överlevnaden. Behandling vid svenska barnhjärtcentra utgörs i första hand av öppen hjärtkirurgi med så kallad kommissurotomi, där sammanväxta klaffblad delas och klaffens funktion förbättras. Internationellt sett är kateterburen ballongvidgning av klaffen ofta förstahandsval. Inget av dessa alternativ är botande och behov av ytterligare behandling blir ofta aktuell

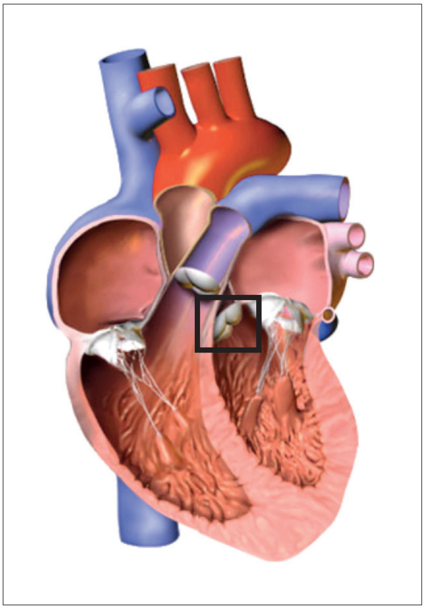

Illustration av normalt hjärta med aortaklaffen inramad.

(BruceBlaus CC BY-SA 4.0, https://commons.wikimedia.org/w/index.php?curid=61465365) på grund av kvarvarande förträngning i klaffen eller tillkomst av klaffläckage. Byte av aortaklaffen blir då nödvändigt. Aortaklaffbyte är associerat med andra problem hos barn än hos vuxna. Detta har att göra med att barnet är en växande individ, att konstgjorda klaffar, mekaniska eller biologiska, inte är tillgängliga i små storlekar samt att livslängden på klaffar är begränsad. En annan nackdel med mekaniska aortaklaffar är behovet av livslång behandling med blodförtunnande läkemedel. Ross-operation, där barnets lungartärklaff får ersätta aortaklaffen är därför ett alternativ då det ger potential för tillväxt av klaffen i takt med barnet. Nackdelar är att högerkammarutflödet ersätts med en conduit eller homograft (dvs klaffvävnad från en avliden donator) som i sinom tid kommer att kräva utbytesoperation. Hos nyfödda och små barn är det enda alternativet till Ross-kirurgi att byta den sjuka aortaklaffen mot en homograft. För illustrationer av behandlingsmetoder se kapitel 1.

Metod och resultat

I studie I redovisas resultatet av en långtidsuppföljning av barn som behandlats för aortastenos vid Barnhjärtcentrum i Göteborg mellan 0–18 års ålder. Studiegruppen omfattade 113 patienter som behandlades mellan 1994–2013. Långtidsöverlevnaden var 96%. Mer än ett ingrepp behövdes hos 38% av barnen och 33% behövde byta sin aortaklaff under uppföljningstiden som i median var 11,2 år.

Studie II var en nationell studie av alla nyfödda i Sverige som behandlats för livshotande, kritisk aortastenos före 30 dagars ålder under åren 1994–2016. Centralt i detta arbete är begreppet kritisk aortastenos vilket definieras som att det nyfödda barnets cirkulation är beroende av att fosterkärlet (ductus arteriosus) kvarstår öppet i kombination med mycket nedsatt hjärtfunktion. Diagnosen säkerställdes genom eftergranskning av hjärtultraljudsundersökningar som utfördes före behandlingen. 61 patienter inkluderades i uppföljningen som har en medianuppföljningstid på 11,8 år. I denna grupp var den transplantationsfria långtidsöverlevnaden 90%.

Studie III undersökte fysisk aktivitet hos 46 barn och ungdomar i åldern 6–18 år behandlade för aortastenos och 44 matchade kontroller. Fysisk aktivitet mättes under 7 dygn med en accelerometer buren i ett elastiskt bälte runt midjan. En accelerometer är en liten monitor som registrerar all rörelse den utsätts för. Data från accelerometern kan sedan behandlas och tolkas för att beskriva hur lång tid som tillbringats i stillasittande, lågintensiv, medelhög och hög fysisk aktivitet. Mätningarna visade att barn och ungdomar behandlade för aortastenos och deras kontrollgrupp i hög grad uppfyller WHO:s rekommendation om daglig fysisk aktivitet. Med en förfinad analysmetod av accelerometerdata kunde dock ett något annorlunda aktivitetsmönster, med mindre tid i högintensiv fysisk aktivitet, skönjas hos barn behandlade för aortastenos jämfört med de friska kontrollpersonerna.

Studie IV jämförde behandlingsresultat hos nyfödda med kritisk respektive icke kritisk aortastenos. Båda grupperna behandlades i nyföddhetstiden, dvs. före 30 dagars ålder. Indikationen för behandling av icke kritisk aortastenos var uttalad förträngning av aortaklaffen men med normal hjärtfunktion medan patienter med kritisk aortastenos uppfyllde kriterierna i studie II. I den kritiska gruppen var överlevnaden 91% och i den icke kritiska gruppen 98%. Andelen barn som inte behövde något ytterligare ingrepp under den 13,5 år långa medianuppföljningstiden var 40% i den kritiska gruppen men 67% i den icke kritiska gruppen, en signifikant skillnad.

I studie V bjöds alla barn och ungdomar 8–18 år som behandlats för aortastenos, samt matchade kontroller, in till en undersökning av livskvalitet och nöjdhet med livet. För undersökning av hälsorelaterad livskvalitet användes enkäten KIDSCREEN-52 och för undersökning av nöjdhet med livet Satisfaction With Life Scale. Inga skillnader i livskvalitet mellan patienter och deras kontroller uppmättes. Däremot skattade patienterna i ungdomsgruppen sitt fysiska välbefinnande lägre än en tidigare undersökt svensk normgrupp. När data för livskvalitet och fysisk aktivitet kombinerades sågs ett positivt samband mellan psykologiskt välbefinnande, nöjdhet med livet och måttlig och intensiv fysisk aktivitet i barngrupperna samt hos kontrollgruppens ungdomar. Lite förvånande rapporterade patienterna i ungdomsgruppen ett negativt samband mellan psykologiskt välbefinnande, nöjdhet med livet och intensiv fysisk aktivitet. Detta samband bekräftades i föräldraenkäten.

Slutsatser

Överlevnad på kort och lång sikt efter behandling av aortastenos under barndomen är god i Sverige. Det är vanligt att fler än ett klaffingrepp behövs under uppväxten och i gruppen kritisk aortastenos är det särskilt vanligt att ett nytt klaffingrepp behövs redan under första levnadsåret.

I gruppen barn och ungdomar behandlade mellan 0–18 års ålder genomgick 33% ett aortaklaffbyte under uppföljningstiden. Behov av klaffbyte var störst i gruppen nyfödda med kritisk aortastenos. Om man enbart tittar på de patienter som hinner fylla 18 år under uppföljningstiden har 87% av patienterna med kritisk aortastenos genomgått aortaklaffbyte jämfört med 33% i gruppen nyfödda med icke kritisk aortastenos.

Barn och ungdomar behandlade för aortastenos uppfyllde i hög grad WHO:s rekommendationer för fysisk aktivitet. När accelerometerdata analyserades med en metod speciellt anpassad för undersökning av fysisk aktivitet hos barn och unga, sågs en skillnad i registrerad fysisk aktivitet mellan patienter och kontroller som inte kunde urskiljas med den vanligtvis använda analysmetoden.

Barn och ungdomar behandlade för aortastenos skattade sin hälsorelaterade livskvalitet och nöjdhet med livet lika högt som kontrollgruppen. När skattning av livskvalitet kombinerades med uppgifter om fysisk aktivitet sågs ett positivt samband mellan psykiskt välmående och nöjdhet med livet med måttlig och intensiv fysisk aktivitet hos patienter och kontroller i barngruppen samt hos ungdomarna i kontrollgruppen. Ett motsatt samband sågs hos patienterna i ungdomsgruppen med lägre skattning av psykiskt välbefinnande och nöjdhet med livet i relation till mer uppmätt intensiv fysisk aktivitet.

List of papers

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

I. Kjellberg-Olofsson C, Berggren H, Söderberg B, Sunnegårdh J.
Treatment of valvular aortic stenosis in children: a 20-year experience in a single institution
Interact Cardiovasc Thorac Surg. 2018 Sep 1;27(3):410-416. doi: 10.1093/icvts/ivy078

II. Kjellberg Olofsson C, Hanseus K, Johansson Ramgren J, Johansson Synnergren M, Sunnegårdh J.
A national study of the outcome after treatment of critical aortic stenosis in the neonate
Cardiol Young. 2020 Sep;30(9):1321-1327. doi: 10.1017/S1047951120002036

III. Skovdahl P*, Kjellberg Olofsson C*, Sunnegardh J, Fridolfsson J, Borjesson M, Buratti S.
Children and Adolescents Treated for Valvular Aortic Stenosis Have Different Physical Activity Patterns Compared to Healthy Controls: A Methodological Study in a National Cohort
Pediatr Cardiol. 2021 Apr;42(4):774-783. doi: 10.1007/s00246-021-02540-1
*Equal contribution

IV. Kjellberg Olofsson C, Hanseus K, Johansson Ramgren J, Johansson Synnergren M, Sunnegårdh J.
Outcomes in neonatal critical and non-critical aortic stenosis: a retrospective cohort study
Submitted

V. Kjellberg Olofsson C, Skovdahl P, Fridolfsson J, Arvidsson D, Börjesson M, Sunnegårdh J, Buratti S.
Life Satisfaction, Health-Related Quality of Life and Physical Activity After Treatment for Valvular Aortic Stenosis
Accepted for publication in Cardiology in the Young

Abbreviations

AR	Aortic regurgitation
AVR	Aortic valve replacement
BAV	Balloon Valvotomy
CHD	Congenital heart disease
CTV	Closed transventricular valvotomy
ECG	Electrocardiography
FEM	Frequency Extended Method
HRQoL	Health-related quality of life
HTx	Heart transplantation
IVS	Interventricular septum
LPA	Light physical activity
LV	Left ventricle
LVFS %	Left ventricular fractional shortening
MET	Metabolic equivalent of task
MPA	Moderate physical activity
MVPA	Moderate to vigorous physical activity
PA	Physical activity
LVPW	Left ventricular posterior wall
QoL	Quality of life
SED	Sedentary time
SAV	Surgical valvotomy
SWLS	Satisfaction With Life Scale
UVH	Univentricular palliation
VAS	Valvular aortic stenosis
VO_2	Oxygen consumption
VPA	Vigorous physical activity
VVPA	Very vigorous physical activity
WHO	World Health Organisation

Content

1.

Introduction

The ambition of this PhD project was to explore some of the consequences of being born with the congenital heart defect valvular aortic stenosis (VAS), during childhood and adolescence. At first glance, isolated VAS may appear to be a less complicated diagnosis and a condition that can readily be corrected, considering the modern expertise in paediatric cardiac surgery. But the diagnosis is sometimes very complex. VAS caught my interest when three teenage boys with congenital VAS were assessed in the paediatric cardiology outpatient clinic and it was found that their condition had progressed during puberty. The question of timing and type of intervention was raised and, last but not least, whether they should be advised against participation in sports. For all three of them, the decision from the surgical team was to wait a bit longer and refrain from intense physical activity in the meantime. Unfortunately, all three boys were heavily involved in sports activities and aimed for careers in sports; thus, the advice to limit their physical activity was the hardest part of the information for them to receive.

There are still many questions left unanswered when it comes to treatment and follow-up of neonates, children and adolescents with VAS. The literature is not convincing regarding what type of primary treatment gives the best long-term outcome, as the goal of treatment is both to relieve the obstruction and at the same time limit the need for reinterventions and aortic valve replacements (AVR). Comparisons of the outcomes of the established treatment methods open surgical aortic valvotomy (SAV) and catheter intervention with balloon aortic valvotomy (BAV), are hampered by the use of different definitions and inclusion criteria in follow-up studies. Another interesting topic is the level of physical activity among children and adolescents treated for VAS. This is especially important because we don't know the consequences of giving advice about limiting physical activity to young people, given the fact that overweight and obesity are on the increase, and that too little physical activity in children and adolescents is described as an increasing problem in our society. Because VAS is a condition that persists from childhood into adolescence, and affects the individual's whole life situation, a third interesting topic is how these young people describe their health-related quality of life (HRQoL) and satisfaction with life.

Congenital valvular aortic stenosis

Congenital heart disease (CHD) is the most common birth defect, occurring in approximately 8–10 in 1000 live births. Of those, 3–5% are diagnosed with VAS [1, 2], and 75–80% of VAS cases are males [3, 4]. The total number of births per year in Sweden is approximately 115 000, giving an expected birth rate of about 35–60 children born with isolated VAS every year. Aortic valve abnormalities have a wide spectrum of severity, from the potentially asymptomatic bicuspid valve to life-threatening critical VAS with ductus-arteriosus-dependent systemic circulation in the neonate. Age at presentation varies from fetal life to old age.

Critical aortic stenosis in the neonate

Critical neonatal VAS is a concept used to describe severe VAS in newborns and sometimes infants. Consensus is lacking about the definition, which causes confusion when data from different studies are compared [5-7]. The two main differences between the definitions are to what age group the term applies and whether duct dependence is obligatory or not. In this work we use a strict definition of critical neonatal VAS, namely, severe VAS with duct-dependent systemic circulation and/or depressed left ventricular function in the neonate younger than 30 days of age [1, 6, 8]. In accordance with this definition, critical neonatal VAS is a life-threatening condition that demands intervention before 30 days of age.

In critical neonatal VAS, the first challenge is the decision between the biventricular or the univentricular pathway in cases with a borderline left ventricle. This decision-making process involves both objective and subjective assessment of left heart structures and whether they are of adequate size and function to support a biventricular circulation. In neonates who meet the prerequisites for a biventricular circulation, the goal of the treatment, apart from saving the child's life, is to relieve the obstruction and limit the risk of regurgitation while preserving the native aortic valve.

Natural history

Before the introduction of echocardiography and Doppler ultrasound as diagnostic tools, isolated VAS was a difficult diagnosis to confirm, as other concomitant heart defects were difficult to exclude by clinical examination alone. For example, even with cardiac catheterisation, subvalvular aortic stenosis was difficult to differentiate from VAS, introducing some uncertainty in natural history data regarding isolated VAS from the early era.

VAS is a progressive disease. Several studies have shown that progression of the stenosis applies at all ages and is a function of age, severity of the stenosis at presentation and the duration of follow-up, both in historic materials and in contemporary studies [9-12]. Studies have reported a more rapid progression during developmental periods with a high growth rate, especially the first year of life and puberty [11, 13]. The onset of symptoms is often late in the natural history of congenital VAS. Symptoms and signs of cardiac congestion seldom occur after 2 years of age. Cardiac syncope and dizziness on exertion are pointed out as ominous signs for an increased risk of sudden death [14]. Hossack et al. showed that, of 153 patients older than 1 year of age at first assessment, 55% still had a mild stenosis 18 years later while the rest of the patients had progressed to a more severe lesion [10]. Of those presenting with moderate stenosis, only 10% still had a moderate stenosis after 15 years of follow-up while the rest had developed a more severe disease, had surgery or died. The Second Natural History Study of Congenital Heart Defects (NHS-2), published in 1993, suggested that 21% of VAS patients with a peak systolic gradient of < 25 mmHg will require an intervention within 25 years of follow-up [4]. With a gradient of > 50 mmHg, 71% will eventually need an intervention, and with a gradient of > 80 mmHg an intervention is clearly indicated due to the increased risk of ventricular arrhythmias and sudden death. The authors also stated that delaying intervention in patients with a gradient of 50–80 mmHg may not be beneficial for the patient. In that study, gradients for comparison were catheter-derived at inclusion but mainly Doppler-derived at the end of follow-up. They based their follow-up data on patients with presentation beyond 2 years of age.

It is also well described in the literature how fetal VAS can gradually progress to a severe stenosis, with a negative impact on the development of the function and growth of the left ventricle and other left-sided structures, and even further to aortic atresia with hypoplastic left heart syndrome [15].

Survival and sudden death

Before the surgical era, and in the early surgical era, critical VAS presenting in the neonate or infant was associated with high mortality. In 1974, Lakier presented a series of 10 neonates with 90% mortality before or at attempted SAV [16]. Campbell presented data in 1968 suggesting a mortality rate of 23% in infants with VAS presenting during the first year of life, and thereafter mortality was estimated to 1.2% per year for the first two decades of life [3]. The NHS-2 reported an overall 25-year survival of 85%, compared to 96% in a corresponding US population. In patients receiving surgical treatment, 87% of the deaths were cardiac. In the medically managed cohort, 53% of the deaths were of cardiac origin with more than half of those being sudden unexpected deaths. Most of the sudden deaths occurred in asymptomatic patients described as having significant valve obstruction and/or aortic regurgitation. The prognosis for patients presenting before 2 years of age was still poor. Data from 25 patients under 2 years old were analysed, with 11 still alive at follow-up; 10 patients were deceased (eight within 7 days of admission), and four were lost to follow-up. However, the conclusion of this natural history data is not quite clear, as some patients underwent surgical treatment.

