Percutaneous pulmonary valve implantation impact on clinical outcome, patients self-reported health, psychosocial function, and hospital costs in patients with congenital heart disease

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LIST OF PAPERS

Paper 1

Andresen, B. Andersen, MA. Lindberg, H. Døhlen, G. Fosse, E. Perceived health after percutaneous valve implantation: in depth interviews in patients and next-of-kin. BMJ Open. 2014 Jul 29; 4(7):e005102. doi: 10.1136/bmjopen-2014-005102.

Paper 2

Andresen B, Mishra V, Lewandowska M, Andersen JG, Andersen MH, Lindberg H, Døhlen G, Fosse E. In hospital cost comparison between percutaneous pulmonary valve implantation and surgery. Eur J Cardiothorac Surg. 2017 Apr 1;51(4):747-753. doi: 10.1093/ejcts/ezw378.

Paper 3

Andresen, B. Døhlen, G. Depp, LM. Lindberg, H. Fosse, E. Andersen, MH. Psychosocial and clinical outcomes of percutaneous versus surgical pulmonary valve implantation. Open Heart. 2018 Mars 5:e000758. doi:10.1136/openhrt-2017-0007582018.

SUMMARY

We studied how replacement of open heart surgery by catheter-based pulmonary valve insertion impacted clinical, self-reported and hospital economic outcome in patients with pulmonary congenital heart disease. A combination of both qualitative and quantitative methodology was applied.

We conducted a longitudinal trial with individual in-depth interviews with the first 10 patients in Norway to receive the percutaneous pulmonary valve implantation (Paper I). The second study aimed at documenting the impact of this new treatment method on hospital economy (Paper II). To expose the patient's voice in understanding the impact of the two treatment techniques, psychosocial function and clinical outcomes were explored in Paper III.

Percutaneous pulmonary valve implantation was nearly complementary to open heart surgery in the clinical outcome parameters, but improved psychosocial outcomes were reflected in the percutaneous group emphasizing the importance of regaining independence and taking control of daily life shortly after the interventional treatment. Pain was tolerated less with age, and associated with a stay in the intensive care unit following surgery. The potential of new treatment options was described as "a light in the tunnel". Relatives highlighted the importance of maintaining normality in everyday life for good family function. As with hospital costs, mean device costs were the main cost driver of patients' receiving a percutaneous pulmonary valve replacement. With a moderate reduction in the present device cost, the percutaneous technique might be cost efficient for society, as the technique holds the potential to reduce postoperative costs significantly compared to open surgery. Intermediate follow-up data revealed significant differences in favor of the percutaneous technique regarding psychosocial function using the Achenbach Youth - and Adult Self Report questionnaires.

FIGURES

PAPERS I-III

INTRODUCTION

The most common problem for children and adults following neonatal repair of complex congenital heart disease is dysfunction of the pulmonary trunk, manifesting either as an obstructive lesion or as a pulmonary regurgitation. [1, 2] These patients need repeated interventions during their lifetime. Surgery has been the only effective intervention option with excellent clinical results since the 1960's. [3] With advances in technology, treatment experience, non-invasive imaging and intensive care, the number of patients with congenital heart disease surviving into adulthood is steadily increasing. Adults with congenital heart disease constitute the fastest growing patient population, now outnumbering children with congenital heart disease. [4, 5]

During the last decade, percutaneous pulmonary valve implantation has become an alternative to open heart surgery for treatment of pulmonary trunk dysfunction. The technique represents a nonsurgical option and was first introduced in 2000. [6] In Norway, the first patients were treated with this technique at Oslo University Hospital in 2007. This early experience indicated that this treatment option has good short and intermediate-term results, allowed postponement of open-heart surgery, and might reduce the number of operations a patient has to undergo during their lifetime. [7-9] New research has focused on the relationship between heart and brain health in patients with congenital heart disease across the lifespan linking cardiovascular and neurovascular diseases as patients age.[4]

On this background we performed a broad evaluation project, including objective, subjective, and economic outcomes. We analyzed clinical and patient-reported outcomes following open heart surgery or percutaneous pulmonary valve implantation, with particular emphasis on patient-reported outcomes. The patient's perspective on treatment is an important quality outcome.[10] Such outcomes can be used for both comparative purposes in the evaluation of different treatment options, and for descriptive purposes. Profiles of patient-reported data provide a source of information about the possible consequences of therapy. This information can be shared with patients when deciding which treatment may be most suitable. Patient-reported experiences and patient reported outcomes are an important element of value-based health care as defined by Michael Porter. [11, 12] He has defined value as the core

issue in healthcare, and as the only goal that can unite the interests of all system participants. He has defined the value as measured for the care of a patient's medical condition over the full cycle of care, and the outcomes as the full set of health results for a patient's condition over the care cycle. According to Michael Porter the patient is the unique source of information that matters the most for him or her.[11] Porter's perspectives have been very useful in investigating patient-reported outcomes following treatment of the right ventricle to pulmonary artery conduit with either surgical- or percutaneous technique. We applied a combination of qualitative and quantitative research methods to shed light on the possible value of the new percutaneous technique as opposed to the conventional surgical treatment.

1.1 HISTORY/BACKGROUND

1.1.1 *THE SURGICAL RIGHT VENTRICLE TO PULMONARY ARTERY CONDUIT EXCHANGE*

Surgical treatment of congenital heart disease first aimed at correcting circulatory disorders outside the heart. Robert E. Gross performed the first surgical closure of a patent ductus arteriosus in 1938.[13]

Tetralogy of Fallot is the most frequent form of cyanotic congenital heart disease (approximately 33 in 100.000 live births). The anomaly was already described by Niels Stenson in 1671,[14] with other early reports by Eduard Sandifort (1777) and William Hunter (1784) among others. Etienne-Louis Arthur Fallot published five serialized contributions in 1888 in *Marseille Medical* regarding what he called 'La Maladie Bleue', he described what we now call the classical tetralogy of pulmonary outflow tract obstruction, ventricular septal defect, aortic overriding and right ventricle hypertrophy.[15]

The first successful method to prolong the lives of children with Tetralogy of Fallot was the development of the so-called Blalock-Taussig shunt. Helen Taussig, a cardiologist in Boston, had observed that children with a cyanotic heart defect and a patent ductus arteriosus lived longer than those without the patent ductus arteriosus. She therefore suggested that a shunt mimicking the function of a patent ductus arteriosus might relieve the tetralogy patients' poor oxygenation. In 1943, Taussig

approached the surgeon Alfred Blalock and his laboratory technician Vivien Thomas in their Hopkins laboratory in Baltimore. The operation involved the joining of the subclavian artery to the pulmonary artery. After performing the subclavian-to-pulmonary anastomosis in some 200 dogs, they started performing the operation successfully on infants in 1945.[16, 17] However, although it prolonged survival, the shunt did not correct the anatomical failure, thereby restoring normal circulation. To do this, surgery inside the heart was necessary. This required pumping and oxygenating the blood mechanically, excluding the heart and lung during the operation.

Dr John Gibbon and his assistant Mary Hopkinson had developed a system for extracorporeal circulation using a roller pump and tested it on cats in Philadelphia. In 1953, Gibbon successfully closed an atrial septal defect using an oxygenator and roller pumps. His next attempts failed, however, and he gave up attempting to repair heart defects. In Minneapolis, two teams were trying to solve the problem of final repair of congenital heart disease. At the Mayo clinic, the team was led by John Kirklin while, at the Minneapolis Medical Center, the surgeon Clarence Walton Lillehei continued experimenting with techniques to perform intracardiac operations. He and his team were convinced that the poor results were due to the extracorporeal technology. Thus, they developed the cross-circulation technique in which a close relative of the child was used as a heart-lung machine, by coupling the circulation of the two individuals together. [18]

In March 1954, Lillehei and his associates Morley Cohen, Herb Warden, and Richard Varco used the cross-circulation technique to correct a ventricular septal defect in an 11-year-old boy. The boy's anesthetized father served as the oxygenator. Blood flow was routed from the patient's caval system to the father's femoral vein and lungs, where it was oxygenated and then returned to the patient's carotid artery. The cardiac defect was repaired with a total pump time of 19 minutes. Over the next 15 months, Lillehei operated on 45 patients with complex interventricular defects; most of these patients were less than two years old. Although cross-circulation was a major advance, it posed a serious risk to the ‘donor’, and was therefore not generally adopted. However, the same year, Dr Richard A. DeWall, working together with Lillehei, developed the first clinically successful bubble oxygenator. On the 13 May 1955 they closed a ventricular septal defect in a three-year-old girl using the DeWall oxygenator.

The operation went well and was followed by a series of pediatric cardiac surgical procedures. In Rochester, John Kirklin and his team performed the second intracardial repair just one month later. In 1960 the programmes were expanded to repairing valvular disease in adults. This was the start of modern heart surgery.

Before the surgical breakthrough in the 1950s, children with unrepaired heart disease such as Tetralogy of Fallot carried a poor prognosis, with only 50% of patients reaching the age of three years and only few surviving to 40 years of age.[19] Since then, major advances in treatment made surgical palliation and corrections of nearly all congenital heart defects possible. Early postoperative survival after repair now exceeds 98%.[20, 21] In Norway, congenital heart defect surgery was introduced at Rikshospitalet, with a replica of the DeWall heart-lung machine in 1959. The number of patients undergoing surgery increased quickly during the 1970s. Until 2003, about 80% of all congenital heart disease surgery in Norway was performed at Rikshospitalet. Since 2003 the hospital became the national center for all such patients in Norway.[21] Over the past 40 years, there have been substantial improvements in postoperative survival within all subgroups of complex congenital heart disease, with early mortality now approaching zero.[21]

Pulmonary valve replacement is the most common operation performed in adults with congenital heart disease requiring surgery. Twenty percent of newborns with complex congenital heart disease have a right ventricle outflow tract defect, which tetralogy of Fallot likely representing the largest group.[22] Other diagnoses involving a dysfunctional right ventricle outflow tract in need of repeated valve exchanges are pulmonary atresia or truncus arteriosus, transposition of the great arteries, common arterial trunk, and others requiring a surgical reconstruction with the use of a patch, bioprostetic valve or valved conduits.[23] Each component can vary in severity, with the variation directly affecting the manifestation and management of the disease. The pulmonary valve is generally small, dysplastic and stenotic, and in some cases absent. [15] Most patients with right-sided lesions need multiple pulmonary valve replacements during their lifetime due to pulmonary stenosis, pulmonary regurgitation, or both. Chronic pulmonary stenosis and regurgitation have serious effects on the hearts of these patients.[22, 24]

Failing surgically implanted bioprosthetic valves demonstrate leaflet calcification, thickness and immobility leading to pulmonary stenosis and/or pulmonary regurgitation.[25]

1.2 IMPORTANT PARAMETERS IN PULMONARY VALVE DISORDER

1.2.1 *FACTORS INFLUENCING PULMONARY VALVE REPLACEMENT*

Although anatomic and physiological correction have been achieved in patients with pulmonary valve dysfunction, complications such as pulmonary regurgitation leading to right ventricular dilatation and dysfunction, recurrent obstruction of the right ventricle outflow tract, prolonged QRS duration, atrial- and ventricular arrhythmia, decreased exercise tolerance, aortic dilatation, regurgitation, and sudden cardiac death are late suvivors.[26, 20, 27, 28]

The timing of the first total correction may influence the outcome. Some studies have indicated that early correction avoiding the traditional palliative procedure of a shunt[27] may improve survival and reduce the need for reoperation.[28-31] However, other studies did not demonstrate any difference in outcomes following primary repair versus following primary palliation and early initial correction. [32, 33] The current policy in the department of thoracic surgery at the University of Oslo is to intervene when the patient becomes symptomatic namely in the case of low saturation. If the patient's anatomy is conductive to avoiding a transannular patch, open repair is chosen. Otherwise, a shunt is placed, and correction by surgical repair is completed before the age of one year.