Contemporary data on sudden death in young patients with VAS are insufficient. In a Swedish study, 76 individuals aged 1–14 years with sudden cardiac death were identified in the Swedish Cause of Death Registry and Swedish National Board of Forensic Medicine database from 2000–2010, giving an incidence of 0.5 per 100 000 patient years [(17)]. Of those, 12 patients had a diagnosis of CHD over the 10-year period. Unfortunately, death from VAS was not specified. Sudden cardiac death in children with CHD in Norway shows a similar and low incidence [(18)] These data point in the same direction as a study by Brown et al. describing sudden death after BAV, with the finding of only one sudden death in 528 patients aged 18 months or older, with a median follow-up of 12 years [(19)]. In the latter two studies, no sudden death occurred during physical activity. Together, these studies support the understanding that sudden death in VAS after the first year of life is rare.

Morphology

The aortic valve is a semilunar valve with three valve leaflets or cusps and three commissures in between. VAS occurs due to an abnormality in the development of the valve leaflets, leading to obstruction of the left ventricular outflow tract. The stenotic valve can be tricuspid, morphologically or functionally bicuspid or unicuspid. The obstruction often occurs due to a combination of one or more of the components annular hypoplasia, dysplastic valve leaflets, fusion of commissures between the valve leaflets, or anomalies in the number of valve leaflets or cusps. The most common leaflet arrangement in VAS is the bicuspid valve with fusion of one of the commissures, most often between the right and left coronary cusp. Dysplastic tricuspid valves or a unicuspid valve with fusion of two or all three commissures are less frequent substrates for the stenosis. In addition, the dysplastic and thickened leaflets can cause impaired coaptation, leading not only to obstruction of blood flow but also to regurgitation.

Physiology

Obstruction of left ventricular outflow causes increased pressure in the left ventricle and increased wall stress. This is met by a compensatory hypertrophy of the myocytes and thereby increased wall thickness to maintain constant wall stress. Over time a remodelling process occurs, with transformation from myocyte hypertrophy to the development of fibrosis in response to the high left ventricular pressure. This in turn causes impaired ventricular relaxation and diastolic dysfunction with decreased ventricular filling. Systolic function is usually preserved but eventually becomes affected as hypertrophy increases. In cases with severe obstruction there is also a negative impact on ventricular function due to endocardial ischaemia as the high intraventricular pressure causes impaired coronary perfusion.

Clinical presentation and diagnostic methods

VAS is still relatively seldom detected by routine fetal ultrasound screening if the left ventricular size and function is still normal compared to the right ventricle (20, 21). Critical VAS is usually diagnosed within the first week of postnatal life when the ductus arteriosus closes. The newborn presents with symptoms of congestive heart failure and symptoms of low cardiac output with tachypnoea, pallor, weak peripheral pulses and a systolic heart murmur. If left ventricular function is severely impaired, no heart murmur might be heard. In asymptomatic newborns or older children, the heart defect is usually detected by auscultation of a typical heart murmur at the base, or to the right of the base, of the heart. In a Swedish report from 2006, eight of nine neonates with critical VAS were detected at routine neonatal screening before discharge from the maternity ward, in comparison to other left-sided obstructive lesions, for example, isolated coarctation of the aorta where only eight of 20 neonates were diagnosed before discharge (22).

Diagnosis is confirmed by echocardiography with evaluation of anatomy, presence of associated heart defects or ductus-arteriosus-dependent systemic circulation and left ventricular function. Gradients across the aortic valve are calculated from Doppler peak velocities using the modified Bernoulli equation. This method overestimates the gradient compared to the catheter-derived peak-to-peak gradient, which is still considered to be the gold standard for measurement of pressure gradients. Instead, the calculated mean Doppler gradient has been shown to correspond well to the catheter-measured peak-to-peak gradient (23) and is used as a more accurate surrogate for catheter-derived gradients. Additional information can be collected from an electrocardiogram (ECG) for signs of strain and left ventricular hypertrophy, and ambulatory ECG can reveal arrhythmias. Exercise tests can be used in asymptomatic patients for detection of signs of exercise-induced ischaemia, blunted blood pressure reaction or arrhythmia. As previously mentioned, cardiac catheterisation is still the gold standard for evaluating pressure gradients but has to a large extent been replaced by echocardiography and Doppler measurements as the main diagnostic tools. However, diagnostic cardiac catheterisation still has a place in cases where there is a discrepancy between symptoms, clinical findings and echocardiographic data or where non-invasive methods give borderline gradients (24). MRI is mainly used for the evaluation of aortic valve regurgitation but can also be useful for acquiring additional morphologic information on dilatation of the ascending aorta and to assess left ventricular fibrosis.

Treatment

Swedish practice

In Sweden two centres have performed paediatric heart surgery since 1993, namely, the Paediatric Heart Centre at the Queen Silvia Children's Hospital in Gothenburg and the Children's Heart Centre at Skåne University Hospital in Lund, in accordance with the licence provided by the National Board of Health and Welfare on national specialised medical care in Sweden (25). No private or other publicly funded alternatives are available for the treatment of congenital VAS in children. At both of the Swedish centres, the preferred initial treatment is SAV. BAV was introduced for primary treatment of VAS at one of the centres in 2000, but in 2006 the team chose to return to SAV as primary intervention, because treatment results were considered more favourable than after BAV. However, BAV was continued as method for reintervention for residual stenosis or restenosis at the same centre. During the time of the studies presented in this thesis, SAV remained the first choice for both primary intervention and reinterventions at the other centre. The Ross procedure was introduced in the mid-1990s, and the first primary neonatal Ross was performed 10 years later.

Indications for treatment

In neonates with critical VAS (duct-dependent systemic circulation or depressed left ventricular function), there is an indication for treatment regardless of valve gradient, as there may be a low gradient across the valve secondary to impaired left ventricular function. In children and adolescents, treatment is indicated when the catheter-derived gradient exceeds 50 mmHg, according to guidelines, in asymptomatic patients (26). Treatment is also indicated at a gradient of 40 mmHg or above if the patient is symptomatic or if signs of ST-T changes are present on resting ECG or exercise test. Indications for valve replacement, in addition to stenosis, includes a combination of stenosis and regurgitation or severe aortic valve regurgitation.

Valvotomy

SAV and BAV are palliative procedures with the goal of achieving relief of valve obstruction, minimising the need for reinterventions due to residual or recurrent stenosis without causing valve regurgitation. Both methods can be used for the primary intervention as well as at repeated interventions on VAS. Over time, the techniques have been refined for both methods and together with the advances in intensive care, the outcome for paediatric patients with severe VAS has improved markedly.

Closed transventricular valvotomy was the first method available for relief of VAS in the early era of congenital paediatric heart surgery [14, 27]. In this method, the apex of the left ventricle was accessed by median sternotomy or left thoracotomy and either a balloon catheter or serial Hegar dilators were introduced through the left ventricular apex, blindly guided through the stenotic aortic valve and followed by a blunt dilatation of the valve (Figure 1). Hence, this method bears more resemblance to the BAV method than to surgical commissurotomy of the modern era, as the valve tears at the weakest point. This method has been replaced by SAV or BAV as it carried a high risk of causing severe aortic valve incompetence.

Open SAV was first described in infants in 1969 [28]. The operation is performed with the patient on cardiopulmonary bypass. Today, this surgical technique involves a commissurotomy where partially fused commissures are incised and the procedure often involves thinning of dysplastic valve leaflets and excision of noduli, enhancing leaflet mobility and thereby increasing the functional valve area [8, 29] (Figure 2). This method of valvotomy, under direct visual control, limits the risk of causing severe valve regurgitation.

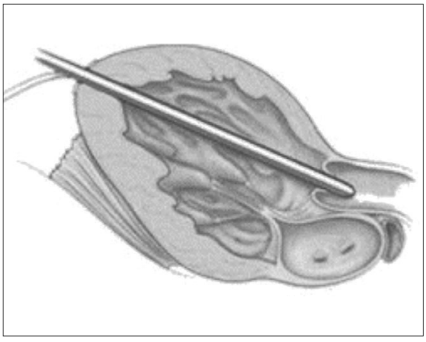

Figure 1. Closed transventricular valvotomy.

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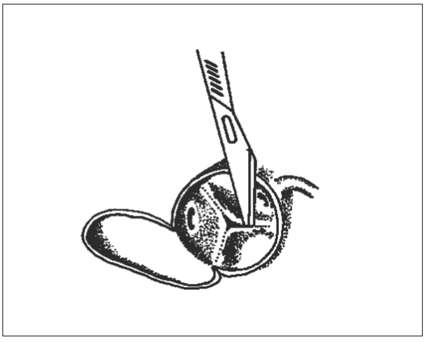

Figure 2. Open surgical valvotomy.

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BAV was first described by Lababidi in 1983 [30, 31] and a few years later reported in neonates and infants [32]. The procedure is usually performed retrograde, with vascular access though the femoral artery, but can also be performed through an antegrade approach. The aortic valve is crossed with catheter or wire. The catheter is exchanged with a balloon catheter and, after hemodynamic evaluation and angiogram, dilatation of the valve is performed with either an adequately sized single balloon or with a double balloon technique (Figure 3). In the early era, this method was associated with a high risk of valve regurgitation because the tearing of leaflets is blind and more difficult to control, given that the valve leaflets may not tear along the commissures. Today, guidelines suggest the use of a balloon with an inflated diameter of 80–100% of the aortic anulus diameter in order to decrease the risk of severe post-procedural regurgitation. In patients with good ventricular function, rapid right-ventricle pacing can be used to stabilize the balloon position [24].

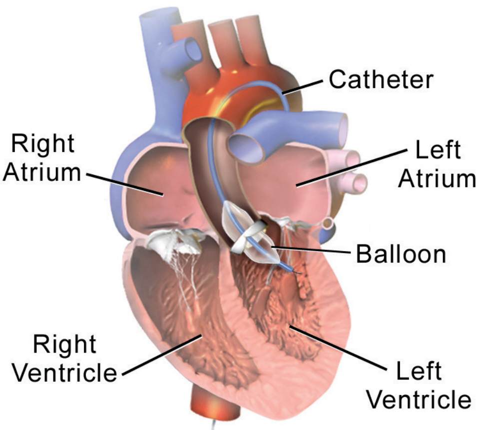

Figure 3. Balloon aortic valvotomy.

Aortic valve replacement

AVR is sometimes unavoidable in congenital VAS. AVR might be required as the primary intervention but is more often used as a reintervention after one or more valvotomies, and the need for AVR increases with age. AVR is associated with different problems in infants and children than in adults. The most obvious obstacle is that the paediatric patient is still growing, making prosthetic valves of limited use in small children, in addition to the fact that prosthetic valves are not available in small sizes. In neonates and infants, the available alternatives for AVR are the Ross procedure or the use of a homograft in the aortic root position.

Mechanical prosthetic valve replacement is an option associated with long durability and positive short-term and mid-term outcomes, and it has been reported in older children and adolescents [33, 34] (Figure 4a). A major disadvantage is the requirement of lifelong anticoagulation therapy with the well-known negative side effects of increased risk of thromboembolism and bleeding complications and, for women of childbearing age, the risk of complications during future pregnancies, including the teratogenic effect of warfarin on the fetus. Anticoagulation treatment might also restrict certain physical activities.

Biological prosthetic valves (Figure 4b) and homografts have a limited lifespan and sometimes degenerate quickly with a potential need for repeated replacements during childhood [35]. With tissue valves there is a low risk of thromboembolic events, and anticoagulation treatment is not needed.

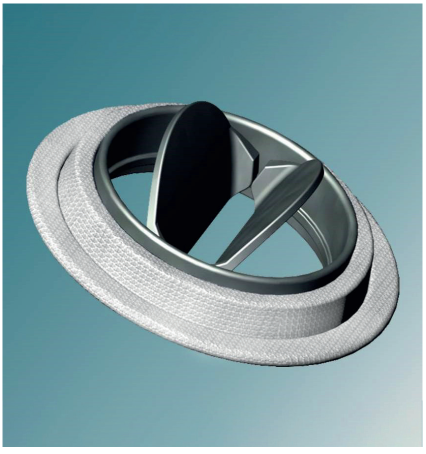

Figure 4a. Prosthetic mechanical aortic valve.

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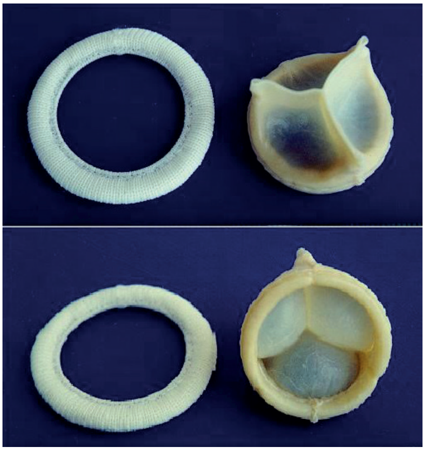

Figure 4b. Prosthetic biological aortic valve.

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The Ross procedure is a complex surgical procedure in which the pulmonary valve is used as an autograft, transplanted to the aortic root position. The coronary arteries are reimplanted in the neo-aortic root, and the pulmonary valve is replaced by a homograft in the right ventricular outflow tract [(36)] (Figure 5). The technique was first described in 1967 and has been more commonly used in the paediatric population since the 1990s [(37-39)]. The Ross procedure is considered the best AVR option for children because the neo-aortic valve has the potential for somatic growth but without any need for anticoagulation. However, the Ross procedure is associated with complications related to development of dilatation of the neo-aortic root and secondary regurgitation in the neo-aortic valve and also to degeneration of the homograft in the right ventricle outflow tract and repeated homograft interventions and replacements. In a systematic review by Ethnel et al., the rate of neo-aortic valve reoperations was lower in neonates and infants, but reinterventions of the right ventricular outflow tract were higher than in older children [(33)].

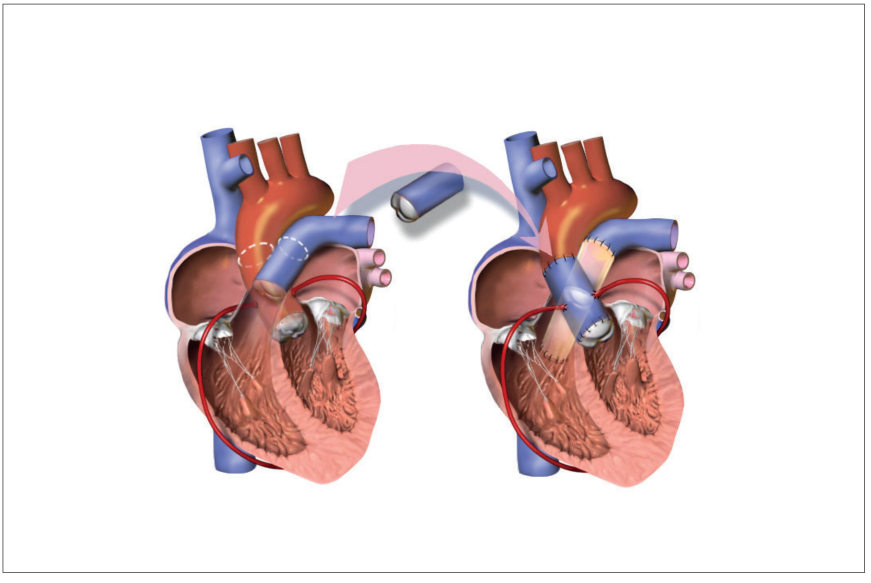


Figure 5. The Ross procedure where the aortic valve is replaced with the pulmonary valve. The coronary arteries are re-implanted in the autograft and the pulmonary valve is replaced by a conduit in the ventricular outflow tract.

Treatment results

Many single-centre studies have reported their results after treatment of VAS. The results have improved considerably over time with both open SAV and BAV, and the answer to what initial treatment method gives the best short-term and long-term results is not yet settled. Paediatric cardiology centres advocating BAV claim their method to be less invasive, requiring a shorter hospital stay, while surgically oriented centres claim better and more precise results with SAV, giving a lower risk of regurgitation and longer freedom from reintervention [(40, 41)]. However, different inclusion criteria regarding, for example, age and presence of concomitant heart disease, and varying follow-up time leads to heterogeneous groups and hampers comparisons of mortality, reinterventions and need for AVR. Criteria for reintervention and a definition of the optimal time for reintervention are missing. Comparisons are also complicated by a lack of information about why some patients were chosen for SAV and others for BAV, at the same centre, where both methods were available. The comparisons of heterogeneous groups might also explain the sometimes contradictory findings in the analysis of risk factors for adverse events, mortality, reinterventions and AVR. There is also a certain conceptual confusion when reporting early and late mortality, which means that comparisons must be treated with caution. Early mortality is sometimes reported as 30-day mortality and sometimes as in-hospital mortality. Late mortality, or late death, may refer to death more than 30 days after the intervention or after hospital discharge. Survival is either described in terms of late survival or late transplant-free survival.

Paediatric patients

In contemporary studies, early mortality after SAV or BAV in paediatric patients aged 0–18 years is comparable between the methods and it is low. Reported rates range from no early mortality to 5% reported by Herrmann et al., Auld et al., Boe et al., Sullivan et al. and Kallio et al. in studies published between 2017 and 2021 [(42-46)]. Late mortality in the same studies was reported to be between zero and 7%, again with no differences between SAV and BAV and with a longer follow-up time being associated with higher figures of late mortality. Auld and Kallio reported zero mortality after both SAV and BAV, Herrmann reported 3.3% after SAV and 4.5% after BAV, and Sullivan reported 7% after BAV. In the report by Herrmann et al., patients under 2 months were excluded.There has been a considerable improvement in survival compared to the first decade of 2000, when early mortality after surgical treatment ranged from 2% to 13% and late mortality from zero to 24% [(47-50)]. After BAV early mortality ranged from zero to 8% and late mortality from zero to 11% [(48, 51-53)], although neonates were not included in two of these studies [(47, 48)].

A comprehensive review by Hill et al. was published in 2016, in which 2368 patients were included in the analysis, including 1835 (77%) in the BAV group and 533 (23%) in the SAV group [54]. The review showed that short-term and long-term mortality after SAV and BAV were similar but time to reintervention was significantly longer after SAV than BAV ($p < 0.001$). Freedom from reintervention at 10 years was 46% (95% CI 40–52) in the BAV group and 73% (95% CI 68–77) in the SAV group, though freedom from AVR did not differ significantly between the groups. A propensity-score-matched study by Auld et al. compared survival and freedom from reintervention from two centres including all paediatric age groups, one centre with a preference for BAV and the other with a preference for SAV, with mean follow-up of 5.3 years [43]. No significant difference in overall reintervention rate or survival rate was found, and freedom from reintervention at the latest follow-up was 69% for BAV and 70% for SAV.

Critical aortic stenosis in the neonate

Outcomes after critical or neonatal VAS are not as easy to compare, as mentioned above, given the lack of consensus about the definition of critical VAS. A recently published study by Zaban et al. included neonates and infants up to 60 days of age, with SAV (n=15) or BAV (n=40); critical VAS was defined as "need for prostaglandin administration prior to procedure" [55]. Critical VAS was present in 47% of the neonates in the SAV group and 32% in the BAV group. Two early deaths were reported out of 15 patients in the SAV group and one late death among 40 patients in the BAV group. There was no difference in pre- or post-procedure gradients. Freedom from reintervention after 1 and 5 years, respectively, was 67% and 67% after SAV and 69% and 43% after BAV (p=0.6). For the BAV group, freedom from reintervention of 28% and 18% was presented at 10 and 15 years with an average follow-up of 11 years, while the SAV group had an average follow-up of only 3 years. BAV was associated with significantly higher incidence of moderate (15%) or severe (2.5%) post-procedural aortic regurgitation, whereas no patient had moderate or severe regurgitation after SAV. Zaban et al.'s definition of critical VAS (age up to 60 days and need for prostaglandin treatment prior to procedure) was also used by Boe et al., who examined register-based data on 1026 neonates (up to 30 days of age) with critical VAS and reported 10% in-hospital deaths after BAV and 17% post-procedural moderate to severe aortic regurgitation [44].

Vergnat and colleagues, in another recent publication, defined critical VAS as all neonates with aortic valve intervention in the first 30 days of life [56]. They included 52 neonates after SAV and 51 after BAV. Early mortality was 4% after SAV and 8% after BAV. Among the hospital survivors there was one additional late death in the SAV group and three late deaths in the BAV group after a median of 13 years of follow-up. In four patients with left ventricular dysfunction, an initial BAV (known as "gentle balloon") was performed to treat left ventricular dysfunction, followed by SAV after left ventricular recovery. These patients were classified as SAV patients. Freedom from surgical reintervention at 10 years was 36% after BAV and 66% after SAV. AVR was needed in 39% of the BAV group and in 23% of the SAV group a median of 5.9 years after the first procedure; no statistically significant difference was found in freedom from AVR (p= 0.24).

Lofland et al. defined critical VAS as "moderate to severely reduced left ventricular function and presence of systemic perfusion dependent on right ventricular output via a patent arterial duct" in a multi-centre study in which neonates with critical VAS were assigned to biventricular pathway (BAV, SAV or AVR), univentricular pathway or heart transplantation [(57)]. A slightly modified version of this definition was stated by McCrindle et al. as "presence of moderate to severe aortic valve stenosis, together with either reduced left ventricular function or presence of systemic perfusion dependent on right ventricular output via a patent arterial duct". They concluded that BAV and SAV for the treatment of critical VAS in the neonate have similar outcomes.

Previous publication of Swedish follow-up data is limited to a study by Rehnström et al. from 2007, including 64 neonates and infants younger than 3 months of age, treated with primary SAV at the Children's Heart Centre in Lund [(58)]. This study reported a 30-day mortality of 5% and a long-term mortality of 10%. Critical VAS was defined as VAS with treatment before 3 months of age. Galoin-Bertail et al. used a similar definition of critical VAS, namely, neonates and infants under 4 months of age treated with SAV [(7)]. They reported 6% early mortality, with all deaths occurring in the neonatal group, and a total mortality of 13%. Event-free survival was 51%, 35% and 18% after 5, 10 and 15 years, respectively.

In reports from the earlier era, mortality is far higher, probably reflecting a time before the introduction of univentricular palliation but also the inclusion of neonates with complex cardiac anomalies. For example, Brown et al. in 2003 reported 33% mortality after SAV, and Agnoletti et al. in 2006 reported 19% mortality after SAV and 54% after BAV [(59, 60)]. Another problem encountered with comparisons between surgical and catheter treatment in the earlier era is that the method of surgical treatment was blunt dilatation of the aortic valve, a method which has since been abandoned. In 2013, Siddiqui et al. compared results after SAV and BAV in treated neonates and infants up to 1 year of age; they reported late mortality of 9.6% after SAV and 11.1% after BAV [(61)]. Considered together with outcome after treatment of VAS reported in the last few years, as previously discussed, this reflects a successive improvement of outcome after treatment over the past decades.

Physical activity and congenital heart disease

Physical activity is essential for normal physical, emotional and psychosocial development during childhood. There is an increasing awareness about the risks associated with a sedentary lifestyle and physical inactivity. Prior research has confirmed positive effects of physical activity on motor skill development, self-esteem, learning, psychosocial health, quality of life (QoL) and cardiovascular health [62]. Physical inactivity, on the other hand, is associated with an increased risk of obesity, cardiovascular disease, hypertension and depression [63, 64].

Today most children born with complex CHD, including VAS, survive to adulthood [65, 66]. This creates new challenges to health-care providers to incorporate a preventive approach to cardiovascular health and to promote a healthy lifestyle during childhood, in addition to routine medical follow-up at the clinic. Several institutions have published recommendations regarding physical activity in children in general but also for children and adults with CHD [67-69]. The recommendation is ≥ 60 min of moderate to vigorous physical activity ("makes you warm and breathe faster") every day and activities that strengthen muscle and bone at least 3 days a week for children and adolescents. Sedentary time should be minimized.

As VAS is a complex and lifelong disease that often requires re-interventions and further surgery, patients sometimes show residual or acquired abnormalities of the left heart structure which might affect cardiovascular capacity [70]. Exercise function is preserved in most patients treated for VAS in infancy, but there may still be reduced peak oxygen consumption (VO_2) in some individuals. This may reflect an inability to increase stroke volume [71].

Traditionally, patients with CHD, including VAS, were advised to restrict their physical activity [72]. This advice from health care providers might be influenced not only by medical risk factors but also by tradition and by legal concerns related to the tragedy of sudden cardiac death in a young person. Unnecessary restrictions might also be imposed by parents, caregivers, educators and sports trainers, a problem that has been recognised for many years [73, 74]. With the more active approach to intervention in children and adolescents with VAS compared to the early era of paediatric cardiology, the perceived risk of sudden death in children and adolescents with congenital VAS is low [75, 76]. Today there is no evidence to support restricting recreational and non-competitive physical activity among patients with CHD except in patients with rhythm disorders [69]. For competitive sports, the Bethesda Conference has established consensus guidelines [77]. Despite this, children and adolescents with VAS are sometimes advised to avoid strenuous physical activities. With a more preventive approach to medical care in children and adolescents, objective measurement of physical activity is essential in identifying patients at risk of physical inactivity.

Studies of physical activity in children with CHD

The physical activity of children with CHD has been compared with healthy controls in several studies, with inconclusive results. Studies by Zaquot et al., Stone et al., Ewalt et al., Arvidsson et al. and Brudy et al. found no difference between children treated for CHD and healthy controls when physical activity was objectively measured with accelerometry [(78-82)]. However, the proportion of children who met the WHO recommendations for physical activity varied among the studies. Voss et al. and Zaquot et al. found no difference in accelerometry-derived metrics between children with CHD of different levels of severity [(78, 83)]. McCrindle et al., but not Hedlund et al., found reduced physical activity levels after Fontan palliation [(84, 85)]. Subjective evaluation measures also show no clear trend, with reports of higher, lower or similar levels of physical activity between CHD patients and controls [(85-88)]. The absence of a clear pattern of differences may reflect the many different questionnaires and scales used in subjective evaluation, or methodological issues when physical activity is objectively measured, or the small sample sizes may have limited the statistical power to detect differences between groups.

Measurement of physical activity

Physical activity is defined as any bodily movement produced by skeletal muscles that requires energy expenditure [(67, 89)]. It should not be confused with exercise (a subcategory of physical activity) or exercise capacity (maximal oxygen consumption). Physical activity is usually presented as time spent in activity of different intensity categories; sedentary behaviour (SED), light physical activity (LPA), moderate physical activity (MPA), moderate-to-vigorous physical activity (MVPA), vigorous physical activity (VPA) and very vigorous physical activity (VVPA).

Physical activity can be quantified either with subjective or objective methods [(36)]. Subjective methods, such as questionnaires or interviews, are cost-effective but tend to overestimate both time spent in and intensity of physical activity reported by children and adolescents, giving poor reliability and validity. The activity pattern of children and adolescents in general is rather complicated to measure as it is characterised by high frequency spontaneous activity of short duration, with rapid variations in high and low intensity [(90)]. The gold standard for objectively measured physical activity is the doubly labelled water method, which gives a precise and accurate measure of free living energy expenditure [91]. In this method, two stable isotopes, deuterium (^2H) and 18-oxygen (^{18}O), are administered orally and the elimination of the two isotopes is measured in urine samples over 1–3 weeks. The difference between the ^2H and ^{18}O elimination rate is calculated as proportional to the production of CO_2. The disadvantage of this method is that the analyses and isotopes are costly, no information on type of physical activity is given and no quantification of duration or intensity is obtained.

Accelerometers are devices that assess both duration, intensity and frequency of physical activity under free living conditions, thus enabling comparison with physical activity guidelines. Triaxial acceleration is registered with high precision. Compared to the doubly labelled water method, accelerometers are cheap and easy to use, both in a research setting and in clinical practice. Their disadvantages are their limited ability to register some activities, for example, swimming, weightlifting and cycling, and also the lack of a standardised measurement protocol. Other objective methods for physical activity measurement are heart rate monitors with indirect measurement of physical activity, pedometers producing a count of daily steps and commercially available activity trackers of varying quality, but these methods do not allow classification according to the guidelines. Furthermore, some children with CHD might have an altered heart rate response to exercise, limiting the use of heart rate monitors and wearable devices when assessing physical activity [92-94].

Accelerometer protocols

Measurement protocol, device placement and setting, raw data processing, value calibration for intensity categories and statistical methods all influence the results of physical activity measurement with accelerometry. Previous studies of physical activity in children with CHD compared to healthy children have shown conflicting results. This might reflect methodological differences complicating comparison, such as differences in the parameter settings mentioned above [95]. A measurement protocol adapted to physical activity measurement in children is essential in the collection of valid data. The measurement model should capture the volume, intensity, duration and frequency of physical activity.

Device placement: Accelerometers can be attached to an elastic band worn on the hip, on the dominant or non-dominant wrist or on the thigh. Data collection differs between the placement sites. Hip-worn devices have been reported to better capture whole body movement [96] and are the most commonly used in published studies of children with CHD [97]. Comparisons of results should be avoided between physical activity measurements from different device placements.

Data collection: Age-adapted instructions on how to wear and use the device and a 7-day measurement protocol with round-the-clock registration facilitate longer wear time and the capture of physical activity over a normal week [98, 99]. A sampling frequency of 30 Hz, or multiples of 30 Hz, is shown to give accurate estimates of acceleration counts [100].

Data processing: The data processing includes settings for raw data filtration, epoch length, value calibration and calibration of cut points. The accelerometer method commonly used in previous research in CHD, ActiGraph counts, shows limitations in capturing intermittent and high-intensity physical activity, which has restricted the correct classification of physical activity [101-103]. These measurement errors are more prominent in children due to their intermittent movement patterns, with short bursts of high-intensity activity alternating with low-intensity activity, compared to older individuals. A recent methodological development is the application of a wider frequency filter on the raw data processing (the frequency extended method, FEM), with the output presented as a detailed spectrum of physical activity intensities. The FEM enables registration and correct classification of more of the high-intensity physical activity in children. The use of short epoch length (time interval) in raw data collection has been shown to improve data collection and classification of physical activity in children whose activity levels change frequently [104]. To convert the accelerometer counts into time spent in different activity intensity categories, a value calibration against indirect calorimetry (reference method: oxygen consumption (VO_2)) is made and thresholds or cut points are applied. The unit MET (metabolic equivalent of task, VO_{2total}/VO_{2rest}) is an established measure of energy expenditure where 1 MET equals energy used at rest (SED) and ≥ 3 MET is a commonly used threshold for MPA. However, the MET is a unit that does not take age or body size into account. Therefore, VO_{2net} (VO_{2total}/VO_{2stand}) has been proposed as a more appropriate unit for calibration, as it enables comparisons of different age groups [105]. The use of pre-calibrated cut points for physical activity classification requires use of the same data collection and processing criteria as in the original calibration study for comparability [105, 106].

Inclusion criteria: Criteria for measurement of a valid day, a valid week and non-wear time should be stated.

Outcome parameters: Physical activity is usually presented in the intensity categories SED, LPA, MPA, MVPA, VPA and VVPA [95]. It can also be presented in a high-resolution intensity spectrum, allowing a more precise presentation, especially VVPA which often occurs in very short episodes (seconds or minutes) [107].

As stated in two recent reviews, by Brudy et al. and Skovdahl et al., there are no clear answers to the question of how physically active CHD patients really are, because of the methodological differences in the available studies [97, 108]. Both reviews recommend that future studies adhere to consistent measurement standards and consider sampling accelerometer protocols adapted for use in children and adolescents, namely, sampling frequency, device placement, epoch length, wear time definitions (valid day and valid week) and data processing, including appropriately calibrated cut points or thresholds. The suggested methodological considerations are summarised in figure 6.

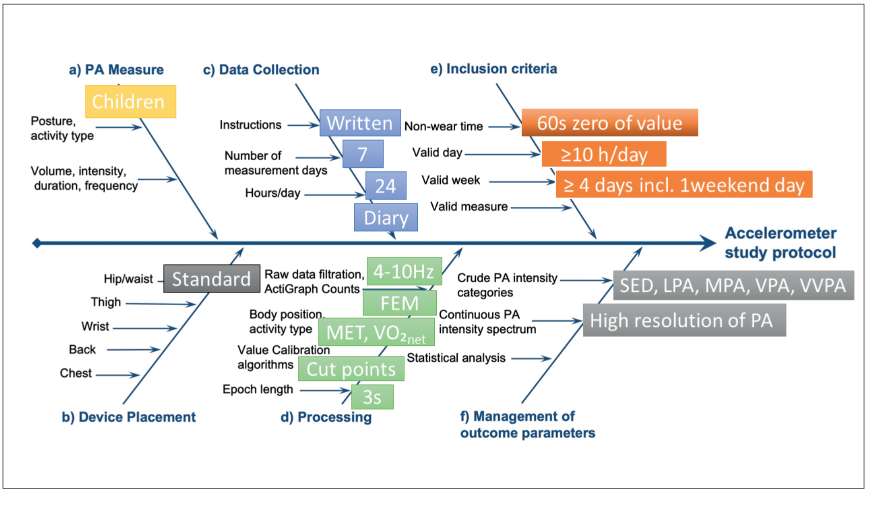


Figure 6. Summary of methodological considerations and suggestions for accelerometer measurement in children. (FEM, frequency extended method; MET, metabolic equivalent of task; SED, sedentary behaviour; LPA, light physical activity; MPA, moderate physical activity; VPA, vigorous physical activity; VVPA, very vigorous physical activity.)

Modified from Skovdahl et al., Cardiol Young. 2021;31(4):518-31.

Health-related quality of life and life satisfaction

The concepts QoL, health, HRQoL and life satisfaction are often confused. Several definitions of each concept exist and there is no generally accepted definition of QoL or HRQoL [(109)]. To complicate matters further, there is an overlap between the concepts, contributing to the confusion. The definition of QoL used by WHO is *"an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns"* [(110)]. The concept "health" was defined by WHO in 1948 as *"a state of complete physical, mental and social well-being, and not merely the absence of disease and infirmity"*. HRQoL is a multidimensional concept that encompasses a number of different domains of relevance for a person's QoL, and it describes the aspects of QoL that are influenced by health. For children, these domains can include physical and psychological well-being, peer relations, home life and school environment [(111)]. HRQoL is sometimes described as a measure of self-perceived health status or subjective health and well-being. Life satisfaction, on the other hand, is a person's global assessment of their satisfaction with life, based on their own criteria [(112, 113)].

The abundance of studies of QoL and HRQoL in the medical field over the last 50 years can be seen as complementing the classical crude outcome factors of morbidity and mortality with patient-reported indicators of improvement and advancements in medical care. Another aim of HRQoL measurements is to aid health care planning: to identify individuals or groups at risk of developing health problems in order to plan for interventions. On the individual level, HRQoL measurement is a tool in clinical practice for screening and early detection of, for example, a need for psychosocial support or school interventions in a child with a chronic disease.