An association between arrhythmias and reoperations is found by the insertion of a transannular patch, since the development of pulmonary regurgitation after surgery using a transannular patch has been frequently documented.[29] Surgeons currently tend to use smaller patches to minimize pulmonary regurgitation and long-term sequelae. Early postoperative arrhythmias indicate higher mortality.[27]

Higher morbidity and complication rates have been reported in infants younger than 3 months of age compared to older infants undergoing an initial correction of Tetralogy of Fallot.[32] Other authors[33]

argue that elective repair can be safely performed in patients older than 55 days without any increase in reintervention rates, irrespective of the patient's size and weight. Residual peak right ventricle outflow tract gradient is emphasized as an effective means of identifying patients with an increased risk of reintervention.[33] Hence, controversy exists about the optimal timing and choice of procedure.[34, 35] Children with Tetralogy of Fallot usually have a higher rate of extracardiac anomalies and syndromes,[36] which might increase the risk of open-heart surgery. Premature infants and neonates, especially those with severe cyanosis or ductus-dependent pulmonary circulation, represent a group of patients in which open-heart surgery is frequently postponed in favor of palliative procedures without cardiopulmonary bypass.

1.2.2 *DURABILITY OF DIFFERENT TYPE OF VALVES*

There are several surgical options for pulmonary valve replacement, including bio prostheses, homografts, mechanical valves, and hand-sewn polytetrafluoroethylene valves.[37-40] Confounding factors may be important when comparing the long-term durability of surgically implanted valves, the most important factors include timing of operation, age, valve size, immunological factors, operative complexity, the type of tissue material, and postoperative valvular gradients. The timing of these operations has always been matter of great controversy, as illustrated by the existence of varied guidelines.

Among these options, bioprosthetic valves are the most widely used because they are readily available and the patient does not need permanent anticoagulation therapy. In a study by Cheul Lee et al.[41] where 181 patients underwent pulmonary valve replacement with bioprosthetic valves, the valves maintained functionality in all patients for five years post-surgery, however, after 10 years, about 80% of patients required a reoperation or had a manifest valve dysfunction.[37,42] This result is fairly compatible with those of earlier studies[39, 43-45] of different surgical methods reporting five-year freedom from repeat pulmonary valve replacement (92% -100%). Younger age and the diagnosis of

pulmonary atresia with ventricle septum defect, have been identified as independent risk factors for repeat pulmonary valve replacement. Stentless porcine valves were less durable than stented valves. However, actual long-term durability of bioprosthetic pulmonary valves implanted into children and young adults has not been established owing to the small number of patients or relatively short duration of follow-up in previous studies.[46, 47]

Furthermore, many studies are limited to a single valve type,[38, 48] and there are few reports on the durability of different types of bio prostheses.[39, 47] Currently, there is no evidence that one specific design or configuration is superior to others in terms of long-term valve function.[49] In a study by Neukamm et al.,[50] 365 operations were performed during an eight-years-period from 2000 to 2008 using different surgical method. They found that homografts and monocusps had a more than 50% lower risk for reoperation than Contegra or bicuspid valves. The mean age of the patients in their study was 5.9 years.

1.2.3 *RADIOLOGY GUIDED INTERVENTIONAL METHODS*

In 1929 the German physician Werner Forssmann passed a thin ureteral catheter into his heart via his own cubital vein and documented its placement on a chest X-ray. His aim was to prove that one could administer drugs directly into the heart. Twelve years later, in 1941, André Frederic Cournand continued Forssmann's experiments and managed to draw blood samples from the heart. Intervention through the blood vessels was introduced as a clinical tool when the Swedish radiologist Sven Ivar Salinger developed a safe technique for transcutaneous techniques for puncturing the vessels transcutanously.

In October 1958, a breakthrough occurred accidentally as the paediatric cardiologist Frank Mason Sones at the Cleveland Clinic was experimenting with injecting contrast dye into the heart. By accident, the catheter became lodged in the right coronary artery and he got a perfect image of the artery and its branches.[51] During the 1960's, diagnostic cardiac catheterization in adults became a

routine procedure, although it was still experimental in children.[52] In 1966 Alois J. Beuren from Germany published an atlas of angiography in congenital heart diseases.[53]

Charles Theodore Dotter is considered the inventor of interventional radiology, and he developed several of the components necessary. He was a leading force in the development of an x-ray tube capable of obtaining millisecond exposures. He was the first to describe flow-directed balloon catheterization, the double-lumen balloon catheter, the safety guidewire, and the 'J' tipped guidewire. In 1964, Dotter performed the first balloon angioplasty for the reopening of a stenotic iliofemoral artery at the Department of Radiology at the University of Oregon Medical School. Dotter later introduced the concepts of percutaneous arterial stenting and stent grafting by placing the first percutaneous 'coil spring graft' in the femoral artery of a dog. He also pioneered the techniques of low-dose fibrinolysis with injection of streptokinase directly into an occluding thrombus.[54]

The first intracardiac procedure for treating patients with congenital heart disease was performed by the cardiologist William J. Rashkind in 1966. He developed procedure using a balloon-tipped catheter to make making an interatrial communication in newborn children transposition of the great arteries.[55] His rationale was that patients with transposition lived longer if they had an atrial septal defect or an open ductus arteriosus. The Rashkind procedure quickly gained acceptance and was first performed in Norway by Svein Jan Sørland in 1969.[56] Bjarne Semb and co-workers reported performing a balloon valvotomy for pulmonary valve stenosis was reported by at Rikshospitalet in 1979.[56] The same year, the German cardiologist Andreas Grüntzig reported the first coronary angioplasties.[57] Balloon treatment of pulmonary valve stenosis was described by Jean S. Kan in 1982[58] and was offered as treatment to neaonates soon thereafter.[59]

In 1967 Werner Porstman published a paper describing the first attempt to close the arterial ductus with a plug introduced through the femoral artery.[60] However, the device used by Porstman was not a success. Rashkind developed an umbrella device concept in 1979[61] which was introduced at Rikshospitalet in 1989.[62]

Several devices followed. The Amplazer nitinol plug was probably the greatest breakthrough in percutaneous closure of persistent ductus arteriosus.[63, 64] By 1998, percutaneous treatment of persistent ductus arteriosus had completely replaced surgical closure at Rikshospitalet.

Rashkind and co-workers continued working on a device to close atrial septal defects using transcutaneous techniques. After Rashkind died, his co-workers continued working on a clamshell device for closure of atrial septal defects.[65] In 1996, the Austrian interventional radiologist Kurt Amplatz developed an atrial septal defect occluder while working as the chairman of Radiology at the University of Minnesota.[66]

At Rikshospitalet, Per G. Bjørnstad initiated an animal study of Amplatzer device[67] and shortly thereafter could present his first clinical experiences with the device.[68]

1.2.4 *PERCUTANEOUS PULMONARY VALVE TECHNIQUE*

Percutaneous pulmonary valve implantation is arguably the most innovative procedure developed to treat congenital heart disease in the past two decades.[69, 70] In August 2000, Philipp Bonhoeffer and collegues[6, 71] conducted a percutaneous pulmonary valve implantation in a lamb model. Although only 7 of 11 implants were successful, the study paved the way for application of the technique in human beings. In October 2000, Bonhoeffer and colleagues from France reported the first human implantation of a percutaneous pulmonary valve, in a 12-year-old boy who had presented with pulmonary atresia, a ventricular septal defect, and a dysfunctional right ventricle to pulmonary conduit.[71] In 2002, the first clinical series was published confirming the success of the procedure.[72] Clinical use of the Melody ® Transcatheter Pulmonary Valve (Medtronic, Inc., Minneapolis, MN, USA) continued in Europe and Canada. Modification of the valve led to CE Marking in September 2006 and U.S. Food and Drug Administration (FDA) approval in 2010.

The Melody valve consists of a bare-metal platinum-iridium stent (CP stent, NuMED, Inc., Hopkinton, New York) and a manually-sewn valved segment of bovine jugular vein. Currently, the Melody valve is available in diameters of 16 and 18 mm, which can be expanded to 18 or 20 mm, and 18, 20, or 22 mm, respectively.[73] The Edwards® valve was initially introduced for transcatheter aortic valve replacement in elderly patients with degenerative aortic valve stenosis, and was first introduced for use in the pulmonary position in 2006. [74]

The Edwards Sapien Pulmonic Transcatheter heart valve (Edwards Lifesciences, Irvine, California) is a trileaflet bovine pericardial tissue valve hand-sutured in a balloon-expandable, radiopaque, stainless-steel stent. It is available in 23-26 and 29 mm diameters that require 22- or 24-F delivery sheaths, respectively. This device contains a unique proximal sealing cuff designed to prevent paravalvular leaks.[75]

1.2.5 *SHORT AND LONGTERM RISK FOLLOWING PERCUTANOUS PULMONARY VALVE IMPLANTATION*

Stent fracture is an important adverse outcome after percutaneous pulmonary Melody valve implantation and was reported in up to 25% of patients in earlier studies.[76] Having one or more pre-stents appears to be protective, reducing the risk of stent fractures, structural failure, and intervention over time. [77] Pre-stenting is a preparation of the right ventricle outflow tract landing zone in patients with stentless conduits. [78] In patients with a wide right ventricle outflow tract, pre-stenting has been shown to inhibit stent migration.[29]

Coronary artery compression is the most important procedural complication related to procedural mortality.[79] Approximately 5–6% of candidates for percutaneous pulmonary valve implantation are at risk for coronary compression after metal stent expansion in the right ventricle outflow tract. [80] Homograft rupture is a relatively frequent complication in patients with calcified conduits, and can

also result from too aggressive dilatations of the oversized balloon. Covered stents may be an alternative to surgical treatment.[29]

Reintervention is common, currently the five-year freedom from reintervention is approximately 92%.[81] The main reason for reintervention is high post-procedural pulmonary gradient, stent compression, or stent fracture.[29] The most important factor responsible for late mortality and reintervention following percutaneous pulmonary valve implantation is infective endocarditis. The epidemiology of infective endocarditis is changing rapidly due to the emergence of resistant microorganisms, the indiscriminate use of antibiotics, and an increase in the implantation of cardiovascular devices.[76] Several cases of early and delayed percutaneous pulmonary valve infective endocarditis have been reported in prospective studies although the factors are not clearly understood. Infective endocarditis is a burden in the congenital heart disease population, particularly in patients with prosthetic valves. The risk is estimated at 2.4 % (0.34-6.03) per/year which is a higher occurrence than after surgical implantation of the pulmonary valve.[73, 82-84]

Two major studies comparing the incidence and outcomes of right-sided endocarditis in percutaneous versus open surgery techniques, showed a 4.5-fold greater risk of infective endocarditis with the percutaneous pulmonary valve implantation technique.[83, 84] Several reasons for this have been discussed. One main difference between the two treatment techniques is the preparation of the percutaneous valve; in percutaneous implantation the valve is being prepared and crimped before the implantation, and when in place, expanded by a balloon, whereas with surgery, prostheses are placed directly without manipulation.[85]

There is a higher reported incidence of endocarditis in patients who have undergone Melody implantation compared to those who received a Sapiens; this may be explained by the much higher distribution of the Melody valve.[29] Suboptimal haemodynamic results (residual gradient, eccentric turbulence, pockets due to incomplete apposition, thrombus formation, asymmetric or incomplete opening with redundancy of leaflet tissue) are possible risk factors. A majority of cases of valve infective endocarditis have been associated with predisposing conditions, including noncompliance

with antibiotic prophylaxis regimens, dental or other invasive procedures, and concomitant bacterial infection.[1, 73, 86] The role of aspirin discontinuation has also been discussed.[84] When comparing Melody valves with Contegra bovine valve conduit, there is no difference in infective endocarditis between Melody- and Contegra valves, suggesting possible tropism of micro-organisms to the bovine material used in making the Melody and Contegra valves.[83] Avoidance of skin lesions, antibiotic prophylaxis prior to interventions with expected distribution of significant bacteremia are important measures. Long-term anticoagulation or antiplatelet therapy is recommended to reduce the incidence of initial thrombus formation in an area of endothelial damage.[85]

1.2.6 *TREATMENT GUIDELINES*

Currently, the criteria for percutaneous pulmonary valve implantation are the same as for surgical pulmonary valve replacement.[87]

In a clinical setting the thresholds for replacing is complex. International guidelines must be considered as suggestions as large randomized studies are lacking. Key factors for discussions are degree of pulmonary stenosis, degree of pulmonary insufficiency, heart function, echocardiography and clinical symptoms. In guidelines,[30] current thresholds for replacing the pulmonary valve are peak instantaneous echocardiography gradient > 50mmHg, right ventricle pressure >0.7 times the left ventricle pressure, progressive and severe dilatation of the right ventricle with dysfunction, free pulmonary regurgitation with progressive or moderate-to-severe right ventricle enlargement (right ventricle end-diastolic volume > 170 mL/m$^{2)}$, moderate to severe right ventricle dysfunction, important tricuspid regurgitation, atrial or ventricular arrhythmias or symptoms such as deteriorating exercise performance or residual pulmonary stenosis with the right ventricle at least two-thirds systemic.

Pulmonary valve replacement is indicated for symptomatic patients with severe pulmonary regurgitation and/or pulmonary stenosis (right ventricle systolic pressure > 60 mmHg, tricuspid regurgitation velocity > 3.5 m/s), and should be considered for asymptomatic patients with severe

pulmonary regurgitation and/or pulmonary stenosis when at least one of the following criteria is present: decrease in objective exercise capacity, progressive right ventricle dilatation, progressive right ventricle systolic dysfunction, progressive tricuspid regurgitation (at least moderate), right ventricle outlet trunk obstruction with right ventricle systolic pressure > 80 mmHg (tricuspid regurgitation velocity >4.3 m/s), or sustained atrial/ventricular arrhythmias.[30, 88]

Other important factors for considering right ventricle outflow tract replacement are substantial coexisting lesions, such as significant aortic regurgitation, tricuspid regurgitation, residual ventricular septal effects, coronary anamalies[89] and aortic root dilatation.[90-92] The aim of restoring pulmonary valve integrity is to preserve right ventricular size and function with the intent of mitigating the development of symptoms and poor long-term outcomes. The alteration of the right ventricle is at some point irreversible.[93] A major factor in determining when to operate is the evaluation of right ventricular size and function. Since the emergence of percutaneous pulmonary valve replacement techniques, the issue of in timing has become even more complicated. The trend currently is towards earlier pulmonary valve replacement.[27, 32, 87] Both surgical and a percutaneous pulmonary valve exchange eliminates pulmonary regurgitation and improves right ventricle dimensions but do not consistently improve right ventricle ejection fraction. [7, 94]

AIMS OF THE STUDY

The aims of the thesis were to compare clinical outcome, patients' self-reported health, psychosocial function and hospital costs in children and adolescents with pulmonary valve disorder following percutaneous pulmonary valve implantation or open heart surgery. The papers comprising this study have the following objectives:

1. To assess the perceived health in patients with right ventricle outflow tract obstruction or insufficiency after percutaneous pulmonary valve implantation measured by in-depth interviews of patients and next of kin (Paper 1).
2. To compare in - hospital cost measured by two different methods between patients treated with percutaneous pulmonary valve implantation and open heart surgery (Paper 2).
3. To investigate and compare psychosocial outcomes, self-reported heart function and clinical outcomes of percutaneous versus surgical pulmonary valve implantation. (Paper 3).

2 RESEARCH QUESTIONS

The following research questions were addressed:

1. How did patients experience the percutaneous pulmonary valve implantation method?
2. How did patients' next-of-kin experience the percutaneous pulmonary valve implantation method?
3. What was the difference in hospital costs between percutaneous pulmonary valve implantation and open heart surgery?
4. Were there differences between the two methods of pulmonary valve replacement in terms of psychosocial and clinical outcomes?

The hypothesis in this thesis was:

H_1 and H_0: The two treatment groups are equal with respect to hospital costs and psychosocial and clinical outcomes.

H_2 and H_0: At 3 months the percutaneous implantation group has better patient-reported outcomes than the surgery group.

3 METHODS

3.1 DESIGN

This thesis represents one qualitative and two quantitative studies with an exploratory, descriptive cohort design. A combination of qualitative- and quantitative prospective and retrospective data was used.[95-97] Qualitative and quantitative methods were employed to comprehensively and thoroughly investigate the patients` own perspectives.

3.2 STUDY POPULATION

3.2.1 *INKLUSION CRITERIA AND RECRUITMENT*

In order to provide insight in subjective meaning and interpretation of the patient and their next-of kin experiences of the new treatment method in a short time perspective, the 10 first patients to undergo the procedure in Norway were consecutively included in a qualitative study. Both patients and next of kin underwent a semi-structured interview before treatment. The closest relatives' questionnaire contained the same topics as of the patient. In order to study in hospital costs, patient- reported and clinical outcomes in two quantitative studies were conducted comprising all patients treated with pulmonary valve replacement from June 2011 to October 2014. A control group of patients requiring surgical pulmonary valve replacement was recruited in parallel to both studies. Data on objective measures were obtained from medical records. Quantitative data on psychosocial functioning was collected through a questionnaire before the intervention/surgery (T0), at 1 (T1), 3 (T2), 6 (T3) and 12 (T4) months after the event. Timing of data was based on expected intervals to maximum benefit of the treatment.

In total 34 consecutive patients were included in the quantitative studies (20 in the percutaneous pulmonary valve group and 14 in the open surgery group), 23 of these patients were children (15 in the percutaneous pulmonary valve group and 8 in the open surgery group). A team of four thoracic surgeons and one interventional cardiologist working in close collaboration performed all right

ventricle outflow tract procedures. A procedural strategy reflecting international guidelines[30] was planned for both pediatric and adult patients, using the same criteria for both procedures. The descriptive studies followed a cohort of patients for one year with self-reported data as well as observed data.

The inclusion criteria were independent of procedure technique, based on international principles of treatment within the field and a consensus set by the local treatment team. The exclusion criteria were: aggressive endocarditis, conduit of >22 mm, and no circumferential foreign material. All included patients had information on their former surgery (conduit type and size), clinical indication, and gradient of their stenosis (as measured by echocardiography, cardiac magnetic resonance imaging, or catheterization). All patients in both groups required pulmonary valve replacement secondary to a failed surgical procedure to repair the right ventricle outflow tract.

4 THEORETICAL FRAMEWORK

4.1 VALUE BASED HEALTH RESEARCH

In order to evaluate the new method in a value-based approach, we used Michael Porter's framework for achieving value in healthcare.[11] A semi-structured interview guide was used when interviewing both patients and next of kin after treatment with the percutaneous technique. The Achenbach System of Empirically Based Assessment instrument was used to measure psychosocial functioning as part of a health concept. The New York Heart Association functional classification of heart failure was used to measure functional capacity. Direct and overhead cost methods were used to evaluate and compare the in-hospital costs of the two treatment techniques. As clinical objective outcome, we recorded change in the measured right ventricle to pulmonary artery pressure gradient and the degree of pulmonary regurgitation before and after treatment. For both methods, complications such as mortality, intervention, and arrhythmia as clinical postoperative outcomes measures were analyzed.

In Michael Porter's value-based health care model, the overarching goal of healthcare is to achieve outcomes of high value for patients, with value defined as the health outcomes achieved per dollar spent (Figure 1). [11] Value is defined to be the preeminent goal in where quality should be measured and centred on the patient, demonstrating better quality at as low cost is possible. Outcomes should be measured for each medical condition covering the full cycle of care, including acute care, related complications, rehabilitation, and reoccurrences.

As shown in Figure 1, value is defined as patient health outcomes achieved relative to cost. Outcomes, the numerator of the value equation, are the actual results of care in terms of patient health. For any medical condition, there is a set of multidimensional outcomes that jointly constitute patient benefit, including survival, functional status, and sustainability of recovery, among others. In Porter's model, patients' circumstances and preferences will affect the importance of these outcomes to some degree. The full set of outcomes, adjusted for individual patient circumstances, constitutes the quality of care for a patient. Costs should reflect the full array of resources involved in caring for the patient's

condition, including inpatient, outpatient, and rehabilitation care, along with all associated drugs, devices, services, and ancillary equipment.[11]

In this thesis, a modified version of Porter's outcome measures hierarchy was used with the goal to clarifying the different aspects and multiple dimensions of quality for patients and how they are related in a lifeline cycle. The modified model served several purposes. First, it encompassed a broad understanding of how value patients defined value and incorporated their experiences, self-reported psychosocial function, and clinical and cost outcomes. Further, it provided a direction for the studies and the various variables included. It also provided a guideline for the statistical analysis strategy. The modified model makes it possible to visualize how findings influence different stages in the model depending on which treatment method was used. Finally, it demonstrated how patient-centered value also contributes to quality and to lower costs in a life-time perspective.