Measures of HRQoL

A considerable number of instruments or questionnaires are available for the measurement of HRQoL in children and adolescents [(114, 115)]. HRQoL instruments can be either generic or disease-specific. One advantages of using a generic tool is the possibility to compare measurements with healthy controls. On the other hand, disease-specific instruments may be better at focusing on domains potentially affected by a specific diagnosis, such as asthma or CHD. The instrument can aim to target either a specific age group or several age groups. Age-adapted self-reports are essential to capture the subjective views of children and adolescents. Children from 8 years of age have been shown to adequately understand and reliably answer questions about their HRQoL [(116)]. As a complement to child self-reports, some measures include a parent proxy report. The instruments can also be designed for a specific national or cultural context or be cross-culturally validated, and they can include different numbers of items and scales to describe different aspects of HRQoL.

In our study (paper V), we choose to investigate HRQoL using the questionnaire KIDSCREEN-52 [111, 117], and to assess life satisfaction using the Satisfaction With Life Scale [112]. The KIDSCREEN instrument was developed within a European collaboration with 13 participating countries, Sweden being one of them. One of the goals of the project was to produce an instrument appropriate for use in different cultural contexts. To date, the questionnaire has been translated into 34 languages and is widely used. The KIDSCEEN-52 was developed as a self-report measure for both healthy and chronically ill children and adolescents from 8–18 years of age, and it includes a parent proxy version. The instrument measures 10 dimensions of HRQoL in a 52-item questionnaire. The items are scored on a five-point scale. European norm data for children and adolescents and Swedish norm data for adolescents are available for comparison. In the development process, construct validity was evaluated based on hypotheses derived from theoretical considerations and assessed for socio-demographic and socio-economic variables, health status, psychosomatic health complaints, mental health and behaviour problems, health care utilisation, social support and family, and family health behaviour.

Measures of life satisfaction

The Satisfaction With Life Scale (SWLS) was developed by Diener at al. and first published in 1985 [112]. It assesses global life satisfaction, in other words, a person's satisfaction with his or her life as a whole. It is a short questionnaire consisting of five items. A child version and an adolescent/adult version are available, as are translations to various languages. The original publication showed high internal consistency and high temporal reliability. This instrument has also been validated in children [113, 118].

HRQoL and life satisfaction in children and adolescents with CHD

Many studies have been published with the aim of describing HRQoL in children and adolescents with CHD, but when compared with healthy children their results are inconclusive. This might be due to weaknesses in the studies, as reported by Bratt and Moons [119]. Other explanations might be that children and adolescents with CHD generally perceive their HRQoL at the same level as their healthy peers. A systematic review of QoL in adolescents and young adults with CHD by Schrøder et al. included 18 studies; two of these reported better QoL in CHD patients than in controls, six reported worse QoL, at least in patients with a severe diagnosis, and 10 reported no difference between patients and controls [120]. Schrøder et al. also performed a meta-analysis with pooled data from the six studies that measured HRQoL with the Pediatric Quality of Life Inventory 4.0 (PedsQL, generic module) in patients with mild, moderate and severe CHD (n=328). The meta-analysis showed that QoL was no lower in children with CHD than in healthy controls. Reiner et al. reported HRQoL in 514 patients with simple, moderate and complex CHD, including patients with univentricular palliation, with a mean age of 13.2 years [154]. HRQoL was measured with the KINDLE self-report, and patients with CHD scored the same or higher than the controls. No differences between the CHD severity groups were found.

A study by Amedro et al. from two tertiary European centres used the KIDSCREEN-52 self-report and KIDSCREEN-27 parent proxy report to compare patients with CHD of mixed severity, aged 8–18 years (n=282), with healthy controls [155]. Self-reported HRQoL was similar in seven of 10 domains but scores were lower for CHD patients in the domains physical well-being, financial resources, and peer and social support. The parent proxy scores were significantly lower in four of five dimensions. Other studies were often carried out at a single centre with a small number of participants, using a variety of HRQoL measures on patients with mixed or specific CHD diagnoses. A common conclusion is that, overall, HRQoL in children and adults with CHD does not differ significantly between CHD severity groups or compared to healthy controls, although divergence can be detected in some domains, for example physical well-being [121-123]. However, there are also reports of lower HRQoL in patients with CHD compared to controls. A multi-centre study by Mellion et al. reported significantly lower HRQoL in patients with moderate and severe CHD than in controls (measured with PedsQL), at a level comparable with paediatric patients with other chronic diseases [124]. Patients with univentricular palliation (Fontan circulation) or after biventricular repair with experience of repeated surgical reinterventions also reported lower HRQoL [85, 125, 126].

No study has specifically addressed HRQoL in patients with VAS. VAS belongs to the group of moderate to severe CHD diagnoses, where many children and adolescents need to relate to a chronic and lifelong disease. Treatment during childhood is palliative, with the prospect of new interventions in the future and possibly an AVR later in life. Some patients have also been exposed to advice on exercise restriction, sometimes for an intended limited period of time, but leading to lifestyle changes and bringing an end to certain sports activities.

These circumstances provide an incentive to investigate HRQoL in children and adolescents with VAS.

HRQoL, life satisfaction and the influence of physical activity

In healthy children, physical activity has a positive relationship with physical, psychological and cognitive health [62]. The relationship is stronger for higher physical activity intensities (MVPA) than for lower intensities (LPA). Hence, it is fair to assume that a similar relationship exists for children and adolescents with CHD [127]. However, as mentioned earlier, physical activity in patients with CHD might be complicated by reduced exercise capacity, secondary to residual or acquired cardiovascular abnormalities [71, 128], and also by overprotective parents [129] and by physical activity restrictions imposed by cardiologists, parents, teachers or coaches [68, 130]. During childhood, the family can support the child to perform at a physical activity level that suits the child's abilities and limitations, and physical activity can be assumed to have a positive relationship with QoL [131]. However, if the child is withheld from physical activities, this may have negative effects on HRQoL, motor development and future physical health [74, 82]. For adolescents, the situation becomes more complicated. Adolescence is a period involving physical, psychological and social changes. It is well known that QoL scores decline during adolescence compared to children, and the decline is more pronounced in girls than in boys [132, 133]. During adolescence, the influence of peers, or peer pressure, becomes more important compared to the influence of family [134, 135]. Physical activity is also associated with social status, at least in boys. The demands of physical capacity for those participating in sports and competition increases with age during this phase. These factors, in combination with the burden of disease, potential physical incapacity compared to peers, the possibility of future surgery and activity restrictions, might give rise to mixed emotions in the adolescent patient. It is not unreasonable to believe that this might affect the ambition to participate in physical activities and sports, and influence the effect of physical activity on HRQoL in children and adolescents with VAS.

2.

Aims

The overall aims of this thesis were to investigate survival and treatment outcome in neonates, children and adolescents treated for isolated valvular aortic stenosis and also, in the children and adolescents to study physical activity, health-related quality of life and life satisfaction.

The specific aims of the studies were:

Paper I

To describe survival, treatment results, reinterventions and need for aortic valve replacement in children and adolescents treated for valvular aortic stenosis with open surgical valvotomy as the preferred primary intervention.

Paper II

To describe survival and treatment results in a complete national cohort of neonates treated for isolated critical valvular aortic stenosis with open surgical valvotomy as the preferred primary intervention.

Paper III

To compare patterns of physical activity between children and adolescents treated for valvular aortic stenosis and healthy controls using an improved accelerometer method. A secondary aim was to study whether the patients and the controls met the WHO recommendations for physical activity for children and adolescents.

Paper IV

To study whether the definition of critical valvular aortic stenosis in the neonate has implications for the interpretation of treatment outcome when comparing results after treatment in the neonatal period.

Paper V

To investigate health-related quality of life and life satisfaction in children and adolescents treated for valvular aortic stenosis compared with healthy controls. A second aim was to investigate the relationships between their objectively measured level of physical activity and their health-related quality of life and life satisfaction.

3.

Overview of included studies

A summary of the papers included in this thesis are presented on the next page.

PAPER	TITLE	AIM	PATIENTS
I	*Treatment of valvular aortic stenosis in children: a 20-year experience in a single institution*	To describe survival, treatment results, reinterventions and the need for aortic valve replacement in children treated for VAS with surgical valvotomy as preferred initial intervention.	Single-centre study. Patients with VAS were identified in the local surgical and catheter registries. Those aged 0–18 years at treatment between 1994–2013 were enrolled.
II	*A national study of the outcome after treatment for critical aortic stenosis in the neonate*	To describe survival and treatment results in a complete national cohort of neonates treated for isolated critical VAS with surgical valvotomy as preferred first intervention.	National study. Neonates aged ≤30 days at treatment for VAS were identified in surgical and catheter registries 1994–2016. Neonates with non-critical VAS were excluded.
III	*Children and Adolescents Treated for Valvular Aortic Stenosis Have Different Physical Activity Patterns Compared to Healthy Controls: A Methodological Study in a National Cohort*	To compare PA patterns between children and adolescents treated for VAS and healthy controls, using an improved accelerometer method.	National study. All patients treated for VAS and aged 6–18 years were invited and compared to matched controls (age, gender and residential area) generated from Statistics Sweden.
IV	*Outcomes in neonatal critical and non-critical aortic stenosis: a retrospective cohort study*	To analyse whether the definition of critical VAS has implications for the interpretation of treatment outcome, by comparing results after treatment in neonates with critical and non-critical VAS.	National study. Neonates aged ≤30 days at treatment were identified in surgical and catheter registries 1994–2018 and divided into critical and non-critical VAS.
V	*Life Satisfaction, Health-Related Quality of Life and Physical Activity After Treatment for Valvular Aortic Stenosis*	To investigate HRQoL and life satisfaction in children and adolescents treated for VAS and in healthy controls. To investigate the association between PA, HRQoL and life satisfaction.	National study. All patients treated for VAS and aged 8–18 years were invited and compared to matched controls (age, gender and residential area) generated from Statistics Sweden.

HRQoL, health-related quality of life; PA, physical activity; VAS, valvular aortic stenosis.

METHODS	STATISTICAL METHODS	RESULTS
Retrospective cohort study. Data retrieved from medical records. Survival cross-checked with the Swedish Population Registry.	Kruskal-Wallis test for difference between groups. Kaplan-Meier survival analysis with log-rank test. Linear regression for association between gradients and left ventricular function measurements.	113 patients were included. No 30-day mortality. Long-term transplant-free survival was 96% with median follow-up of 11.2 years. 38% had a reintervention and 33% had an aortic valve replacement.
Retrospective cohort study. Data were retrieved from medical records and preoperative echocardiograms. Survival was cross-checked with the Swedish Population Registry.	Kruskal-Wallis test for difference between groups. Kaplan-Meier analysis with log-rank test.	61 patients were included. No 30-day mortality but four late deaths. Long-term transplant-free survival was 90% with median follow-up of 11.8 years. 48% had a reintervention and 38% had an aortic valve replacement during follow-up.
Cross-sectional matched-control study. PA was objectively measured with a traditional accelerometer method and with a new frequency extended method.	Mean and bootstrapped 95% confidence interval for PA intensity spectrum. Two-tailed t-test for independent groups for comparison of PA intensity. Chi-squared test for group comparisons.	46 participants with VAS and 44 controls completed PA measurement. With the frequency extended method, less PA in the highest intensity spectra was found in patients than in controls. Patients also reported less sports participation.
Retrospective cohort study. Data were retrieved from medical records and pre-operative echocardiograms Survival was cross-checked with the Swedish Population Registry.	T-test, chi-squared test or independent-samples Mann–Whitney U test for group comparisons. Kaplan-Meier analysis with log-rank test. Risk factor analysis with Cox proportional hazards and logistic regression models for survival and reinterventions.	65 neonates treated for critical VAS and 42 for non-critical VAS were included. Significant differences between the groups were identified in freedom from reintervention and in risk factors for reintervention with median follow up of 13.5 years..
Cross-sectional matched-control study. HRQoL was measured with the KIDSCREEN-52 questionnaire. Life satisfaction was measured with the Satisfaction with Life Scale. PA was objectively measured with accelerometry.	T-test for group differences. Bivariate Spearman correlation for the association between PA intensity and HRQoL and life satisfaction.	48 patients and 43 healthy controls were included. Overall, HRQoL did not differ between patients and controls. In adolescent patients a negative correlation was found between psychological well-being, life satisfaction and time spent in high-intensity PA.

4.

Materials and methods

Patients and study design

The participants in the five studies in this thesis were all treated for isolated congenital VAS during childhood or adolescence. The patients were identified in the local surgical and catheter registries at the two surgical paediatric heart centres in Sweden, the Queen Silvia Children's Hospital, Gothenburg and Skåne University Hospital in Lund, in accordance with the licence provided by the Swedish National Board of Health and Welfare for specialized medical care. This ensures complete national coverage of patients with VAS, as there are no private alternatives available in Sweden. The inclusion criterion in all studies was isolated VAS. Patients treated for additional heart defects before, or at the time of, the first intervention were not included. The preferred treatment at first intervention at both centres is surgical valvotomy, and only patients intended for biventricular repair were included.

Paper I: In this retrospective single-centre cohort study, we included all patients aged 0–18 years treated for isolated VAS at the Queen Silvia Children's Hospital, Gothenburg, Sweden, from 1 January 1994 to 31 December 2013, in order to study a complete geographical cohort. The Heart Centre at the Queen Silvia Children's Hospital is the referral centre for paediatric heart surgery and catheter interventions for approximately half of the Swedish paediatric population.

Paper II: This was a nationwide retrospective cohort study covering all patients treated for isolated critical VAS in the neonatal period (< 30 days of age), treated in Sweden from 1 January 1994 to 31 December 2016 at the paediatric heart centres at the Queen Silvia Children's Hospital and at Skåne University Hospital in Lund. Critical VAS was defined as severe VAS with either duct-dependent systemic circulation or depressed left ventricular function (left ventricular fractional shortening ≤ 27%) or both. Neonates treated for non-critical VAS were excluded.

Paper IV: This national, retrospective cohort study includes all patients treated for isolated VAS in the neonatal period (< 30 days) from 1 January 1994, to 31 December 2018 at the paediatric heart centres at the Queen Silvia Children's Hospital and at Skåne University Hospital in Lund. The same strict definition of critical VAS as in paper II was used. The indication for treatment in the non-critical VAS group was a mean Doppler gradient of ≥ 50 mmHg. The strict definition of critical and non-critical VAS divided the cohort into two well-defined groups. The two groups were compared regarding survival, reinterventions, valve replacements and risk factors for reintervention.

Papers III and V: In these national cross-sectional case-control studies, all children (6–12 years) and adolescents (13–18 years) who had undergone treatment for isolated VAS as of January 2019 were identified in registers at the two paediatric heart centres in Lund and Gothenburg. All identified patients aged 6–18 years were invited to the physical activity study, and all patients aged 8–18 years were invited to the HRQoL and life satisfaction study. Five controls for each patient, matched for age, gender and postcode, were generated from Statistics Sweden (www.scb.se) (Figure 7).

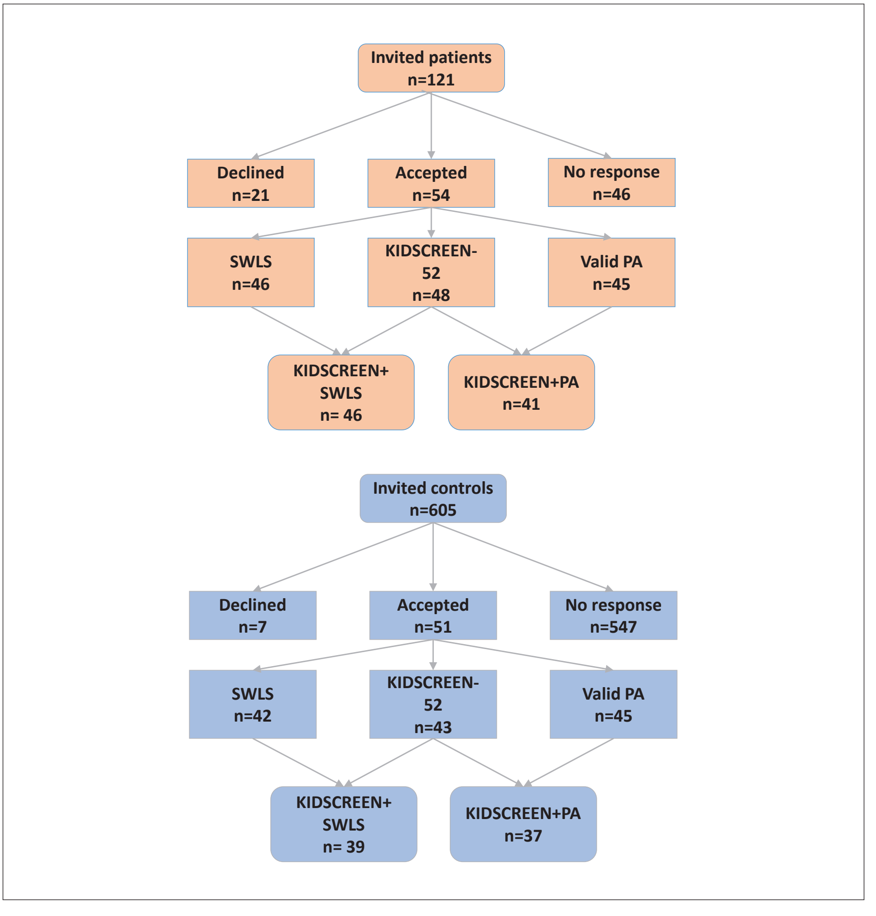


Figure 7. Flowchart of the recruitment process for study participants in Papers III and IV. (PA, physical activity; SWLS, Satisfaction With Life Scale.)