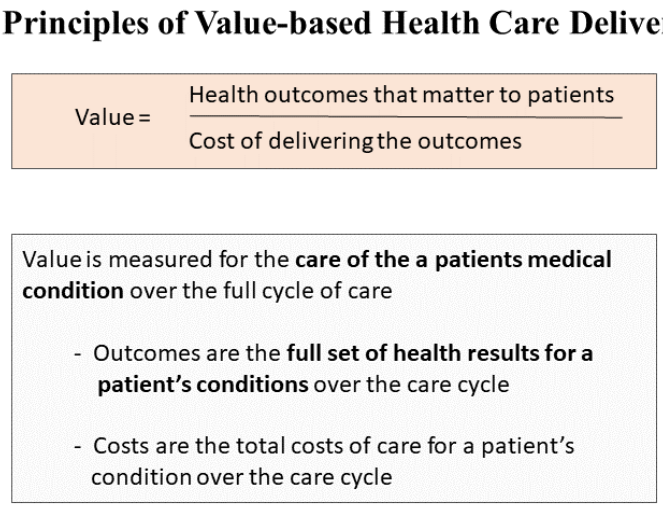

Figure 1: Porter ME. 2010.

In Michael Porter's framework, for any medical condition or patient population, multiple outcomes collectively define success; the full set of outcomes can be arrayed in a three-tiered hierarchy (Figure 2). The top tier of outcomes is generally the most important, with lower-tier outcomes reflecting a progression of results contingent on success at higher tiers. Each tier of the hierarchy contains two broad levels, each of which involves one or more distinct outcome *dimensions*. Outcome dimensions capture specific aspects of health and are the critical dimensions of quality in healthcare. For each dimension, success is measured with one or more specific *measures* or *metrics*. Finally, for each measure there are often several choices in terms of the *timing* and *frequency* of measurement.[11]

Porter's Outcome Measure Hierarchy

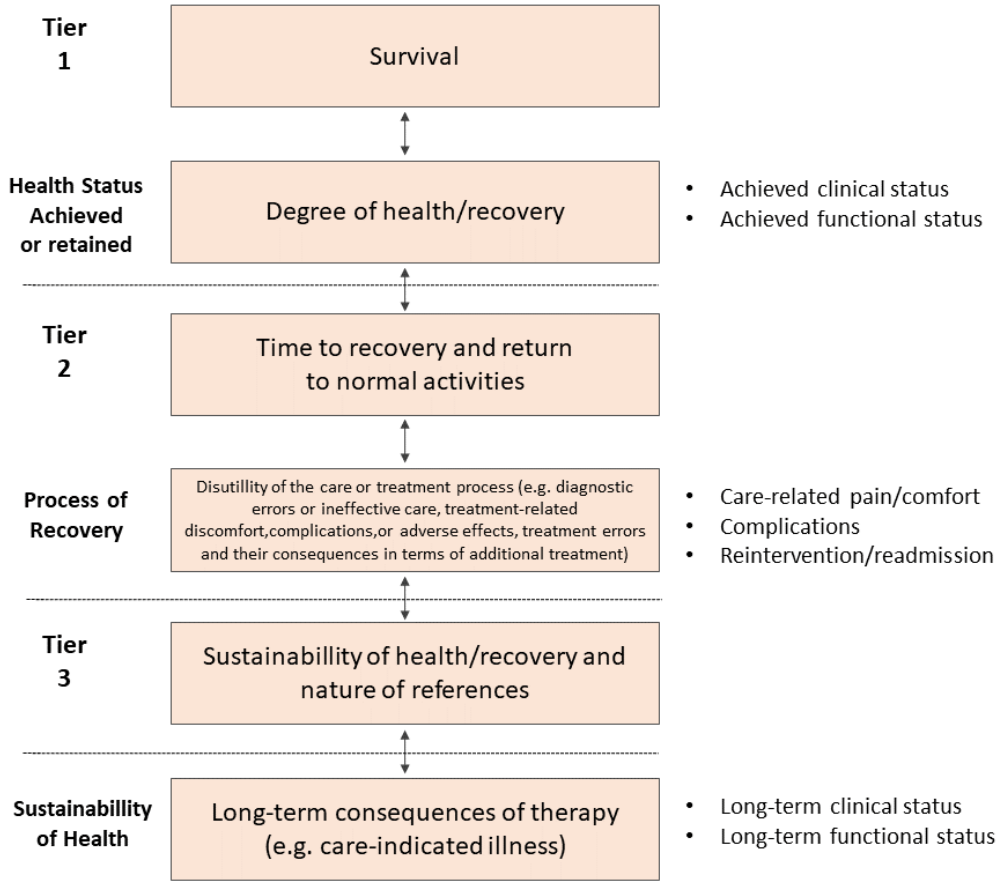

Figure 2: Porter ME. 2010.

In today's aging society, more people are living with chronic diseases such as congenital heart disease. Heart failure, dementia, and diabetes are more frequently seen in people of congenital heart disease than in the general population, and preventive initiatives are important in order to maximize health in a long-term perspective.

4.2 HEALTH AND WELL-BEEING

Health is a subjective concept. The World Health Organization (WHO) has defined health as 'a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity' (http://www.who.int.). However, this definition is now considered limited, and Huber et al. have argued that it is no longer viable, since chronic disease is widespread and the world population is growing older.[98] Human beings possess the ability to adapt and self-manage when exposed to challenges. If human beings' capacity for adaptability is taken into account, and health is deemed something other than complete well-being, the instruments for measuring health already exists, including methods for measuring a person's functional status, quality of life, and sense of well-being.

4.3 QUALITATIVE AND QUANTITATIVE METHODS

Pairing quantitative and qualitative components of a study can achieve various aims, including corroborating findings and generating more complete data; moreover, results from one method can be used to enhance insights attained with the complementary method.[96, 99]

A combination of methodological approaches was used in this thesis to capitalize on, and profile the complexity of the patients' experiences of the two different treatment techniques, diverse costs, and clinical outcomes. The design of this PhD-work is partially mixed in that while each study had equal status they were nonetheless published in different journals. The studies were designed sequentially to complement and strengthen each other.

Besides quantitative data with predetermined response categories, in-depth interviews were chosen to capture patients' perspectives regarding their experiences of the new treatment method. In the tradition of naturalistic inquiry, reality is considered to be constructed based on individual perception. [100]

4.3.1 *PATIENT-REPORTED OUTCOMES*

Patient-reported outcome is defined by the US Food and Drug administration as 'any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else.' [101] The term patient-reported outcome refers to the source of the report rather than the content[102] and is an umbrella term for a wide range of outcomes related to healthcare, including the impact of an intervention on health and quality of life, satisfaction with treatment, or utility-based preferences. [103] The defining characteristics are the patient as a source of data, [104], as the requester and/or recipient of healthcare. [105]

Patient-reported outcomes are associated with the experience of an illness more than the disease itself and provide a unique source of insight. [106] There is growing acknowledgement of the importance of patient-reported outcomes when evaluating healthcare interventions. [107] The impact of an intervention can be measured across a range of outcomes from the purely symptomatic to more complex concepts (functional capacity), to extremely complex concepts such as quality of life. [108] A central challenge is the ability to link patient-reported outcomes to clinical endpoints. [109] In this thesis, theoretical modelling and patient-reported and objective assessments are combined to investigate these links in patients undergoing percutaneous pulmonary valve implantation versus conventional open-heart surgery. Patient-reported outcome research may help identify vulnerable and resilient subgroups among patients undergoing these two different treatments, as well as contribute to new knowledge to improve treatment strategies in the future. Moreover, patients' own assessments can promote their involvement in decision-making at the individual as well as the group level, with the possibility of extending this influence into cost-utility analyses. [110]

4.3.2 *PSYCHOSOCIAL FUNCTION AS PART OF A HEALTH CONCEPT*

Neurodevelopmental deficits are common and significantly disabling complications of congenital heart disease and its treatment[111, 112] affecting over 50% of surviving infants.[113] Causes are likely multifactorial. Gene mutations, altered cerebral perfusion in utero, and immaturity in neonates all play important roles. [114-118] Developmental problems among children with congenital heart disease may start in infancy but neurodevelopmental deficits often become apparent in childhood and adolescence.[119-122]

Many school-age survivors of infant cardiac surgery require supportive services including tutoring, special education, and physical, occupational, and speech therapy. To better address scholastic concerns, it is important to understand the underlying contributors. [120] The neurodevelopmental and psychosocial morbidity related to congenital heart disease and its treatment often limit ultimate educational achievements, employability, lifelong earnings, insurability, and quality of life for many patients.

4.3.3 *PSYCHOSOCIAL MEASURES*

The Achenbach System of Empirically Based Assessment [123] was used to assess psychosocial function before treatment and twice postoperatively in both groups. This is a generic, comprehensive, self-administered outcome measure of social functioning. It was translated into Norwegian by I. H. Vandvik in 1986–88 andrevised by T. S. Nøvik in 1993. The instrument has been shown to be a highly reliable and valid questionnaire. It is translated to several different languages and has been used in several Norwegian studies.[124-126] It has been used extensively to measure psychosocial function and quality of life in children and adults with congenital heart disease. [127, 128,129, 130]

The assessments comprise 112 items that are used to measure symptoms using 8 subscales: Anxiety/Depression, Withdrawal, Social complaints, Thought problems, Attention problems, Intrusive behavior, Aggressive behavior, and Delinquent behavior. Items are scored on a three-point scale, and

lower scores indicate poorer functioning.[123, 131] The Youth Self-Report questionnaire targets patients aged 11 to 18 years, while the Adult Self-Report questionnaire targets patients aged 18 to 59 years; each questionnaire was used as appropriate. A questionnaire was administered to all patients 11 years and older. The timing of data collection was based on the time intervals that were expected to maximize the treatment benefit and intermediate results. All patients were instructed to complete the questionnaire according to their perceived status of well-being at that time.

4.3.4 *SELF-REPORTED NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION OF HEART FAILURE*

The functional capacity was classified according to the New York Heart Association functional classification with a score of 1 to 4 based on patient outcomes at preoperative assessment (T0), at 1 (T1), 3 (T2), 6 (T3) and 12 (T4) months follow-up. A score of 1 meant the patient had no limitation on physical activity, a score of 2 meant the patient had a slight limitation in physical activity, a score of 3, meant the patient had marked limitations of physical activity and a score of 4 meant the patients was unable to perform physical activity without discomfort.

4.4 CLINICAL OUTCOMES

The following clinical data were collected and documented before surgical intervention and twice postoperatively (at three months and one year) in both groups: change in the measured right ventricle to pulmonary artery pressure gradient and the degree of pulmonary regurgitation. The right ventricle to pulmonary artery gradient pressure was measured in mmHg, while pulmonary regurgitation was graded in five levels (0–4) defined as none, trace, mild, severe, and free.[30]

The following acute adverse events were registered in both groups: mortality, reoperation or re-intervention, bleeding and arrhythmia demanding an intervention.

4.4.1 *PULMONARY STENOSIS*

Pulmonary valve function was described in terms of valve stenosis and valve insufficiency.

Pulmonary valve stenosis was quantified as peak blood velocity in the valve area measured by transthoracic echocardiography. Peak velocity was converted to pressure gradient using the simple Bernoulli equation $\Delta P = 4 \times V2$.

Pulmonary stenosis was measured using external echocardiography as the change in the measured right ventricle to pulmonary artery pressure gradient.

4.4.2 *PULMONARY REGURGITATION*

Pulmonary regurgitation occur in congenital or established conduits between the right ventricle and the pulmonary artery in patients with complex congenital heart defects when the native outflow tract is not amenable to reconstruction, including pulmonary atresia, common arterial trunk, Tetralogy of Fallot, absent pulmonary valve syndrome, Rastelli procedure and Ross operation.[30]

The pulmonary regurgitation rate was graded using transthoracic echocardiography according to a five-point scale: None, trace, small, large, and free.

Pulmonary regurgitation was measured using external echocardiography as the change in the measured right ventricle to pulmonary artery degree of pulmonary regurgitation.

The change in pulmonary stenosis and pulmonary regurgitation data was collected before treatment (T0), at 1 (T1), 3 (T2), 6 (T3) and 12 (T4) month follow-up.

4.5 ECONOMIC OUTCOMES

4.5.1 *IN-HOSPITAL COSTS*

Economic evaluation has been defined as 'the comparative analysis of alternative courses of action in terms of both their costs and their consequences.'[132] All economic evaluations assess costs, but their approaches to measuring and valuing the consequences of health interventions may differ. Increasing concerns about containing rising healthcare costs while preserving and enhancing access to high quality medical care have stimulated interest in more appropriate use of medical interventions. To address this issue, both clinicians and policy makers have expressed greater interest in, and devoted more effort to, 'evidence-based medicine,' 'comparative effectiveness research,', and 'health technology assessment.' These three concepts are all related to evidence-based decision making, but they are often not clearly differentiated from one another. Health technology assessment has been defined as 'a multidisciplinary field of policy analysis, studying the medical, economic, social and ethical implications of development, diffusion and use of health technology.[132]

Health technology assessment inherently requires consideration of the integration of medical interventions into clinical care and thus requires consideration of the specific contexts (e.g. care practices and structure; prices) in which the technology will be used, as well as societal factors (e.g., population health state preference values). In principle, health technology assessment explores all elements of a technology's value, not just those that can be demonstrated in randomized clinical trials. An important issue in health technology assessment is explicit assessment of the long-term benefit-risk trade-off, to ensure that unintended harmful consequences are not offsetting the intended clinical benefits. Economic evaluations are increasingly used for decision making and are an important component of health technology assessment programs internationally.[133]

4.5.2 *COST ASSESSMENT METHODS – DIRECT AND INDIRECT COST*

Cost may be an important factor in the choice of technology. Since the relative health benefits of these two treatments and their potential for increased costs to patients, their families and society have not yet been assessed, it was of great interest to evaluate and compare in-hospital costs. In order to provide accurate information regarding the cost of the individual patient during the in-hospital stay, we used the micro-costing method, [134] which is known as useful when introducing new technology. This method, termed "the direct costs" in this thesis, which aimed to document the accurate cost of each patient, calculating the variations between the patients in both treatment groups, required prospective data. The direct cost method enabled us to minimize the use of estimates, since it allowed for registration of the specific cost of the patients' level of activity and the direct cost of consumption. The other cost assessment method, was the overhead cost method with the overhead cost ultimately also allocated to the individual patient.[135] In the overhead cost assessment method, cost was based on the average estimated cost of each hour at different wards at Oslo University Hospital, Rikshospitalet and was defined as length of stay.

4.6 SUMMARY OF ARTICLES

4.6.1 *QUALITATIVE STUDY OF PATIENTS' AND NEXT OF KIN EXPERIENCES OF A NEW METHOD (PAPER 1)*

4.6.2 *INTERVIEW GUIDE*

Prior to the interviews with the patient and the next of kin, a semi-structured interview guide was prepared to ensure that relevant themes were discussed.[136, 137] The interview guide included open-ended questions on a predetermined set of topics. The themes included the experience of life satisfaction in the early rehabilitation period after treatment, possible changes in physical, psychological and social limitations, possible influence of family and friend networks and life perspectives.

4.6.3 *PILOT STUDY*

In order to validate the interview guide and ensure that the pre-determined issues were covered, four patients (two children and two adults) were recruited for a pilot study. The interview guide was then revised according to their feedback.

4.6.4 *INVITATION TO PARTICIPATE*

Patients or their relatives (when appropriate if the child was younger than18 years of age) received an informational letter before hospitalization. They also received information about the study and it aims, when they arrived at the hospital, both orally and in writing. The consent form was included with the information letters, the signed forms were collected at the hospital before treatment.

4.6.5 *IN-DEPTH INTERVIEWS*

All interviews were conducted and audiotaped between three and six months after the procedure and lasted for about an hour. The interviews were performed by the candidate and a supervisor. The candidate had clinical experience with patients, but neither had an existing health-care relationship with any of the participants. Open ended questions were used to get the patients to elaborate on their experience to get the richest information possible. The starting questions were ‘How are you? How is your life today?’ Other questions were ‘How did you experience your rehabilitation after your last treatment?’ and ‘How was the influence in everyday living?’ Interview questions were modified according to the patients’ age; in general, children and teenagers were asked more follow-up questions compared to adults.

In the interview with next of kind, the questions were open-ended and asked in a way that allowed informants to explore their experiences of how the rehabilitation situation influenced their child and their daily family life. At the end of the interview participants were asked if they had anything to add. All informants were given the opportunity to discuss their interview situation and to add other or related experiences.

4.6.6 *IN HOSPITAL COSTS (PAPER 2)*

In order to describe and compare cost savings, the impact of the in-hospital costs of the two treatment techniques was estimated. Patient-specific costs (direct costs) were estimated as the overhead costs (indirect costs), derived from the in hospital pre- and postoperative care.[135, 138, 139]

4.6.7 *PSYCHOSOCIAL FUNCTION AND CLINICAL OUTCOMES (PAPER 3)*

Clinical outcomes included in this paper were mortality, re-intervention or reoperation, arrhythmia, right ventricle to pulmonary artery pressure gradient, and the degree of pulmonary regurgitation.

Knowledge is limited regarding the relationship between patient-reported outcomes psychosocial function and clinical data in patients who have undergone percutaneous pulmonary valve implantation compared to open heart surgery.

4.7 ETHICAL CONSIDERATIONS

The Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects[139] and the Norwegian laws on health research[140] and data protection[141] were followed throughout this studies. The research protocol was approved by the Regional Medical Research Committee for South East Norway. The project was also approved by the Oslo University Hospital data protection officer. The participants gave their written informed consent, and were guaranteed anonymity and confidentiality and the right to withdraw from the study at any time. Two researchers were present at each interview in order to individualize and protect the children's and teenagers' integrity.

All collected data were coded and de-identified to protect the participants. The code book was stored in a locked storage unit to which only the head researcher had the key. The de-identified data were stored in the hospital's secure server for research to maintain data security.[139]

5 RESULTS

5.1 PATIENT EXPERIENCE (PAPER 1 AND 3)

The results from the semi-structured interviews (Paper 1) showed that all patients recognized the significance of regaining independence and taking control of daily life shortly after treatment, minimizing the social stigma associated with being chronically ill, and spending much time in hospital during their lifetime. Minimal pain and discomfort was communicated. Pain was described as tolerated less as growing older. There was a gender difference between how patients described improvements after treatment. Five of the boys, median age of 18 years, referred mainly to physical endurance, while three of the girls, median age of 17 years, emphasized the possibility of taking part in social activities as the main issue. All patients emphasized the importance of being able to fulfil everyday roles and being in physical control shortly after treatment. They also described positive aspects of future treatment. There was a general trend towards expressing renewed hope regarding new treatment options such as the percutaneous techniques. Surgery was associated with anxiety and insecurity.

The results from the semi-structured interviews (Paper 1) with the next of kin indicated that the relative minor nature of interference in daily family life experienced with the minimally invasive technique was appreciated. Minimizing pain and avoiding stays in the intensive care unit was of great importance to parents/close relatives. Parents referred to these benefits as ‘worth gold’ for the family. Normalization seemed to be a management strategy and the minimally invasive technique was experienced as important when it came to achieving normality.

In Paper 3, which compared quantitative self-reported data on psychosocial function between the two treatment methods, we found significant differences in the Achenbach System of Empirically Based Assessment scores favoring the percutaneous pulmonary valve implantation group, specifically in the Thought problems subscale at 1 year ($p=0.015$), Attention problems subscale at 3 months ($p=0.016$) and 1 year ($p=0.007$) after treatment. No such differences were found within the surgical group. No significant differences were found between groups.

In the percutaneous group, the New York Heart Association functional classification score was reduced from baseline 2 (1–4) to 1(1–2) after 3 months (p=0.021) (Paper 3). After 1 year the New York Heart Association functional classification score was still significant 1(1–3) (p=0.034). In the surgery group, the New York Heart Association functional classification score was significantly reduced from baseline 2 (1–3) to 3 months 1 (1–2) (p=0.004), and improvement was not significant at 1 year.

5.2 COSTS (PAPER 2)

In estimating patient-specific costs, we found that, the cost equipment, particularly of the stents and the valve itself was by far the main cost-driving factor in the percutaneous pulmonary valve implantation group, representing 96% of the direct costs. In the open surgery group the main costs derived from postoperative care and particular the stay in the intensive care unit. The difference in the cost of postoperative stay between the groups was statistically significant ($p \leq 0.001$) favoring the percutaneous pulmonary valve implantation group. The device-related costs in the open surgery group represented 13.5% of the direct costs.

5.3 CLINICAL OUTCOME (PAPER 3)

In comparing clinical outcomes between treatment methods, pulmonary regurgitation level was reduced significantly in the percutaneous group from baseline 3 (0–4) to 3 months 0 (0–2) ($p < 0.001$), at 1 year the improvement remained significant at 0 (0–2) (p=0.003). In the surgery group, the pulmonary regurgitation level was reduced significantly from baseline 4 (0–4) to 3 months 1 (0–2). One year after treatment the level remained significant at 1(0–2) (p=0.003) (Table 2).

No acute adverse events occurred in the percutaneous pulmonary vale implantation group. One patient in the open surgery group underwent a reoperation and needed a blood transfusion because of bleeding. Another patient required a pacemaker implantation after surgery because of a permanent

heart block. One patient in this group developed ventricular tachycardia before surgery and received an implantable cardioverter defibrillator after surgery.

5.4 ASSOCIATION BETWEEN CLINICAL- AND PSYCHOSOCIAL OUTCOMES

When adjusting for the right ventricle to pulmonary artery pressure gradient in both treatment groups at 3 months, a significant change in the Attention problems subscale ($p=0.038$) was noted in the percutaneous group. No significant findings were noted concerning The Achenbach System of Empirically Based Assessment scores in the open surgery group. There were no significant findings when comparing groups.

In figure 3, the findings of the studies are linked to Michael Porter's theory. A modified version is presented related to the research questions of the thesis.

Measured Outcome Hierarchy on the surgical and the percutaneous treatment approach. A modified version of Porter's Outcome Measures Hierchy.