Data collection and methods

Clinical data

Medical records were reviewed for demographic data, diagnosis, details of interventions and reinterventions, and cause of death. Echocardiographic parameters, such as Doppler mean and peak gradients, size of aortic valve annulus, aortic regurgitation, left ventricular measurements and left ventricular function, were obtained from echocardiography reports. Aortic regurgitation was graded I–II (mild), III (moderate) or IV (severe). For the evaluation of aortic regurgitation before reintervention, MRI was also used. Catheter-derived gradients were collected from cardiac catheter reports. Valve leaflet morphology data were collected from the surgical reports for all patients undergoing surgery and from echocardiography reports for patients undergoing balloon valvotomy. Additional information was also collected from electrocardiograms and from cardiopulmonary exercise tests. Survival was checked against the Swedish Population Registry.

Review of preoperative echocardiograms

To validate the diagnosis of critical versus non-critical VAS in papers II and III, the preoperative echocardiograms were reviewed for duct-dependent systemic circulation (defined as right-to-left flow over a persistent ductus arteriosus) and left ventricular function (measured with left ventricular fractional shortening). The presence of left ventricular endocardial fibroelastosis was noted. As echocardiography has methodological limitations in the assessment of endocardial fibroelastosis, findings were only described as 0 (none), 1 (focal) or 2 (extensive).

Measurement of physical activity, health-related quality of life and life satisfaction

Physical activity was objectively measured with accelerometry. HRQoL was measured with the KIDSCREEN-52 instrument, and life satisfaction was measured with the Satisfaction With Life Scale, SWLS [(112)].

An invitation to participate was sent by mail, as were reminders to both patients and controls. In addition, one parent of the non-responding patients was contacted by telephone to allow for questions about the study and to verify that the invitation had been received. Written consent was obtained from participants and/or parents.

An accelerometer and the questionnaires were delivered by mail with age-customized instructions.

To avoid differences related to seasonal variation, physical activity, HRQoL and life satisfaction were measured during the same week in patients and controls.

Objectively measured physical activity

Physical activity was objectively measured by collecting free-living accelerometer data with the triaxial accelerometer Axivity AX3 (Axivity Ltd., Newcastle upon Tyne, UK). A calibration study was included to acquire calibrated cut points for physical activity intensity categories by age group by measuring VO_{2net} (VO_{2total}- VO_{2stand}) for both the traditional ActiGraph accelerometer method and the frequency extended method (FEM) [105]. WHO recommendations for physical activity in children and adolescents were applied to the physical activity measurements, both using the stricter recommendations of ≥ 60 min MVPA at least 6 days per week [83] and the wider criterion of ≥ 60 min per day on average per week [67].

Accelerometer protocol: The sensor was worn on an elastic belt over the right hip for 7 consecutive days and only taken off during activities with water contact (showering, swimming). A diary was provided for documentation of daytime activities, sports participation and sleep time. The OmGUI software (Axivity Ltd., Newcastle upon Tyne, UK) was used for accelerometer initialization and data extraction. A sampling frequency of 50 Hz was used, with sensitivity ±8 g where 1 g is equivalent to earth's gravity. A short epoch length of 3 seconds was chosen, as recommended for measurement in children [104]. The accelerometer data from the three axes were combined to a vector magnitude and resampled to 30 Hz.

The accelerometer data were processed with both the traditional ActiGraph method, using a narrow frequency filter, and with the frequency extended method (FEM), which uses a wider filter and includes data from higher movement frequencies and higher physical activity intensities [101, 103]. From both methods, two different physical activity outputs were provided. In the first output, data were presented as time spent in the traditional basic physical activity categories: sedentary time (SED), light physical activity (LPA), moderate physical activity (MPA), moderate-to-vigorous physical activity (MVPA), vigorous physical activity (VPA) and very vigorous physical activity (VVPA). In the second output, data were presented on a resolution spectrum of 22 physical activity intervals.

A calibration study was included to determine the cut points for the physical activity intensity categories in order to interpret and compare results between different age groups and with previous research. Both the short epoch length of 3 s and the wider 10 Hz frequency filter aim to capture more of the intermittent, high intensity sporadic movement pattern in children. Non-wear time was defined as 60 minutes with zero registered accelerometer counts; a valid day was defined as ≥ 10 hours' wear time and a valid week was defined as measurements on ≥ 3 weekdays plus ≥ 1 weekend day.

Health-related quality of life

To investigate subjective health and well-being, the KIDSCREEN-52 instrument [111] was used. KIDSCREEN-52 is a self-report measure for both healthy and chronically ill children and adolescents aged 8–18 years. The instrument includes a child version, an adolescent version and a parent proxy version of the questionnaire [117]. The instrument measures 10 dimensions of HRQoL: Physical well-being (5 items), Psychological well-being (6 items), Moods and Emotions (7 items), Self-perception (5 items), Autonomy (5 items), Parent relations and home life (6 items), Social support and peers (6 items), School environment (6 items), Social acceptance (Bullying) (3 items), Financial resources (3 items). The items are scored on a five-point scale. The subdomain scores are summed and transformed into Rash scores and in a second step into T-scores for easier comparison, as a T-score always has a mean of 50 and SD of 10. European norm data for children and adolescents and Swedish norm data for adolescents are available for comparison. The Cronbach's alpha values were satisfactory in the self-reports, with a range of .72–.84, with the exception of the physical well-being subscale, which showed an alpha of .69. In the proxy reports, the range for the alpha values was .76–.91, except for the self-esteem scale, with a value of .63.

Life satisfaction

To measure life satisfaction in children aged 8–12, the child version of the SWLS was used [118]. The scale consists of five questions (for example, *"In most ways my life is close to the way I want it to be"*). The answer alternatives range from 1 = Disagree a lot to 5 = Agree a lot. The adult version of the SWLS was used for adolescents aged 13–18 [112]. This scale has been used previously in a Swedish setting [136]. The adult version also consists of five items (for example, *"In most ways my life is close to my ideal*) but the answer alternatives range from 1 = Strongly disagree to 7 = Strongly agree. The values are calculated by using the mean score across the five items, and a higher value is interpreted as representing a better life satisfaction. The Cronbach's alpha value was .77 for the child scale and .82 for the adolescent scale.

Statistical methods

In all papers, normally distributed continuous variables were expressed as mean ± SD and parameters without normal distribution as median and range. Categorical variables were reported as absolute numbers and percentages. T-tests for two independent groups were used to compare means for normally distributed variables. For group comparisons of continuous variables with skewed distribution, the Kruskal–Wallis one-way analysis of variance or independent-samples Mann–Whitney U test was used, as appropriate. For categorical variables, chi-squared tests were calculated. The Kaplan–Meier method and log-rank test were used to analyse and compare survival and freedom from reintervention. For all tests, $p < 0.05$ was considered statistically significant. Further specific statistical methods used in the papers are presented below. The SPSS statistical software was used for statistical analysis in paper I, II and IV; Matlab was used in paper III, and both SPSS and Matlab were used in paper V.

Paper I: Linear regression was used for the association between aortic valve Doppler gradients and left ventricular echocardiographic measurements and for the association between Doppler mean gradient and catheter-derived peak-to-peak gradient.

Paper III: Across the physical activity spectrum, mean group differences and bootstrapped 95% confidence intervals were determined. T-tests for independent groups were performed for each traditional physical activity intensity category, for sports participation and for group characteristics.

Paper IV: Risk factors for reintervention and aortic valve replacement were analyzed with the Cox proportional hazards regression model. Variables with $p < 0.1$ in the univariable analysis were included in a multivariable regression model. In addition, duct dependency and left ventricular function were included as clinically relevant variables in the multivariable model for critical VAS, as was aortic annulus z-score in the multivariable model for non-critical VAS. An adjusted logistic regression model was used to analyse the association between the size of the aortic valve and event-free survival in patients with duct-dependent systemic circulation.

Paper V: For calculations of group differences in HRQoL (KIDSCREEN-52) and life satisfaction (SWLS), t-tests for independent groups were performed. Physical activity in the five intensity categories and sports participation were analysed in relation to HRQoL and life satisfaction using bivariate Spearman correlations. Adjustment for multiple tests was not performed, as this method also has limitations; instead, the outcomes of all tests were presented as recommended by Perneger et al. [137]. The associations were also presented as scatter plots with lines fitted by linear regression.

Ethical considerations

All procedures contributing to this work comply with the ethical standards of the national guidelines on human experimentation in Sweden and with the Declaration of Helsinki [138] and were approved by the Central Ethical Review Board in Gothenburg, approval number 518-16 with supplementary permit T1123-17, (Papers I, II and IV) and approval number 582-18 with supplementary permit T958-18 and additional ethical permit number 1026-17 (Papers III and V).

In papers I, II and IV, patient data, including medical history, clinical condition and information about treatment results, were collected from medical records. Patient data were coded, and the code key was stored safely. The participating individuals cannot be identified in the published information. The risk of compromising the integrity of the included patients was considered to be very low, and the benefit of aggregated data and accumulated knowledge for future patients outweighed this risk.

In papers III and V, the study subjects were invited by mail with written information to patients and controls customised for the child and adolescent age groups. Written consent was obtained from all parents and/or participants. Participants were informed that they could leave the study at any time. The sensors carried in study III have been used by children and adolescents in several previous studies and have been well tolerated. The questionnaires used in study V are well validated and were not considered to cause any harm to the participants.

5.

Results

Paper I

This study investigates short and long-term outcome after treatment of isolated VAS from birth to 18 years of age in patients with geographical affiliation to the Paediatric Heart Centre at the Queen Silvia Children's Hospital in Gothenburg, Sweden, in accordance with the licence provided by the National Board of Health and Welfare on national specialised medical care in Sweden. From 1994 to 2013, 113 patients were identified, 28% female and 72% male. Median age at diagnosis was 2 days (ranging from the first day of life to 13.6 years). Median follow-up was 11.2 years (range 2–21.2 years).

Interventions

At first intervention for VAS there were 44 patients younger than 30 days (neonates), 31 were aged 1 month to 1 year (infants) and 38 were older than 1 year (children). Median age at primary procedure was 2.8 months (range 0–17.9 years). In all age groups the most common treatment method was SAV (n=92) followed by BAV (n=11), closed transapical valvotomy (n=2) and primary AVR (Ross procedure n=4, mechanical prosthesis n=3, biological prosthesis n=1). For the distribution of interventions in the three age groups, see Figure 8. Adequate initial gradient reductions were achieved with all treatment methods. At discharge from hospital, trivial aortic regurgitation, or none at all, was seen in 102 patients and mild regurgitation in 11 patients. No patient had moderate or severe aortic regurgitation at discharge.

Survival

There was no in-hospital mortality or 30-day mortality. Late mortality occurred in two patients. The first was a 10-month-old boy whose cause of death was pneumonia and heart failure. The second was an adult patient with multiple health problems who died at 28 years of age (15 years after the initial BAV). Death was the result of graft failure after a heart transplantation that in turn was secondary to acute heart failure following open heart surgery for AVR. A heart transplantation was needed in two additional patients at 1.5 and 15 years of age, and in one patient palliation by means of univentricular heart surgery was performed at 10 days of age. Long-term transplant-free survival was 96%. Three patients were lost to follow-up due to emigration at 3, 13 and 14 years of age that occurred 3, 11 and 14 years after the first intervention, respectively.

Reinterventions

Residual stenosis was the most common reason for reintervention, and BAV was the most frequently used treatment method at the first reintervention. Reinterventions were more frequent in patients having had their primary intervention during the neonatal period than in those with the initial intervention in infancy or later (Figure 8), but time from primary intervention to reintervention did not differ significantly between these age groups. Freedom from reintervention was 80%, 69%, 61%, 57% and 56% at 1, 5, 10, 15 and 20 years, respectively. When neonates (aged under 30 days) were excluded from the analysis, freedom from reintervention was 94%, 80%, 71%, 70% and 70%. AVR was required in 34 of 113 patients (33%) during follow-up.

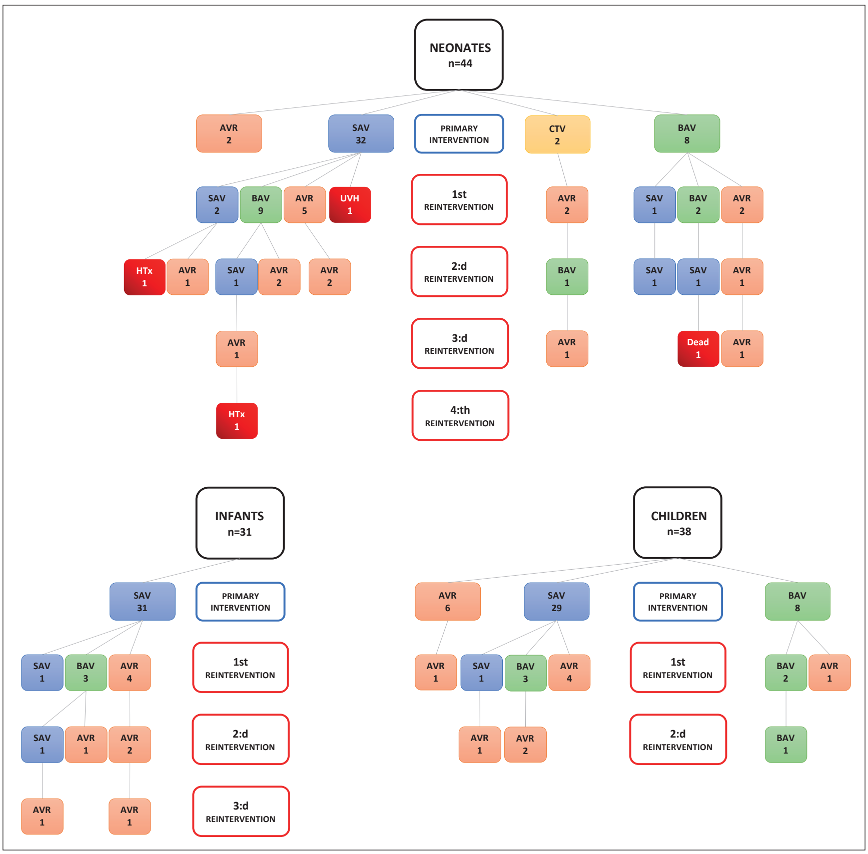


Figure 8. Primary interventions and reinterventions in neonates (≤ 30 days), infants (1 month to 1 year) and children (1–18 years) treated for VAS. (SAV, surgical aortic valvotomy; BAV, balloon aortic valvotomy; CTV, closed transventricular valvotomy; AVR, aortic valve replacement; HTx, heart transplantation; UVH, univentricular palliation.)

Paper II

This paper further investigated outcome measures after treatment of isolated critical VAS in neonates in a national study. We identified 117 neonates treated for isolated VAS in the surgical and catheter registries at the paediatric heart centres in Gothenburg and Lund from 1994 to 2016, constituting a complete national cohort with median follow up of 11.8 years (range 1.1-23.8 years). No patient was lost to follow up. We excluded 15 patients with critical VAS, with severe hypoplasia of the aortic annulus and the left ventricle and extensive endocardial fibroelastosis, who were assigned to univentricular palliation with Norwood surgery as the initial intervention. After review of the preoperative echocardiograms, 61 patients fulfilled the inclusion criteria for isolated critical VAS (duct-dependent systemic circulation and/or depressed left ventricular function), with biventricular repair. In addition, we excluded 41 neonates who had severe VAS but did not fulfil the criteria for critical VAS.

The cohort consisted of 50 males and 11 females. There were no statistically significant differences in patient characteristics or echocardiographic measurements between the two centres. A diagnosis of critical VAS was confirmed within the first 7 days of life (median day 1). Endocardial fibroelastosis was extensive in 11 neonates and focal endocardial fibroelastosis was seen in 22. Mean left ventricular fractional shortening was 23% (SD 9.5). Severely depressed left ventricular fractional shortening < 15% was seen in 13 neonates. Duct dependency was verified in 36 neonates. The preoperative echocardiograms of all patients were reviewed for duct-dependent systemic circulation and left ventricle function. Complete echocardiograms were retrieved for 50 patients. For the remainder, a small number of measurements were missing, mostly in echocardiograms registered in the early part of the study period.

Interventions

SAV was the initial treatment of choice at both centres (n=52). BAV was introduced in 2000 and, by 2006, six neonates had a BAV procedure as the primary intervention. Thereafter, surgical treatment was again determined to be the first choice of primary intervention. In 1995–1996, two premature neonates who were small for gestational age (1.5 and 2.2 kg) had closed transventricular valvotomy. One patient had a primary Ross intervention. No patient was discharged with moderate or severe regurgitation.

Survival

There was no 30-day mortality, but four male patients died later at 2 months, 10 months, 2 years and 21 years of age, respectively. Causes of death were in the first case acute infection and progressive heart failure before hospital discharge and, in the second case, septic infection with pneumonia and rapidly deteriorating heart function. The third death occurred while on mechanical circulatory support after repeated replacements of homografts in the aortic root position and pulmonary hypertension. The last case was a young adult male with an initial closed transventricular valvotomy and later lethal endocarditis in a biological aortic prosthesis. Two patients had heart transplants at 1.5 and 15 years of age, respectively, giving long-term transplant-free survival of 90%. Two patients with borderline left ventricles were converted to univentricular palliation at 10 days and 66 days of age, respectively.

Reintervention

Reintervention was necessary in 29 patients in addition to the four patients who required heart transplantation or conversion to univentricular palliation. Freedom from reintervention was 66%, 61%, 54%, 49% and 46% at 1, 5, 10, 15 and 20 years respectively. Median time to reintervention was shorter after BAV (2.0 months, range 17 days to 3.4 months) than after SAV (4.9 months, range 10 days to 17.3 years). The two centres had different valve sparing approaches for relief of residual stenosis: repeated SAV at one centre and BAV at the other centre.

Aortic valve replacement

AVR was performed in 23 patients. There was no difference in time to valve replacement between the two centres, despite their different approaches to restenosis. Repeated replacements were needed in seven patients. At the end of follow-up, 33 patients (54%) were alive with a native aortic valve and 20 (33%) after an AVR (Ross n=11, biological prosthesis n= 1, mechanical prosthesis n= 6 and homograft in aortic root position n= 2).

Paper III

There were two aims of this paper. The first was to assess physical activity in children and adolescents treated for VAS compared with matched healthy controls. The assessment was combined with a methodological study in which two different methods of processing accelerometer data were compared. The two methods were the traditional ActiGraph method and the FEM. The output from each method is presented both as crude intensity categories (SED, LPA, MPA, VPA, VVPA) and as a high-resolution spectrum of intensity categories. A calibration study provided the cut points for the physical activity intensity categories. A second aim was to compare our physical activity measurements with the WHO recommendation for physical activity in children and adolescents.

Valid accelerometer measurements were collected from 27 children and 29 matched controls and from 19 adolescents and 15 matched controls from all over Sweden (Figure 9).

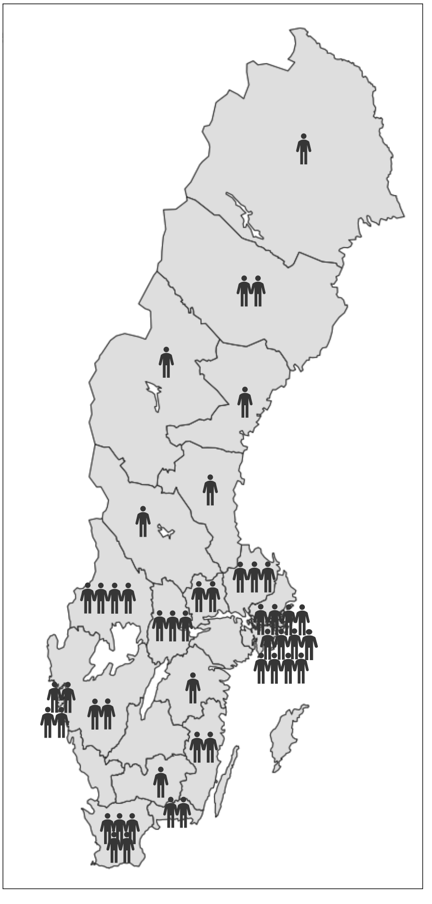


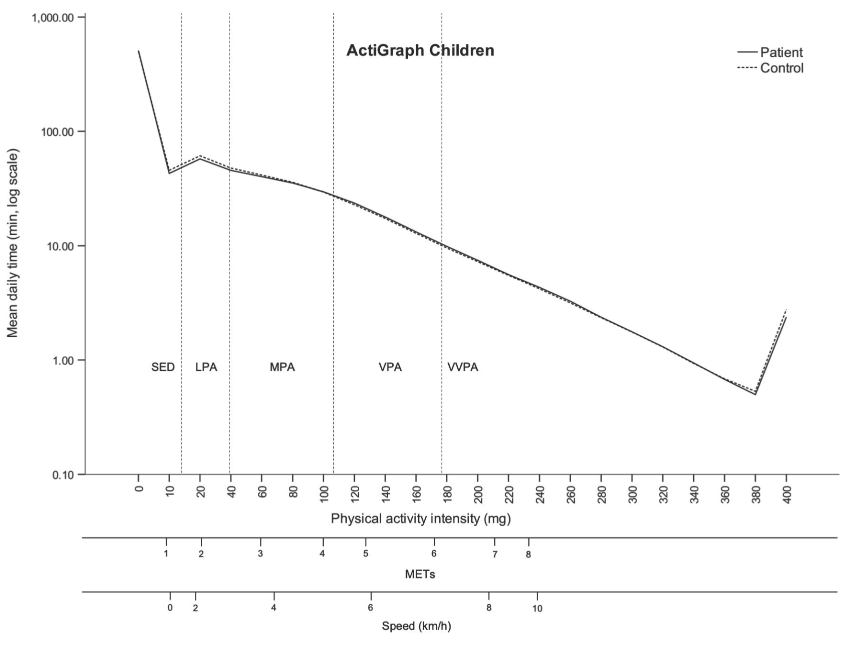
Figure 9. Geographical distribution of patients in papers III and V.

Accelerometer measurements

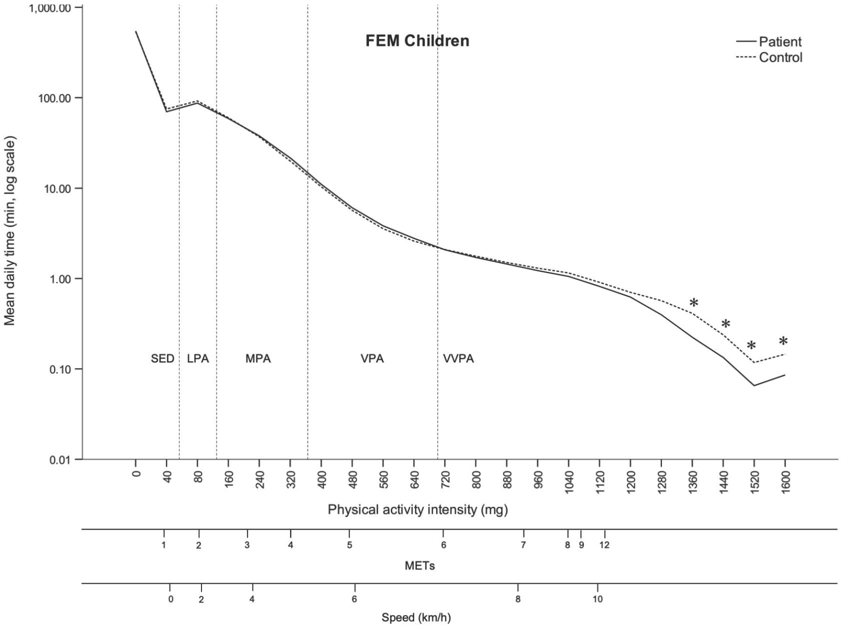
In children with VAS there was a pattern of less physical activity in the highest intensity spectrum compared to controls when accelerometer data were analysed with the FEM in the detailed physical activity intensity spectrum. This difference was statistically significant. (Figure 10a). When physical activity data were categorized into the traditional, crude physical activity intensities, this pattern became weaker and the difference between patients and controls was no longer statistically significant. Using the ActiGraph method, this pattern was not evident with the detailed physical activity presentation nor with the crude physical activity classification (Figure 10b). A trend towards more SED was seen in VAS children using both methods; however, the difference between patients and controls was not statistically significant.

In adolescents, a pattern of less physical activity in the higher intensities was seen with both the FEM and the ActiGraph method (Figure 10 c and d). A statistically significant difference was detected using FEM, showing less time spent in VPA for patients than for controls when applying the crude classification (p = 0.049). Using the ActiGraph method, the pattern was similar, but a significant difference was detected only in VVPA intensity with the detailed physical activity intensity spectrum. Interpretation of the data in the highest intensities is hampered by the limited amount of data at this end of the intensity spectrum.

10a.

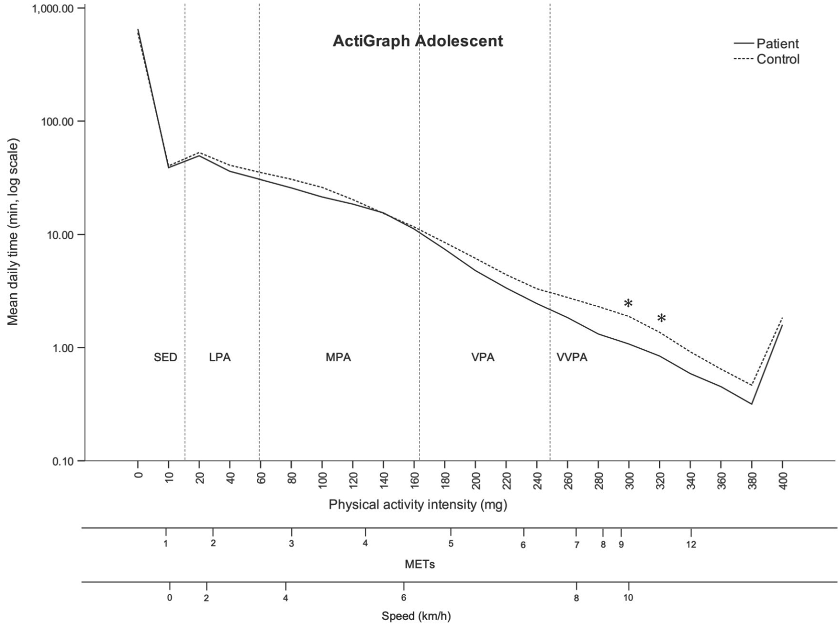


10b.



FEM Children
Patient
Control
Mean daily time (min, log scale)
1,000.00
100.00
10.00
1.00
0.10
0.01
SED
LPA
MPA
VPA
VVPA
*
0
40
80
160
240
320
400
480
560
640
720
800
880
960
1040
1120
1200
1280
1360
1440
1520
1600
Physical activity intensity (mg)
1
2
3
4
5
6
7
8
9
12
METs
0
2
4
6
8
10
Speed (km/h)

10c.



ActiGraph Adolescent
Patient
Control
Mean daily time (min, log scale)
1,000.00
100.00
10.00
1.00
0.10
SED
LPA
MPA
VPA
VVPA
*
0
10
20
40
60
80
100
120
140
160
180
200
220
240
260
280
300
320
340
360
380
400
Physical activity intensity (mg)
1
2
3
4
5
6
7
8
9
12
METs
0
2
4
6
8
10
Speed (km/h)

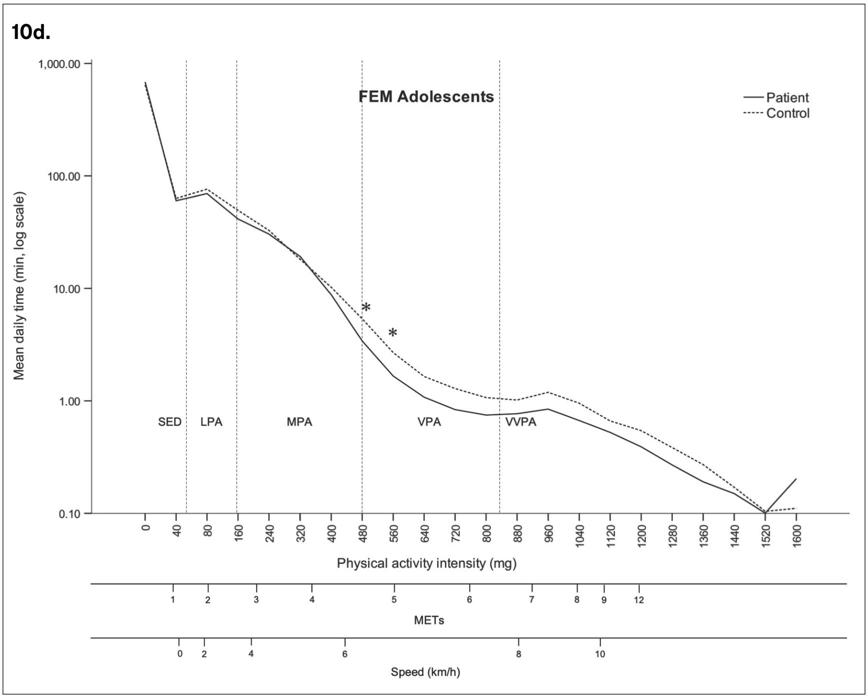


Figure 10 a–d. Time spent (minutes) across the physical activity intensity spectrum for patients and controls by accelerometer method (ActiGraph, FEM) and by age group. Values are presented on a logarithmic scale. Physical activity intensity is indicated in acceleration (mg) but also by the MET-value and speed of moving to facilitate understanding. Vertical dotted lines indicate cut-points for crude intensity categories. *Indicates when the bootstrapped 95% confidence interval of the percent difference between groups at the specific physical activity intensity spectrum category do not overlap zero % difference (paper III). (FEM, frequency extended method; MET, metabolic equivalent of task; SED, sedentary time, LPA, light physical activity; MPA, moderate physical activity; VPA, vigorous physical activity; VVPA, very vigorous physical activity.)

WHO recommendations

All children fulfilled the WHO recommendations of on average ≥ 60 min MVPA per day. When the stricter criterion of ≥ 60 min of MVPA six days out of seven was applied, 93% fulfilled the recommendations, with no difference between patients and heathy controls. In adolescents, 95% of the patients and 94% of the controls fulfilled the WHO recommendations of on average ≥ 60min MVPA per day. Using the stricter criterion, 54% of the patients and 56% of the controls met the requirements (n.s).

Sports participation

Sports participation was less frequent in patients than in the controls. The difference was statistically significant in both the children and the adolescents (p = 0.009).

Paper IV

The aim of this study was to elucidate the differences in outcome between neonates treated for critical VAS and neonates with non-critical VAS. Comparisons of outcome after different initial treatment methods are often biased by confounding factors misleading the interpretation of the results. Using a strict definition of critical and non-critical VAS, we compared survival, treatment outcome and risk factors for reintervention between the two groups.

A complete national cohort of 107 neonates treated for isolated VAS with biventricular circulation from 1994 to 2018 was identified. Median follow up was 13.0 years (range 1-26 years) in the critical VAS group and 14.6 years (range 1-26 years) in the non-critical VAS group. No patient was lost to follow up Based on a review of the preoperative echocardiograms with the application of strict criteria for critical VAS, 65 neonates were classified as having critical VAS and 42 as having non-critical VAS. The indication for treatment of patients with non-critical VAS was Doppler mean gradient ≥ 50 mmHg. SAV was the most common initial treatment method in both groups: 56 of 65 with critical VAS (86%) and 38 of 42 with non-critical VAS (90%). Other treatments used were BAV (n=6), closed transventricular valvotomy (n=2), Ross procedure (n=1) for neonates with critical VAS and BAV (n=2) and Ross procedure (n=1) for the non-critical group. Adequate gradient reduction was achieved in both groups, and no patient was discharged with more than mild aortic regurgitation. There were no statistically significant differences between the two groups in gestational age, birth weight, age at diagnosis, age at initial treatment or follow-up time.

Survival

There was no 30-day mortality. One patient died at 2 months of age before hospital discharge. Hence, short-term survival was 98.5% in the critical VAS group and 100% in the non-critical VAS group. Long-term transplant-free survival was 91% in the critical VAS group and 98% in the non-critical VAS group, with three late deaths and two heart transplantations in the critical VAS group and one late death in the non-critical VAS group. The difference was not statistically significant (p=0.07). Two patients with critical VAS were reassigned to univentricular palliation after failure of biventricular strategy.

Reinterventions

Residual or recurrent stenosis was the most common indication for reintervention. Reinterventions were more frequently needed in the critical VAS patients (38 of 65; 58%) than in non-critical VAS patients (14 of 42; 33%). Time to reintervention was significantly shorter in critical VAS patients (3.6 months) than in non-critical VAS patients (3.9 years) (p= 0.008). Freedom from reintervention after 1, 5, 10, 15 and 20 years was 63%, 58%, 52%, 45% and 42% in critical VAS patients and 86%, 81%, 71%, 67% and 67% in non-critical VAS patients, respectively.

AVR was almost as frequent in both groups up to 10 years of age. Thereafter, replacements were more often required in the critical group, and from 18 years of age upwards, 13 of 15 patients with critical VAS and 3 of 9 patients with non-critical VAS had required an AVR. Among transplant-free late survivors, 23 of 60 (38%) with critical VAS and 11 of 42 (26%) non-critical VAS had an AVR (excluding patients who had undergone conversion to univentricular palliation or heart transplantation). Event-free survival was 40% in the critical VAS group and 67% in the non-critical VAS group (p=0.002). The Kaplan-Meier curve illustrates cumulative events including death, transplantation, conversion to single ventricle palliation or any other reintervention after first intervention, with a statistically significant difference between the two groups (p=0.003) (Figure 11).

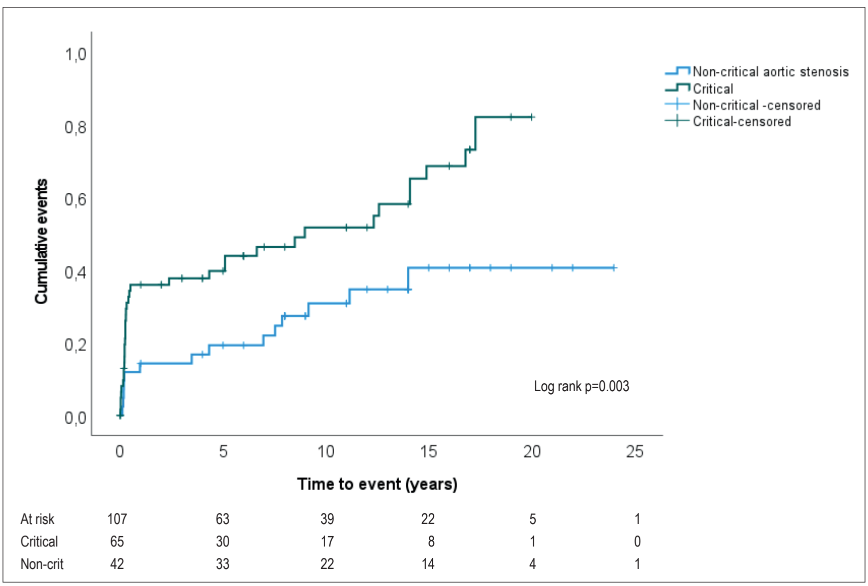


Figure 11. Kaplan-Meier curve illustrating time to event for patients with critical and non-critical VAS. The concept *event* includes death, conversion to univentricular palliation, heart transplantation or reintervention.