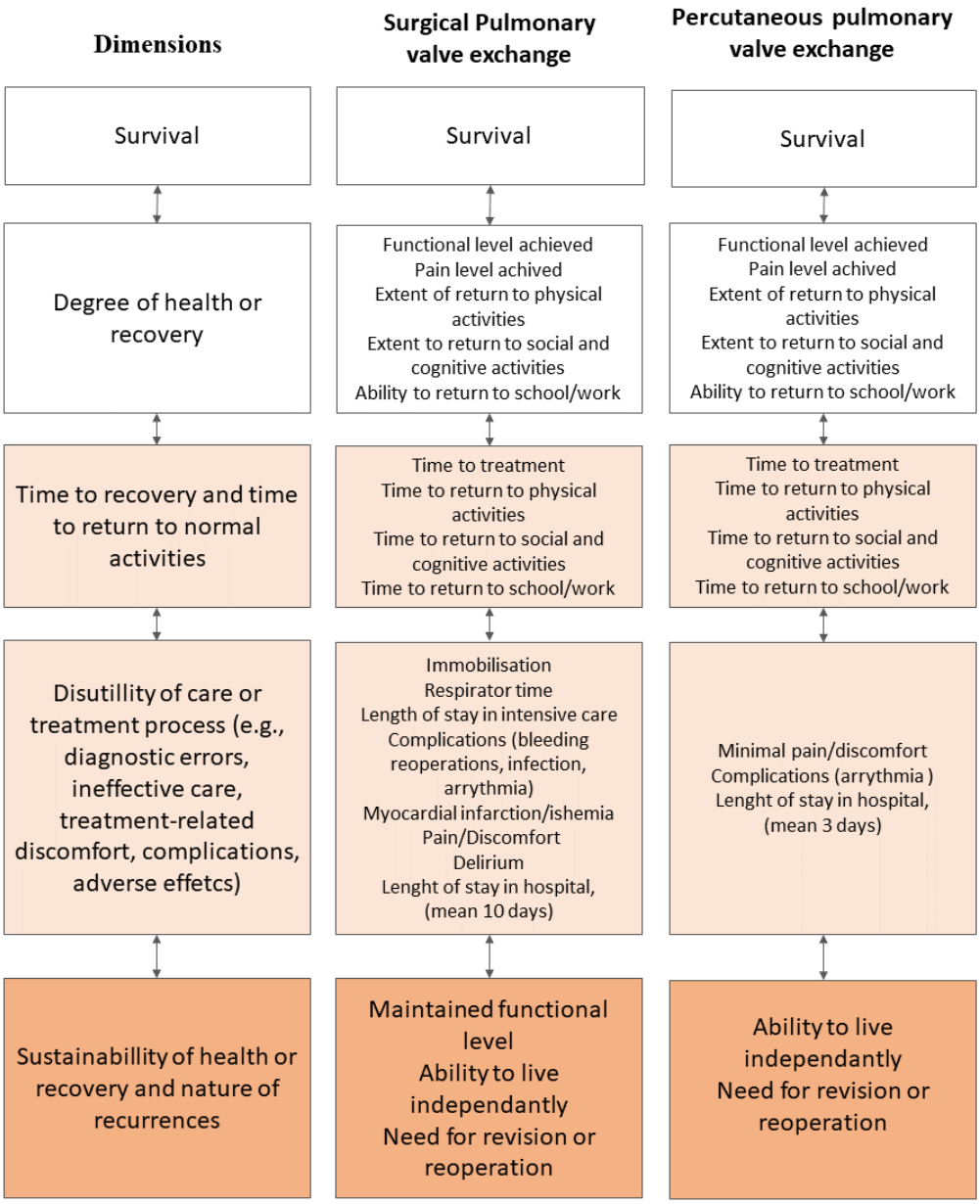

Figure 3.

6 DISCUSSION AND MAIN FINDINGS

6.1 PATIENT EXPERIENCES AND SELF-REPORTED OUTCOME

6.1.1 *NORMALITY, BEING IN CONTROL SHORTLY AFTER TREATMENT, FUTURE PERSPECTIVE*

The main results from patient's experiences and patient-reported outcomes presented a favorable view of the percutaneous technique. Normalization of everyday life was a main issue regarding patient experiences, including generating more strength in early rehabilitation and being able to recover their identity shortly after treatment. In line with existing research[142, 143] we found it was of main importance to patients to experience themselves as competent, normal people as quickly as possible after treatment. Minimizing inequality and social stigma was a big issue, especially for the younger patients.[142] Being reunited with peers and minimizing alienation were main issues, supporting the use of the percutaneous technique over surgery. Our results are consistent with Porter's view of the patient as the unique source of the most relevant information. The qualitative, individual in-depth interviews uncovered information about which quality indicators were most important to the patients regarding the new treatment option in regard to daily living and their outlook for the future. Shearer et al.,[144] who interviewed patients aged 13–17, stated that patients' life experiences were the same as those of their peers; the most substantial influence of congenital heart disease on their lives was seen in their use of various methods to feel the same as others, avoid alienation in friendships, and maintain normal interactions. Chong et al.,[145] referring to experiences from a review of qualitative studies in children, described patients were oscillating between sickness and health, 'caught in the middle between normality and abnormality'. Social activities and periods of feeling relatively well were opportunities to 'forget' the sick body.[146] Chong et al. have described experiences of the congenital heart disease as a part-time job; you have to put your life on hold … in the hospital, to do this job you don't want to do.[145]

Difficulties with academic achievement were described, including frustration of having to repeat a school grade and frustration with hospital appointments and surgical procedures that caused them to miss school and major academic assessments. As for adults, Claessens et al.[147] , who interviewed

young adult patients from 25 to 40, found that the life of adult congenital heart disease patients was a constant process of achieving normalization. Our findings were similar with normalization being described as the overarching goal.

Another main finding in our research was that patients' experienced of the percutaneous valve implantation as a positive advancement in terms of treatment options, they mentioned having renewed hope and positive feelings about the future, despite being aware of the fact that they would need of new valve exchanges in the years to come.

In contrast, patients described surgery as a major trauma, and repeated major surgery was associated with anxiety and insecurity. In a systematic review describing the experiences of children and adolescents with complex congenital heart disease, including 44 qualitative studies from 12 countries with 995 patients up to 21 years, Chong et al.[145] document that patients expressed anxieties about the treatment burden and disease progression of congenital heart disease, as well as concerns about their condition deteriorating and fear at the possibility of surgery. Patients described how they were traumatized by invasive procedures in general (e.g. cardiac catherization and open-heart surgery), having initially been hopeful about the definitive nature of medications and surgical procedures they were 'devastated' by unanticipated complications and treatment failure[145]. Research has described patients' feelings of life threat and fragility after surgical treatment.[148,149]

Among pediatric patients with complex congenital heart disease, there is a distinctive pattern of neurodevelopmental and behavioral impairment characterized by mild cognitive impairment, impaired social interaction, and impairments in core communication skills, including pragmatic language, as well as inattention, impulsive behavior, and impaired executive function.[119, 150, 151]

Concerns about behavioral and psychosocial issues have been raised regarding children and adolescents with two-ventricle as well as single-ventricle congenital heart disease.[120, 151-156] The prevalence of 'internalizing' problems (i.e. anxiety, depression, withdrawal, somatization) and

'externalizing' problems (i.e. attention, aggression) ranges from approximately 15 to 25% in the congenital heart disease according to parent reporting.[120, 122, 151, 154, 155]

New research has focused on the relationship between heart and brain health in patients with congenital heart disease across the lifespan, linking cardiovascular and neurovascular diseases as patients age.[4, 157] Preoperative factors such as gene mutations and altered cerebral perfusion in utero have been associated with abnormalities of brain structure and immaturity in neonates with congenital heart disease. [114] Patient characteristics as well as cumulative postoperative morbidity (sequelae of the heart disease itself) and medical, interventional and/or surgical management (perioperative injury, emboli/stroke, factors associated with prolonged postoperative phase), are variables increasingly addressed in new research.[4, 158] The subtle effects of multiple factors may become apparent in psychosocial function years after exposure and are probably difficult to detect and document during early childhood.[159]

A significant finding was that The Achenbach System of Empirically Based Assessment questionnaire indicated a reduction in thought and attention problems in patients treated percutaneously. Although most children with complex congenital heart disease have intelligence within the normal range, school-age children with congenital heart disease have a higher incidence of problems with visual-spatial or visual motor integration, executive functioning, academic attention, and hyperactivity, even after successful cardiac surgical correction or palliation.[160, 161, 162-164] In addition, Uzark et al. found low emotional, social, and school functioning in 23% of studied children with congenital heart disease from 8 to 12 years of age. [121] Sanz et al.[165] reported that school-age children with congenital heart disease have an increased prevalence of difficulties of executive function, especially problems with working memory and flexibility, that are underserved by the school system, suggesting that many children who qualify for services and support in school settings are not receiving them. Children with congenital heart disease are currently more likely to receive services if they have problems related to impulsivity; impulsive children can be disruptive in a classroom setting.[165] Executive functioning has been identified as a specific area of cognitive impairment in congenital heart disease that is critical to social development and academic learning.[122, 166-168] Executive functioning describes a set of behaviors

responsible for purposeful, goal-directed activity. It is used to organize and direct cognitive activity, emotional responses, and overt behavior. Developmentally, these skills emerge during the toddler/preschool years and develop substantially through childhood, adolescence, and early adulthood as environmental demands increase. Given this trajectory, difficulties in executive functioning become more apparent over time. Children with executive dysfunction are often overlooked by general practitioners and schools, as intellectual development can be unrelated to executive skills problems, or problems with executive skills may be masked by stronger intellectual skills in some testing.[169, 170] Nevertheless, executive dysfunction is strongly related to a child's development, learning, behavior, and academic success. It has been suggested that executive functioning is a better predictor of classroom performance and academic achievement than intellectual or early academic skills.[171, 172] If the new percutaneous treatment method can have a positive influence and reduce some of the burden created by these challenges as our research suggests, it is of great importance.

Eearly identification of neurodevelopmental delays gives children and adolescents the best chance to reach their full potential. According to Marino et al.,[173] no practice guidelines for the evaluation and management of these impairment currently exists despite the well-documented presence of neurodevelopmental delays in the congenital heart disease population.[119, 174-176] Because the developmental surveillance and screening regimen currently used during routine pediatric care is not designed to prioritize children at known risk for neurodevelopmental delays, congenital heart disease patients may be not immediately be referred for evaluation and early intervention. An integrated interdisciplinary care plan should be provided for assistance and support at different stages and developmental milestones in the patient's life cycle based on knowledge provided both from the healthcare provider and the patient experiencing the treatment. In a lifespan perspective the potential benefits of early intervention and prevention need to be identified and differentiated, and, it is necessary to translate and differentiate modified risk factors experienced by these patients. [4]

As one of initiators of value-based care within health services, Porter[11] states that for any medical condition, there is a set of multidimensional outcomes that jointly constitute patient benefit. For patients with congenital heart disease, he supports regular screening and early identification of

neurodevelopmental delays as a quality preventive initiative that will likely reduce the degree of sequelae provide a higher quality for the individual patient over a full life cycle of care. A focus on neurodevelopmental delays will in the long run lead to better health at a lower cost because of the implementation of preventive initiatives. Porter[11] promotes shared decision-making, with patients defining what is most important in their health care plan, increasing clinician responsiveness to patient priorities and needs.

Patient engagement is a key strategy to achieve the aims of healthcare, namely optimal experience, outcomes, and efficiency.[12, 177] In our pilot study, we invited patients to evaluate our interview guide to guide us towards the exact issues/themes in need of exploration.

Further research is needed to discover links between specific aspects of neurodevelopmental outcome and to identify developmental deficits that may be improved through intervention. As for new treatment options such as the percutaneous pulmonary valve implantation, our findings in favor of the mini-invasive technique will hopefully encourage regular screening.

The prevalence of comorbid psychiatric disorders is three to four 4 times higher among adults with neurocognitive impairment than in the general population. In a cohort of 280 patients with congenital heart disease evaluated at a mean age of 32 years, 50% met diagnostic criteria for at least one mood or anxiety disorder.[178] Therefore, careful review of depression or anxiety symptoms and their potential overlap with symptoms of medical illness or medication side effects must be part of the clinical evaluation of this patient group. However, social adjustment and patient-perceived health status are more predictive of depression and anxiety than medical variables.[179] Difficulties in these areas are related to factors that include impaired peer relationships, family overprotection, and delayed progression into independent adulthood.[180, 181] Many adults with congenital heart disease struggle to assume greater independence and control over their health care and lifestyle and can have gaps in their knowledge about their disease, treatment, and prevention of complications.[182]

Attempts to achieve patient-centered value-based health services will create increased demands on the health care system in the future, including on patients and their informal caregivers in the development and establishment of outcome measures. Outcome measures must be standardized to implement evaluation of specific conditions at an aggregated level and sensitive enough to capture each patient's individual needs and goals.[183] Porter[11]suggests national surveillance to 'ensure universal, consistent and fair measurement'. These are challenging tasks for national healthcare departments with fragmented healthcare systems, with patients with multi-setting, lifelong care needs. Thus, collaboration beyond organizational boundaries is needed to establish healthcare systems with patient trajectories. Besides national registers that collect data on processes and outcomes, evaluation in value-based healthcare should include standardized patient-reported outcome measures.[183]

6.2 NEXT-OF-KIN OUTCOMES

6.2.1 *NORMALISATION- A PREVENTIVE HEALTH STRATEGY*

The patients' next of kin, all expressed a deep wish for normalization of family life, this was seen as part of a preventive health strategy involving their child/close relative, their family, and society. They reported that the new percutaneous treatment strategy simplified their lives and reduced their use of sick days thereby reducing or avoiding negative effects of treatment, such as a social stigma, for all family members. Family stress has been defined as 'a systematic response of the family as a unit, often related to loss or anticipated loss and manifesting as change in family function; 'such as family disorganization, family conflict and role dysfunction, all of which can be magnified by ambiguity and uncertainty that accompanies critical and emergent health changes.'[184]

Families of critically ill children experience significant disruption of their 'normal' lives – both during hospitalization and in the weeks, months and years that follow.[185] A qualitative study exploring parents' experiences during the transition from a pediatric intensive care unit to a surgical ward following their child's surgery documented critical moments for parents of children with congenital

heart disease describing repeated hospitalizations as a 'rollercoaster itself.'[186] The moment when parents have their child hospitalized for heart surgery is critical. All of the parents in our studies had had their child go through open-heart surgery before and were well aware of the stress and anxiety related to this situation. Therefore, the hope and gratitude several of the parents expressed regarding a less invasive treatment method were related to the discomfort and time in hospital mainly for the child, but also for siblings and the family as a unit.

6.3 PATIENT-REPORTED OUTCOMES

6.3.1 *THE NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION OF HEART FAILURE*

We observed an improvement in the New York Heart Association classification-scores in all patients in both groups, but the improvement was sustained for a longer time in the percutaneous pulmonary valve implantation group. Adjustment to the stress of chronic illness is a complicated, multifactorial process and involves a highly subjective, personal interpretation of the impact of disease on one's life, which makes the self-reported perspective of the individual adolescent uniquely important. [121, 187] Successful adjustment is reflected in behaviors and perceptions that are age-appropriate, normative, healthy, and follow a trajectory toward positive, autonomous adult functioning.[188]

Jackson et al. [189] found that lesion severity did not significantly contribute to explaining the variability of physical or emotional quality of life, demonstrating the New York Heart classification score as the only variable that explained a unique proportion of variance in emotional quality of life. As Porter argues, the individual perceptions of disease burden can only be experienced by patients themselves. These perceptions should be closely monitored as it is demonstrated to affect morbidity and mortality in long-term follow-up of patients.

6.4 CLINICAL OUTCOME

Both treatment methods led to significant clinical improvement. Complications such as re-intervention, bleeding, and arrhythmia were observed in the surgery group only.

The percutaneous technique has become an alternative to surgical intervention, and we can thus expect that new devices will be added to the percutaneous pulmonary valve implantation armamentarium, making the percutaneous approach a feasible alternative to open-heart surgery for the majority of patients with right ventricle outlet dysfunction in the near future. [190]

Concerning incidence and outcome of infective endocarditis following the percutaneous versus surgical pulmonary valve replacement, no higher risk of endocarditis were found within the percutaneous group referred in a study of Lluri et al.[191] Researchers in this study compared the outcome of infective endocarditis in 208 patients undergoing percutaneous pulmonary valve replacement versus 134 patients treated by surgery. Patients in the percutaneous pulmonary valve implantation group were more likely to have a prior history of infective endocarditis in the right ventricle to pulmonary artery conduit, the patients at highest risk were those with stenotic right ventricle to pulmonary artery conduits who were treated with pulmonary valve implantation.[191] Kheiwa et al.[190] claim that the number of patients requiring surgical pulmonary valve replacement will likely diminish and that percutaneous valve replacement will become the first line in management over the next decade in patients requiring an exchange of a dysfunctional pulmonary valve.

Electrical remodeling after percutaneous pulmonary valve implantation has been reported with a significant reduction in QRS > 180 $msec^2$ and might reduce the incidence of sudden death in at-risk patients. More than 10.000 percutaneous pulmonary valve procedures have now been performed worldwide.[192] Still, there will be a subset of patients for whom surgical pulmonary valve replacement will be the only viable treatment option.[190]

6.5 PULMONARY STENOSIS AND PULMONARY REGURGITATION

A significant correlation between heart function, degree of pulmonary stenosis, and psychosocial outcomes with respect to the Anxiety/Depression subscale was observed in favor for the percutaneous treatment at three months. This finding may indicate that the reduction in the right ventricle to pulmonary artery gradient pressure resulted in reductions in anxiety and depression after treatment in this group.

This was not a randomized study, and the groups differed with respect to type of pulmonary valve lesion. Patients with predominantly valve stenosis were offered percutaneous pulmonary valve implantation, while most patients in the surgery group had pulmonary regurgitation caused by mixed underlying diseases. Therefore, we cannot rule out the possibility that differences in underlying disease physiology may have impacted on the psychosocial outcomes. Concerning timing and difference in indication between pulmonary stenosis and pulmonary regurgitation exchanging the pulmonary valve, Hascoet et al. [75] stated in their review that the promising results of percutaneous pulmonary valve implantation may allow earlier intervention in the evolving process of conduit degeneration to reverse the effect of pressure and/or volume overload on the right ventricle. However, the long-term outcome of repeated valve-in-valve procedures with this treatment option is unknown.

A minority of patients have residual stenosis as the dominant lesion in patients in need of a valve exchange. In the case of Tetralogy of Fallot with pulmonary atresia or those with coronary anomalies that cross the right ventricle outflow tract, right ventricle to pulmonary artery conduits can deteriorate over time resulting in conduit stenosis, regurgitation or both.[30]

Historically, there was little concern about the development of pulmonary regurgitation. Many patients underwent repair with generous transannular patches with or without pulmonary valvectomy.[87] Pulmonary regurgitation was considered to be benign because right ventricular volume overload can be well tolerated for a long time. Today we know that degeneration of biological material of bioprostheses and valved conduits results in progressive right ventricle outlet tract dysfunction,

including pulmonary stenosis and pulmonary regurgitation requiring valve exchanges throughout the lifetime.[29] With individual variations, research describes that after total correction with a patch, significant pulmonary regurgitation was observed in 48% of patients directly after the operation and in 85% of patients two years after surgery. In patients who received a valved homograft, significant right ventricle outlet dysfunction (pulmonary regurgitation and/or pulmonary stenosis) was observed in 50-55% of patients in the 10 years after the first correction and 5-6 years after the second procedure.[193, 194]

Further, Hascoet et al. maintained that in case of right ventricle obstruction, there is growing evidence for the efficiency of the percutaneous option on clinical outcome, as stated in the European Society of Cardiology guidelines.[7, 30, 195, 196] Early intervention is necessary; however, stenting alone may be efficient and may delay the need for percutaneous pulmonary valve option.[197] Pulmonary regurgitation is often well tolerated for a long time, the impact of early percutaneous pulmonary valve implantation in these cases is more controversial.[7, 195] It is the degree of right ventricle dilation rather than the severity of the pulmonary regurgitation that should prompt the percutaneous pulmonary valve implantation.[198] Long-term follow-up will help determine when percutaneous pulmonary valve implantation is indication compared to surgery and global management of this patient population.

The long-term haemodynamic consequences of pressure overload to the right ventricle include ventricular hypertrophy and diminished compliance which can lead to increased right ventricle end-diastolic and right atrial pressures.[87] Complications and late risk factors for poor outcome (ventricle tachycardia and sudden death) after the exchange of a dysfunctional pulmonary valve may occur. Due to the recognition of unexpected late outcomes associated with right ventricle dilatation and dysfunction from chronically severe pulmonary regurgitation, attention has turned to eliminating pulmonary regurgitation as the nexus of late complications[199] and optimal timing for treatment. There is no debate surrounding the indication of pulmonary valve replacement for significant pulmonary regurgitation in symptomatic Tetralogy of Fallot patients; however there is continued controversy in asymptomatic patients.[87] Branch pulmonary stenosis increases afterload to the right ventricle and is associated with worsening pulmonary regurgitation.[88, 200]

In a retrospective study conducted from 2007 to 2013 aiming to characterize long-term changes in ventricular change and function in patients with pulmonary stenosis compared to patients with Tetralogy of Fallot with similar degrees of pulmonary regurgitation Joynt et al.[200] concluded that surgical repair had similar effects on right ventricle dilatation and diastolic function compared to patients with Tetralogy of Fallot, but differential effects on ventricular systolic function largely related to differences in the outflow tract. They suggest further study to clarify whether the criteria for pulmonary replacement in patients with pulmonary stenosis should differ from those with Tetralogy of Fallot, who exhibit different patterns of scarring and ventricular remodelling.