Risk factor analysis

Risk factors for reintervention and AVR were analysed in a Cox proportional hazards regression model. In the multivariable model, for patients with critical VAS, a smaller aortic annulus z-score was an independent risk factor for both reintervention and AVR; higher residual gradient after primary intervention was a risk factor for reintervention, and any regurgitation after primary intervention was a risk factor for AVR. In patients with non-critical VAS, a higher residual gradient was an independent risk factor for reintervention. No association was found between valve leaflet morphology and the risk of reintervention or AVR.

Paper V

The overall aim of this paper was to investigate HRQoL and life satisfaction and the relationship between these two concepts and physical activity in children and adolescents treated for VAS.

HRQoL

The KIDSCREEN-52 questionnaire was completed by 48 patients and 43 healthy controls. It did not reveal any statistically significant differences between any of the domains of HRQoL reported by the patients and their healthy controls when divided into the two age groups. In the parent proxy reports there was a difference in the *"autonomy"* domain, where the parents of the adolescent patients reported lower scores than the control group parents. The children with VAS reported significantly higher scores for *"autonomy"* and *"social support"* in comparison to the European norm values (Table 1). The child control group reported higher scores for *"self-perception"* and *"social acceptance"* compared to the European norms. The adolescent patients reported lower *"physical well-being"* in comparison to both Swedish and European norm values (Table 2). Both adolescent patients and controls reported significantly higher scores for the domains *"parent relations and home life"* and *"school environment"*. All groups, including the Swedish norm values, showed significantly higher scores for *"financial support"* compared to the European norms, except for adolescents with VAS. The results are illustrated in figure 12.

Table 1. HRQoL self-report scores between children aged 8–11 with and without VAS: comparisons between groups and against the European norms.

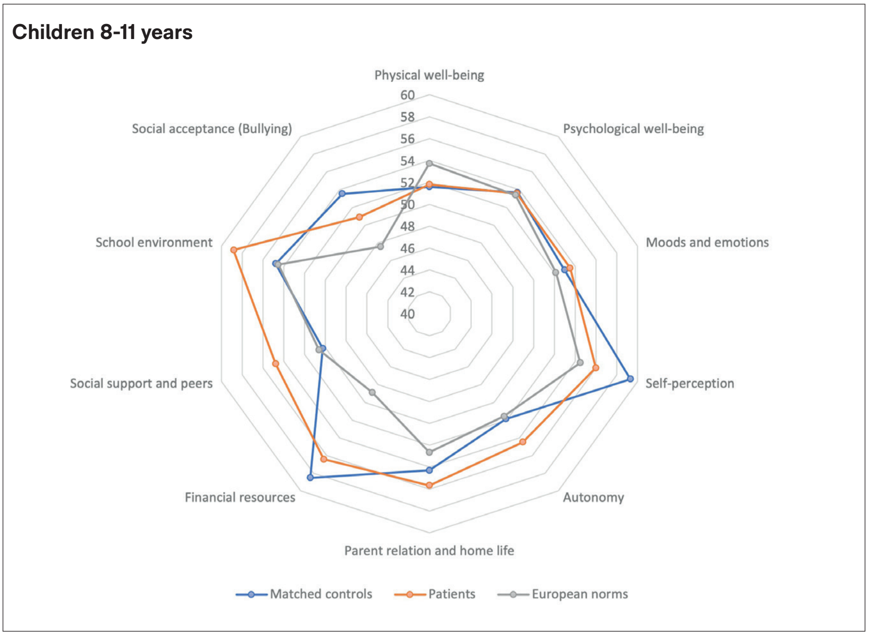
KIDSCREEN-52 Children 8–11 years	Controls			Patients			European norms		Controls vs European norms	Patients vs European norms
	M	SD	n	M	SD	n	M	SD	p	p
Physical well-being	51.59	6.55	20	51.81	8.62	20	53.72	9.96	0.162	0.334
Psychological well-being	53.69	4.52	20	53.59	7.31	20	53.38	9.40	0.761	0.900
Moods and emotions	52.97	7.47	20	53.51	7.63	20	52.15	9.97	0.628	0.435
Self-perception	59.31	7.98	20	55.98	8.18	20	54.48	9.74	0.014*	0.422
Autonomy	51.87	9.03	20	54.49	5.98	20	51.57	9.67	0.885	0.042*
Parent relation and home life	54.29	7.64	20	55.67	7.30	20	52.65	9.18	0.349	0.080
Financial resources	58.51	5.97	20	56.42	6.27	19	48.88	10.45	<.001***	<.001***
Social support and peers	50.25	7.37	20	54.78	8.34	20	50.62	10.05	0.826	0.038*
School environment	54.78	10.54	20	58.83	10.06	20	54.52	10.46	0.914	0.070
Social acceptance (Bullying)	53.54	7.64	19	50.91	10.04	20	47.58	10.54	0.003**	0.155

Note: For European reference norms from KIDSCREEN-52, see Appendix Table A7_A-3
* p < .05, ** p <.01, *** p <.001.

Table 2. HRQL self-report scores between adolescents aged 12–18 with and without VAS: comparisons between groups and against the Swedish and European norms

KIDSCREEN-52 Adolescents 12–18 years	Controls			Patients			Swedish norms		Controls vs Swedish norms	Patients vs Swedish norms	European norms		Controls vs European norms	Patients vs European norms
	M	SD	n	M	SD	n	M	SD	p	p	M	SD	p	p
Physical well-being	47.99	10.93	23	45.92	5.57	28	48.58	9.76	0.797	0.017*	48.57	9.64	0.801	0.018*
Psychological well-being	49.35	8.25	23	47.91	8.30	28	49.99	10.08	0.712	0.195	48.70	9.92	0.711	0.618
Moods and emotions	52.87	10.51	23	51.03	10.34	28	50.70	11.08	0.333	0.866	49.18	9.89	0.106	0.351
Self-perception	51.23	11.34	23	51.92	9.60	27	50.27	10.70	0.687	0.380	48.28	9.56	0.225	0.060
Autonomy	55.71	6.11	23	52.49	9.54	28	51.29	9.61	0.002**	0.511	49.40	10.06	<.001***	0.098
Parent relation and home life	55.32	7.62	23	54.47	8.61	28	52.45	10.11	0.084	0.225	48.98	10.11	<.001***	0.002**
Financial resources	56.94	7.84	22	55.52	7.84	28	52.58	9.14	0.016*	0.057	50.42	9.80	<.001***	0.002**
Social support and peers	53.13	10.29	23	49.77	8.74	28	51.61	9.70	0.486	0.276	49.76	9.97	0.130	0.993
School environment	53.42	8.68	23	53.07	7.03	28	51.30	9.39	0.254	0.193	48.25	9.24	0.009	0.001***
Social acceptance (Bullying)	54.43	8.07	23	53.10	9.17	28	52.65	9.24	0.303	0.799	50.94	9.62	.050*	0.224

Note: for European reference norms from KIDSCREEN-52, see Appendix Table A7_A-3
* p < .05, ** p < .01, *** p < .001



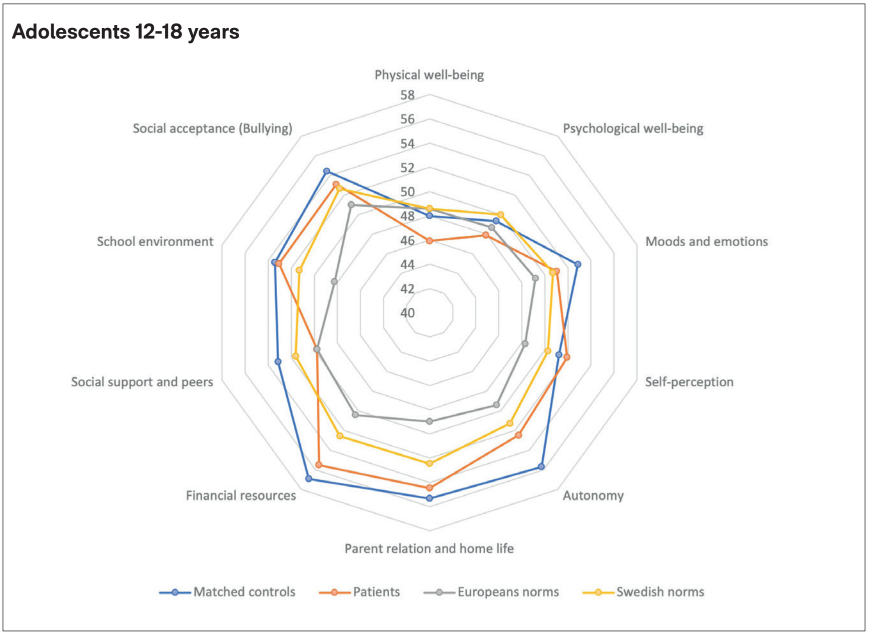


Figure 12. KIDSCREEN-52 sum scores for each scale comparing patients and matched controls with European norms for children and with Swedish and European norms for adolescents.

Life satisfaction

The Satisfaction With Life Scale (SWLS) was completed by 46 patients and 39 controls. No difference was found between the patients in the child group (*mean*=4.61, *SD*=0.54) and their controls (*mean*=4.63, *SD*=0.46) *p*=0.91 or between adolescent patients (*mean*=5.6, *SD*=1.05) and their controls (*mean*=5.24, *SD*=1.85) *p*=0.80.

HRQoL, life satisfaction and physical activity

Forty-one patients and 37 controls had valid data from KIDSCREEN-52 and SWLS and objectively measured physical activity. A positive correlation was found in the patients in the child group between MVPA and physical and psychological well-being. In adolescent patients' self-reports and their parents' proxy reports, a pattern of negative correlations was found between both MVPA and sports participation and psychological well-being and life satisfaction. As sports participation correlated highly with high-intensity physical activity, it can be assumed that a lot of the time spent in VPA and VVPA was associated with participation in high-intensity sports activities. The parent proxy reports showed a strong negative correlation between sedentary time and psychological well-being in the children with VAS and between sedentary time and physical well-being in control children. Sedentary time was also negatively correlated with life satisfaction, psychological well-being and physical well-being for the adolescent controls.

6.

Discussion

This thesis aims to present survival, treatment outcome, physical activity, HRQoL and life satisfaction after treatment for VAS in children. Since BAV was introduced in the 1980s as an alternative treatment to SAV, the discussion has been animated regarding which treatment method gives the best short-term and long-term outcome in paediatric VAS, especially in patients treated during the neonatal period. Since then, the techniques for both SAV and BAV have evolved and improved but the superiority of one over the other remains to be proven [40, 41]. The discussion needs to be based on contemporary treatment results. In papers I, II and IV, we presented population-based treatment results in which the vast majority of patients had had SAV as their primary treatment. This limits selection bias because it means that virtually all patients eligible for a valvotomy were offered SAV. The exception was during a limited period when a few patients had a primary BAV of the aortic valve. To make the study groups as homogeneous as possible, we only included patients with isolated VAS. Paper IV highlights the differences in outcome after neonatal treatment of critical and non-critical VAS. The findings underline the fact that comparison of results between different treatment methods in neonates has to be carried out with caution. The treatment outcome was strongly associated with the diagnosis of critical versus non-critical VAS, and neonates with critical VAS had a worse prognosis than neonates with non-critical VAS.

With a more preventive approach to medical aftercare in paediatric cardiology, physical activity, HRQoL and life satisfaction have become increasingly important outcome measures to complement the classical outcomes of survival and reintervention rates. In paper III, we objectively measured physical activity with accelerometry. Previous studies have failed to find differences in physical activity between children with CHD and healthy controls, which has sometimes been attributed to methodological issues. Using an improved method, we were able to detect differences between patients and controls. We also analysed the physical activity patterns of children and adolescents treated for VAS and a control group to establish whether they fulfilled the WHO recommendations for physical activity. In paper V, we studied HRQoL, life satisfaction and their relation to physical activity. Previous experience has indicated that children and adolescents with CHD report HRQoL that is similar to the HRQoL of healthy peers. The generic instrument KIDSCREEN-52 was chosen for the measurement of HRQoL because we wanted to compare the results with healthy controls. To obtain a broader picture, global life satisfaction was measured with the SWLS. Finally, the results of the objectively measured physical activity, HRQoL and life satisfaction were combined to study the association between the three measures.

Survival and treatment outcome

An important finding in papers I, II and IV was the low early and late mortality in critically ill neonates as well as in older children after treatment of VAS. SAV was the favoured primary intervention in Sweden during the study period and surgical management is still the preferred initial treatment. SAV is sometimes questioned as primary intervention in neonates with critical VAS and severely depressed left venticular function. In these papers we present results after SAV also in the most vulnerable patients with critical VAS.

Outcome after treatment in paediatric patients

Paper I was a single-centre study where all patients (n=113) who had a primary intervention for VAS between birth and 18 years of age at the Queen Silvia Children´s Heart Centre in Gothenburg were included. The patients were divided into three groups: neonates (up to 30 days old), infants (aged from 1 month to 1 year) and children (aged over 1 year) at primary intervention. The study period started in 1994, after the centralisation of paediatric heart surgery to two centres in Sweden. Accordingly, our data is based on approximately half of the Swedish population of children with VAS, as no private alternative for treatment of CHD in children is available in this country. The median follow-up time was 11.2 (2–21.2) years. SAV was the primary intervention in 81% of the patients and BAV in 10%. There was no 30-day mortality. During the follow-up period, two patients died and both deaths were cardiac related. The 10-year survival after first intervention was 99% in this study. This compares well with the comprehensive review by Hill et al., who reported 10-year survival of 90% after initial SAV and 87% after BAV (54).

No patient in our cohort had moderate or severe aortic regurgitation (grade 3–4 of 4) post intervention; 11 patients had mild aortic regurgitation and the rest had trivial or no aortic regurgitation. Reintervention was needed in 48 patients (43%) and 10-year freedom from reintervention was 61% in our paediatric cohort. There was no significant difference in time between the first intervention and the reintervention between the three age groups. Repeated reinterventions were more common after neonatal treatment than in infants and children who had their first treatment after one month of life (Figure 8), as previously reported (139). AVR was performed in 34 (33%) of the patients, and was more common as the primary intervention in adolescents than in younger patients.. In comparison, Auld et al. reported moderate or severe aortic regurgitation post intervention in 15 of 65 patients (23%) after BAV and in 1 of 77 patients (1%) after SAV. With the limited follow-up in that study of mean 5.3 years, no difference in reinterventions was seen [140]. With a longer mean follow-up of 11.1 years, Herrmann et al. also reported a higher incidence of moderate aortic regurgitation after BAV (12.5%) than after SAV (2%) in a study excluding patients who had their first treatment at under 2 months of age. Overall, reintervention was required in 39% of SAV patients and 51% of BAV patients, and AVR was required in 30% and 27%, respectively [42]. These two recent publications in paediatric populations indicate that post-intervention aortic regurgitation is still more common after BAV than after SAV, despite technical modifications of the BAV procedure. In two reviews, including partly different data, the 10-year freedom from reintervention was stated to be on average 67–73% after SAV and 46–54% after BAV, providing some support for the argument that reinterventions are more often required after BAV than SAV in paediatric populations [54, 141].

Outcome after treatment of neonatal patients

In paper II, we studied all neonates treated for critical VAS by the age of 30 days in Sweden (n=61). Inclusion was based on the definition of critical VAS as duct-dependent systemic circulation and/or impaired left ventricular function. The study period was 1994–2016, giving a median follow-up of 11.8 years (range 1.1–23.8). Only two patients had a prenatal diagnosis. The detection of VAS with preserved left ventricular function and morphology is uncommon at second trimester fetal screening in Sweden (unpublished data from The Swedish Registry of Congenital Heart Disease, G. Bergman, personal communication). The same experience is described from other centres [20]. In cases where the diagnosis is prenatally detected, the prediction of a future need for univentricular palliation or biventricular repair is complex [142].

In our study, primary intervention was SAV in 85% and BAV in 10%. Depressed left ventricular function and endocardial fibroelastosis have been described as risk factors for mortality in neonates [7, 60, 143]. Despite the severe clinical condition of the neonates included in this study, with focal or extensive endocardial fibroelastosis present in half of the study group and a mean left ventricular fractional shortening of 23% (SD 9.5), there was no 30-day mortality. There was one early death (before hospital discharge) and three late deaths. One can speculate that the patient who died early, the two patients who eventually required heart transplants and the two patients who were converted to univentricular palliation might have benefitted from a Norwood palliation as a primary intervention [57]. But these adverse events also emphasize the ambition of the teams to strive for biventricular repair even in neonates in the "grey zone" with a poorly functioning, borderline-sized left ventricle, and still the overall long-term transplant-free survival was 90%. Similar figures to ours for early mortality after SAV or BAV have been reported in studies published during the last decade [7, 44, 56, 61], with long-term transplant-free survival between 73% and 91% [5, 45, 139]. Moderate to severe aortic regurgitation after treatment is more commonly reported after BAV than SAV in the neonatal period, just as for older patients [6, 7, 45, 55].

As in paper I, no patient was discharged with moderate or severe aortic regurgitation in the paper II cohort. Freedom from reintervention is generally reported to be shorter after BAV than after SAV [5, 53, 60, 61, 141]. Freedom from reintervention at 10 years was 54% in the present study. Median time to reintervention was shorter after BAV than SAV and no significant difference was found in time to reintervention between the two heart centres. An interesting finding was that, despite different reintervention strategies between the two heart centres (SAV at one centre and BAV at the other), time to AVR was the same at both centres ($p = 0.66$). AVR was performed in 23 of the 60 hospital survivors who were free from heart transplantation or univentricular palliation. The improvement of perioperative care and of cardiopulmonary bypass methods have probably contributed to decreased mortality after SAV, as have the refinement of BAV protocols, and survival after SAV and BAV are similar [40, 41]. Based on the literature and the data presented in this thesis, the statement that BAV is a less invasive procedure than SAV can be questioned. Vergnat et al. and Zaban et al. present no significant difference in hospital stay after SAV or BAV [55, 56].

Comparing our results after treatment of critical VAS with other studies proved more difficult than expected, mainly because definitions of the criteria for critical VAS were not uniform in the various studies. Our results clearly showed a more favourable prognosis in neonates with non-critical VAS than in neonates with critical VAS. This has implications when comparing results after treatment in neonates; therefore, a study of neonates including both strictly defined critical VAS and non-critical VAS was justified.

In paper IV, we studied all neonates with treatment for isolated VAS up to 30 days of age during a 24-year period. A complete national cohort of 65 neonates with critical VAS and 42 with non-critical VAS was identified. Only patients intended for biventricular repair were included. Median follow-up was 13.0 years (range 1–26) in the critical VAS group and 14.6 years (range 1–26) in the non-critical VAS group. Early survival was 100% in neonates with non-critical VAS versus 98.5% in those with critical VAS, and long-term transplant-free survival was 98%

for non-critical VAS and 91% for critical VAS. The difference in transplant-free survival was not statistically significant (p = 0.134).

Reintervention was performed in 33% of the neonates with non-critical VAS after a median of 3.9 years, whereas 58% of the neonates with critical VAS underwent reintervention after a median of 3.6 months (p = 0.008). In fact, freedom from reintervention at 1, 5, 10, 15 and 20 years of 86%, 81%, 71%, 67% and 67%, respectively, in the neonates with non-critical VAS in paper IV are very similar to our results for infants and children with VAS in paper I (94%, 80%, 71%, 70% and 70%, respectively) and in parity with or better than other cohorts of paediatric patients or study groups of neonates with both critical and non-critical VAS [5, 55, 144]. These findings support the hypothesis that the prognosis for neonates with non-critical VAS is more favourable than for the neonates with critical VAS in paper IV, who had a freedom from reintervention at 1, 5, 10, 15 and 20 years of 63%, 58%, 52%, 45% and 42%, respectively.

In late survivors, AVR was needed in 11 of 42 patients with non-critical VAS (26%) and in 23 of 60 patients with critical VAS (38%), which was not a significant difference. A more striking difference was that the need for AVR was similar in the two groups up to 10 years of age, but by 18 years of age, 3 of 9 patients born with non-critical VAS (33%) had required an AVR compared to 13 of 15 patients born with critical VAS (87%). A statistically significant difference in freedom from any event after first intervention was also demonstrated (Figure 11; p=0.003). Finally, multivariate risk factor analysis showed that a lower aortic annulus z-score and higher residual gradient at hospital discharge were independent risk factors for reintervention. A lower aortic annulus z-score and any aortic regurgitation after first intervention were risk factors for AVR in the critical VAS group. In the non-critical VAS group, the only independent risk factor identified was residual gradient after intervention as a risk factor for reintervention. We did not find valve leaflet morphology as a risk factor associated with reintervention or AVR in either group, as previously shown by Loomba et al., although this was contradicted by Vergnat et al. and Hraska et al. [40, 56, 145]. As there were few deaths or heart transplants in our material, multivariable analysis for predictors of early and late transplant-free survival was not meaningful. Other risk factors have been suggested and found relevant in some studies but not in others [56, 60, 61, 143, 146]. Differences between studies might be influenced by small sample sizes and comparison of heterogenous groups.

Objectively measured physical activity

There is robust evidence for the beneficial effects of physical activity on physical fitness, cardiometabolic health, development of cognitive, motor and social skills, symptoms of depression and preventing obesity in children and adolescents [62, 147]. More time spent in sedentary behaviour and more recreational screen time are associated with poorer health outcome, and this is considered an increasing global health problem [148]. There is also an increasing tendency for adolescents to be less physically active than children. This decline starts at the time of school entry [149]. The recommendations for daily physical activity in children and adolescents from WHO, paediatric cardiology societies and Swedish authorities all specify at least 60 minutes of moderate to vigorous physical activity every day and muscle strengthening activities three times a week [67, 68]. Many studies have objectively measured physical activity in children with CHD but clear evidence of differences compared to healthy peers is lacking except in special circumstances, for example, children and adolescents after univentricular palliation versus healthy controls [78-85]. Still, some have expressed concern that the methods for physical activity assessment used so far may not be sufficiently sensitive to differences and that we thereby miss the opportunity to capture a negative behaviour pattern in patients with extra vulnerability for future cardiovascular disease and metabolic syndrome [64, 150, 151].

In paper III we took some of the methodological shortcomings of previous studies into account [97, 108]. The most important finding in this study was that processing collected accelerometer data with FEM, and presenting physical activity in a detailed intensity spectrum, revealed differences not detected with the traditional ActiGraph method. The pattern in children previously treated for VAS included significantly less activity in the highest intensity spectra compared to the healthy controls. Translated to crude physical activity classifications, this intensity corresponds to VVPA. The difference was not detected with the traditional ActiGraph method.

There are a number of explanations for the misclassification of physical activity in children. One reason is that children's free-living movement pattern typically alternates between rather short sequences of physical activity of different intensity levels with short bursts of very intense activity (VVPA) in between [102]. These high-intensity bursts typically last for seconds rather than minutes. Another source for misclassification is that younger and shorter individuals move with higher frequency than taller individuals [101]. When acceleration is processed using the ActiGraph method with a narrow frequency filter, more of the child's physical activity is excluded. Processing accelerometer data with FEM, using a 10

Hz filter and short epoch length, contributes to the capture and classification of this intermittent movement of children (101, 103, 104). The problem of misclassification is more pronounced at high and very high intensity physical activity levels than for light physical activity, because of the very short bouts of high intensity physical activity (103). Therefore, sedentary behaviour is more often correctly identified and classified. In adolescent patients, there was generally a pattern of less activity in the higher intensities compared to the age-matched controls but also compared to the children, with a statistically significant difference in VPA using the ActiGraph method and in VVPA using the FEM. For adolescents there was less difference between analysis with FEM and with ActiGraph. This may be because ActiGraph captures and classifies physical activity more correctly in adolescents than in children, as the method was originally developed and validated for adults, and adolescents have more in common with adults than children do. For both children and adolescents, there were no statistically significant differences in sedentary time between patients and controls. Cut points were calibrated against VO_{2net} to set a reference measure of metabolic effort equivalent by age.

Sports participation was self-reported, and patients in both age groups reported significantly less sports participation (in times per week) compared to the controls (p=0.009). This confirms previous studies (81, 83) and supports our accelerometer data, in which less high-intensity physical activity was associated with participation in fewer sports activities. Physical activity recommendations were fulfilled to a high degree, both in patients and controls, when using the WHO criteria of at least 60 minutes of MVPA on average per day (100% of child patients and controls alike, and 95% of adolescent patients and 94% of the adolescent controls). With the stricter criteria of at least 60 minutes of MVPA six of seven days per week, the recommendation was still reached to a high degree in children (93% of patients and controls alike), but less so in adolescents (54% of patients and 56% of controls). However, the physical activity recommendations were developed from a different methodology than accelerometry. This is important to be aware of when using accelerometer data for this purpose, even though it is common to do so.

In paper III we found significant differences in physical activity pattern when comparing children and adolescents treated for VAS with healthy controls. In the light of previous studies reporting inconsistent findings of physical activity in patients with CHD compared to healthy controls, our results must be interpreted with caution, considering that FEM is a novel method for processing accelerometer data and we had a rather small sample size. However, this method is promising and has the potential to improve physical activity assessment in children.

HRQoL, life satisfaction and their association with physical activity

The most important finding in Paper V was that children and adolescents born with VAS reported HRQoL and life satisfaction that was at the same level as their healthy controls. This is in line with other studies reporting HRQoL and life satisfaction in children and adolescents with CHD [120, 152].

We assessed HRQoL with the KIDSCREEN-52 (long version), using both self-reports and parent proxy report. This instrument is designed to identify children at risk in terms of subjective health, and it assesses HRQoL as a multidimensional construct including physical, emotional, mental, social and behavioural aspects of well-being and functioning. The measure is divided into 10 domains of HRQoL [111]. Another way of looking at QoL is by using the construct life satisfaction or subjective well-being. Here, individuals make a global assessment of their QoL using their own criteria. The SWLS aims to assess a person's satisfaction with life as a whole, focusing on a judgement of subjective well-being from a positive viewpoint rather than including both positive and negative statements [112, 113]. Both KIDSCREEN and SWLS are age-adapted for children and adolescents. We obtained valid KIDSCREEN measurements from 48 patients and 43 matched controls. Overall, no significant differences were found in HRQoL between patients and controls in the self-reports. When comparing the results of our study participants with norm values, there were a number of significant differences both between the patients and the European norms and between controls and the European norms. The European norm values are generally lower than both Swedish norms and the patients and controls in our study (Figure 12). The domain Physical well-being was the only exception, with a significantly lower T-value in adolescents treated for VAS compared to both European and Swedish norm values. However, there was no significant difference between the patients and the matched controls. As the European norms are generally lower, this illustrates the importance of comparisons with Swedish norm values or matched controls [133]. The only statistically significant difference between parent proxy reports for patients and controls was that parents of the adolescent patients reported lower values for the Autonomy domain than the control parents. The SWLS was completed by 46 patients and 39 controls. No differences in subjective well-being were found between the child patients and their controls or between adolescent patients and their controls.

The correlation between HRQoL, life satisfaction and objectively measured physical activity was investigated by using the accelerometer data from paper III. Complete data for all three measures were available for 41 patients and 37 matched controls. An interesting finding was that a pattern of negative correlations was found in adolescent patients between the measures of high-intensity physical activity and sports participation and the HRQoL measure psychological well-being and life satisfaction. This negative correlation was evident in both the patient KIDSCREEN self-report and the parent proxy report, as well as in the SWLS self-report. There was no such pattern in adolescent controls or in the children. For children, both patients and controls, the correlations were positive between both psychological and physical well-being and physical activity as well as sports participation in self-reports and proxy reports. Sedentary time displayed negative correlations in children (patients and controls) and adolescent controls for life satisfaction, psychological and physical well-being, but not in adolescent patients.

The somewhat unexpected finding of the negative correlation of MVPA with life satisfaction and with the HRQoL domain of psychological well-being might have several explanations. Adolescence is a time of ground-breaking changes, both mentally and physically, and HRQoL is generally reported to be lower in adolescents than in children [133]. The influence of the family on the life of the adolescent, and the family's protective abilities, decrease and are replaced by the increasing importance of peers [131, 134, 135, 153]. During adolescence, performance requirements for sports participation increase and it is possible that physical limitations that previously had no significance may now be revealed in some patients [71]. They may also experience little improvement from endurance training over time [94]. Another complicating aspect is that some individuals are given exercise restrictions sometime during childhood by cardiologists, parents, coaches or teachers. Even if these restrictions are removed when they reach adolescence, the experience might give rise to mixed emotions and even a sense of insecurity when performing high-intensity physical activity or participating in sports. All the factors discussed here, together or separately, might have a negative influence on psychological well-being and life satisfaction in adolescents treated for VAS when performing high-intensity physical activity.

Strengths and limitations

A strength of the present studies is that all patients treated for VAS in Sweden were identified in the surgical and catheter registries at the two paediatric heart centres in Sweden to obtain complete cohorts. But despite the inclusion of all eligible patients treated for VAS at one or both centres, the studies in this thesis all have limitations regarding sample size and number of outcome events.

In papers I, II and IV, all cases over a period of more than 20 years were included. A strength is that only three patients were lost to follow-up, due to emigration, in paper I and no drop-out occurred in papers II and IV. In the studies of physical activity, HRQoL and life satisfaction, all eligible patients in the selected age range were invited and after three reminders the participation rate was 43% among the patients; a higher response rate would have been desirable. Consequently, there is a risk that the studies are statistically underpowered, precluding identification of statistically significant differences. As VAS is much more common in males, it was not possible to make gender comparisons. This would have been particularly interesting in the studies of physical activity, HRQoL and life satisfaction, where gender differences are often found.

The retrospective study design in papers I, II and IV is a limitation; the study period dates back to 1994 and some information may be difficult to recover. All medical charts were retrieved but the data were not always consistently reported. In addition, a few preoperative echocardiograms were incomplete. Nonetheless, the long follow-up time (more than 11 years in median) have made it possible to collect a significant number of outcome events from complete cohorts of patients treated for VAS.

Another strength is that patient selection bias related to the choice of primary intervention was limited, as one method (SAV) was clearly preferred over the other (BAV). A weakness when comparing reinterventions is that uniform criteria for reinterventions are not available in the guidelines. This adds a possible confounding factor when time to reintervention is compared in the literature.

A strength of paper III is that physical activity was objectively measured, and we believe that the new method FEM offers advantages when measuring physical activity in children and adolescents. This is also a strength of paper V, as HRQoL and life satisfaction were correlated with the objectively measured physical activity. A weakness of papers III and V is the loss of possible participants in the recruitment process and that the analysis of the non-participants is limited. It is possible that the study group consisted of healthier, happier and more physically active patients and controls than the non-participants, but the reverse relationship is also possible.

7.

Conclusions

Short-term and long-term survival after treatment for VAS was high in our cohorts of neonates, infants and children with SAV as the preferred primary intervention. In the single-centre paediatric cohort, long-term transplant-free survival was 96%; in the national cohort of neonatal critical VAS it was 91%, and in the neonatal non-critical VAS group it was even higher, 98%. Median follow-up time was relatively long compared to most other published studies, from a median of 11.2 years (range 2–21) to 13.5 years (range 1–26) in our studies, with minimal drop-out.

Reinterventions were common after treatment for VAS during childhood. Reintervention within the first year was more common after treatment for critical VAS in neonates. It is notable that no patient was discharged with moderate or severe aortic regurgitation. Our results are consistent with reintervention rates after SAV in the literature, supporting the claim that SAV is associated with longer freedom from reintervention than BAV. However, comparisons of outcome after treatment for VAS are hampered by inconsistencies in the definition of critical neonatal VAS. The importance of the definition of neonatal critical VAS for treatment outcome was illustrated by a significantly shorter event-free survival in neonates with critical VAS vs. neonates with non-critical VAS.

The primary goal of treatment for VAS in children is to relieve the stenosis without causing significant aortic regurgitation, and to postpone the need for AVR until later in life. Among our transplant-free late survivors, AVR was performed in 34 of 110 paediatric patients (33%), in 11 of 41 neonates with non-critical VAS (26%) and in 23 of 62 neonates with critical VAS (37%). In the latter group, only 2 of 15 patients were free from AVR at 18 years of age.

The WHO guidelines recommending at least 60 minutes of MVPA on average per day were fulfilled to a high degree in both children and adolescents treated for VAS, as well as in the controls. When accelerometer data was processed with an improved frequency extended method, a different physical activity pattern in children treated for VAS compared to matched healthy controls was revealed. Significantly less physical activity was registered in the highest range of the detailed activity spectrum (VVPA) compared to controls. Comparing adolescent patients and controls, a significantly lower time spent in VPA was seen in the patients. The patients of both age groups reported less sports participation than the control groups.

Children and adolescents treated for VAS rated their HRQoL and life satisfaction as high as the matched controls. Compared to Swedish norm values, the adolescent patients rated their physical well-being lower. In adolescent patients, negative correlations were found between, on the one hand, the QoL measures psychological well-being (self-reported and in parent proxy reports) and life satisfaction and, on the other hand, objectively measured physical activity and sports participation. This indicates that there might be a complex association between physical activity and certain domains of HRQoL and life satisfaction in adolescents treated for VAS.

8.

Future perspectives

Contemporary studies show favourable results for short-term and long-term survival after treatment for VAS during childhood. However, treatment methods must still be improved to decrease the need for reinterventions and for the development of alternatives to AVR in neonates, infants and children.

Evaluations of treatment results would benefit from a greater stringency in their inclusion criteria. A uniform definition of neonatal critical VAS would facilitate comparison of treatment outcomes.

Randomised controlled trials are the gold standard when comparing the outcome of different treatment strategies. However, randomised controlled studies of outcome after treatment of VAS would not be feasible in neonates and children, as the number of patients is small and treatment practice is based on expert opinion and institutional practice. To obtain a larger sample, one possibility would be to compare national cohorts from the Nordic countries; in these countries, health care is similarly organised, with paediatric heart surgery centralised to one or two centres in each country but with different institutional choices of preferred initial treatment method. A propensity-score-matched study would probably add valuable information.

The use of the FEM for processing accelerometer data showed promising results in identifying a different pattern of physical activity in children treated for VAS compared to the traditional ActiGraph method. However, the FEM needs to be further evaluated in larger populations of children and adolescents with CHD as well as in healthy controls and in children with other chronic diseases.

With a more preventive approach to follow-up of patients with CHD, promotion of physical activity becomes important to decrease long-term cardiovascular morbidity. By objectively measuring physical activity with accelerometry and assessing HRQoL in addition to the regular medical follow- up visits, we enhance our ability to identify patients who would benefit from intervention programs and provide a better foundation for proper counselling and individual support on physical activity in all CHD patients.

9.

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10.

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