6.6 COSTS

In a long-term perspective based on patient experiences and patient reported outcomes, the percutaneous pulmonary valve was the treatment option with the least negative impact, although it was the most expensive at the time we did our work. According to Porter's visions of a value-based health care system, the lifecycle perspective of the patients is the driving factor, and quality indicators are defined according to patient preferences. He argues that patients' perspectives constitute necessary knowledge for reporting the full set of patient health outcomes. According to him, this knowledge will contribute to chronic patient groups' receiving better quality care, and this information can help prevent unnecessary discomfort, reinterventions, and complications. In this perspective, the value of this knowledge will therefore be cost saving for the society in the long run. Because quality will be reflected in preventive actions based on regular screening of patient-reported outcomes, it will be differentiated and initiatives can therefore be implemented in patients at most risk.

One weakness of our study is weakness our study that we did not publish recorded costs after discharge from the hospital. In order to get a full picture of the cost safety of the percutaneous technique, costs related to the first year after discharge should also have been monitored. These data have been collected, but have not yet been analyzed.

As percutaneous techniques become more frequent and more companies enter the market, a reduction in the device cost may be expected, thus leading to a more favorable in-hospital cost outcome.

6.7 METHODOLOGICAL CONSIDERATIONS

In Paper I, both children and adults participated in in-depth interviews. Responses from the younger children were less detailed than those from the elder group and contained fewer citations. Therefore it is possible we had less information from this age group and was not able to capture the complexity of the children's experiences. Further, the study was framed according to the concepts of Western medicine and values. It is possible patients' experiences would differ in a different cultural or geographical setting.

In Paper II, comparing the in-hospital costs of the percutaneous versus the surgical treatment options, we observed our data to be skewed, as it often is in these types of studies. One possible approach when data are not normally distributed is to transform the data to a logarithmic scale. We chose to use bootstrapping along with parametric methods for both data sets to allow comparison of arithmetic means when analyzing costs and length of stay hours. Bootstrapping is a procedure to estimate population distribution using information based on a number of resamples from the original sample. The bootstrap method creates a large number of datasets and computes the statistics on each of them. Within cost studies, mean values are important in order to be able to compare costs between groups.

In Paper III, a mixed-effect linear regression model was used to fit multiple data points per patient. The outcome variables were the psychosocial function score, the New York Heart Association functional classification score, cardiac function, and length of stay. In the mixed model, patient identification was a random variable while time and group with interaction time × group were treated as fixed variables. The p-values were not adjusted for multiple outcomes because of small sample sizes. Our findings should be interpreted cautiously. The most important limitation is the small sample size and missing data, which could have increased the probability of type II errors. Our study

population, which mainly comprised teenagers, probably accounts for missing data. This vulnerable patient population is often asked to participate in ongoing research, which probably influences their willingness to communicate or share experiences. Our population also exhibited large age differences. The instrument used to assess psychosocial function included only children older than 11 years, resulting in a response rate of 63% for the ASEBA scores.

The prospective data mainly used with follow-up data is strength of this thesis. Self-reporting contributes to a more comprehensive assessment, which represents an advantage over the established objective measures of illness severity. We used a well-established and validated instrument to measure psychosocial function and self-reported data. Increasingly more studies are showing that the New York Heart Association functional classification score is a complementary classification to the level of disease severity because it involves the self-reporting of symptoms by the patient.[201] Our findings should be interpreted cautiously.

In order to get a full picture of the cost safety of the percutaneous technique, costs related to the first year after discharge should also have been monitored.

6.7.1 *CRITERIA FOR EVALUATING INTERFERENCE, GENERALIZABILITY AND TRANSFERABILITY*

Small populations in both groups were presented a challenge, and these small sample sizes influenced the generalizability in the quantitative part our thesis. The results are not widely generalizable as the data reflect the practice at a single treatment center, and the study was not randomized and had a slightly different population in the intervention and the control group. We collected data over a three-years period after which we to stopped inclusion even though we wanted to include more patients in both groups. This decision was based on the opportunity to publish our findings within a reasonable time frame.

The transition from adolescence to adulthood was a major challenge. Adolescence is associated with struggles due to the changes in the balance of independence and dependence on others (peers, parents, siblings).[202] The natural developmental stages of adolescence are associated with ambivalent feelings with big differences in coping between individuals. These challenges are difficult to measure and might have influenced our results.

This is a short-term follow-up study, and there may be a bias towards a positive result due to gratefulness of patients and their relatives.

6.7.2 *SELECTION FOR VARABLES IN REGRESSION ANALYSIS*

A linear regression analysis was performed to evaluate the effect of an independent variable (explanatory) to a dependent variable (selected). There might be confounding variables which could affect the outcome variable, and which need to be included as independent variables in the regression model. The number of independent variables was not indefinite, but we needed to restrict the number in our model because of limited sample sizes. Additionally, confounding variables might have been overlooked in our model.

7 CONCLUSION

In a life-span perspective, neurodevelopmental sequelae in children and adolescents with congenital heart disease evolve during adulthood[4] and preventive initiatives are important in order to maximize health in the long term.

In this thesis we have described the important psychological impact of repeated heart surgery on patients and their families, including the burden of surgery itself and having to live with the knowledge that surgery must inevitably be repeated within a few years. We studied the effect of a new and less invasive treatment and found a considerable benefit in patient experiences and psychosocial function. Many would argue that the experiences of patients and next of kin and patient-reported outcomes are the only real measures for patients living with chronic disease. We have further studied the economic consequences and the haemodynamic results of the new treatment. Haemodynamically the new treatment is in line with traditional surgery, however we found fewer complications with the new, less invasive treatment option. When comparing the total in-hospital cost of the two treatment options, we found the price of the interventional valve to be much higher than that of the surgical valve. The most important cost associated with surgery was the stay in the intensive care unit, which was significantly reduced with the mini invasive technique. With only a slight reduction in device cost, the new treatment will become cost effective for society, as this technique holds the potential to reduce the postoperative costs compared to surgery.

Since percutaneous pulmonary valve implantation is a fairly new treatment in patients with pulmonary valve dysfunction, there is a lack of long-term data evaluating the differences in psychosocial function between patients treated with this new technique and those treated with open heart surgery. According to our findings, we may assume that being treated with this mini-invasive method may indicate a less negative impact on neurodevelopmental sequelae treated percutaneously, and in the long run might have a preventive impact on the patients' well-being throughout the life cycle.

8 FUTURE RESEARCH

Surveillance, screening, evaluation, and reevaluation of developmental deficits and developmental delays in the pediatric congenital heart disease population are essential steps to ensuring appropriate interventions to maximize overall development and quality of life for these children. As the population of paediatric and adult patients with congenital heart disease increases, risk stratification may be beneficial in efficiently promoting early recognition of neurodevelopmental morbidities and implementing supportive therapies. Heightened and ongoing surveillance and screening are important for all paediatric patients with congenital heart disease. For those classified as being at high risk for developmental deficits, initial and periodic re-evaluation will allow care providers to monitor patient development and potential developmental deficits.

Further research on the efficacy of interventions and refinement of the criteria for high risk are needed to optimize preventive and interventional strategies for developmental deficits in children with congenital heart disease.[173] As life expectancy continues to increase, the window of opportunity for repeated injury continues to lengthen, and a significant proportion of patients with complex congenital heart disease may thus need specialized services into adulthood and old age.

9 CLINICAL IMPLICATIONS

Involve the patients in the full cycle of care as a unique resource of information is essential in to maximize lifelong functioning. To include patient-reported outcome measures as a routine in national health registries is necessary. Acknowledge and support the patients' family expertise and take this knowledge into account is important. Collaboration is needed between units when the child is transferred from the pediatric unit to adult care. Patient and close family members needs education, engagement, follow up and help to increase self-care skills to prevent of unnecessary complications, readmissions and discomfort. In a transition process, parents need to be supported during the shift of roles. From having the main responsibility for their adolescent' health, the parents become a facilitator

in the process. Parents can be key-facilitators of their child's health condition, supporting them to become experts of their own condition and care. Important factors are being involved in the transition planning from the very beginning to facilitate their gradual handling over the responsibility to the adolescent.

Care delivered by a dedicated, multidisciplinary team who measures outcomes, costs and processes for each patient using a common measurement platform is important. The health care providers should prepare and implement different teaching approaches to both the patient and his family in introducing new methods and treatment. The follow-up must be on a regular basis, concrete information is important. Nontraditional methods for providing information and support might be group meetings, web-based techniques and peer support.

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Perceived health after percutaneous pulmonary valve implantation: in-depth interviews of patients and next-of-kin

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ABSTRACT

Objective: Percutaneous pulmonary valve implantation is an alternative to open heart surgery in selected patients with pulmonary outflow tract disorder. The technique may reduce the number of open-chest surgeries in these patients. This study was conducted to understand how the patients and their next-of-kin experienced this new treatment option.

Design: Qualitative explorative design with individual in-depth interviews.

Setting: Oslo University Hospital, the only cardiac centre in Norway offering advanced surgical and interventional treatment to patient with congenital heart defects, serving the whole Norwegian population.

Participants: During a 2-year period a total of 10 patients, median age 17 (7–30) and 18 next-of-kin were consecutively selected for individual in-depth interviews 3–6 months after the pulmonary valve implantation. The verbatim transcripts were analysed using a phenomenological methodology.

Results: Patients emphasised the importance of regaining independence and taking control of daily life shortly after the new interventional treatment. Renewed hope towards treatment options was described as 'a light in the tunnel'. Next-of-kin emphasised the importance both for the patient and their family of resuming normal life quickly after the procedure. The physical burden was experienced as minor after the minimally invasive intervention, compared to their previous experience with surgical procedures.

Main outcome measure: The importance of maintaining normality in everyday life for a good family function.

Conclusions: The repeated surgeries during infancy and adolescence of patients with congenital heart disease represent a heavy burden both for the patient and their family. All families especially emphasised the importance of resuming normal life quickly after each procedure. The novel technique of pulmonary valve implantation is thus a favourable approach because of minor interference in daily life.

Strengths and limitations of this study

- Data were collected through in-depth interviews and it thereby reflects actual experiences.
- The qualitative approach gave a deeper and unique understanding of the patients and their relatives' experiences in early rehabilitation phase after the percutaneous pulmonary intervention.
- The study was framed in the concepts of Western medicine and values. It is possible that the experiences would differ in a different cultural or geographical setting.
- There were few citations from the younger children and therefore a possible lack of information within this group. The broad age differences were challenging in gaining in-depth knowledge within each group.
- This is a short-term follow-up study, and there may be a bias towards positive results due to gratefulness of patients and relatives.

INTRODUCTION

Advances in surgical and interventional techniques and medical care create new life expectations in patients with congenital heart disease. To date, approximately 90% survive to adulthood and constitute a relatively new and growing patient population,[1] increasing with an estimate of 5% per year.[2] Approximately 8 of 1000 children are born with congenital heart disease, of these 10% have a pulmonary valve abnormality.[3] These patients typically undergo palliative or corrective surgery early in life.[4] Living longer, they are in need of an increasing number of surgical interventions when they outgrow the size of a replaced conduit or when the pulmonary valve becomes stenotic or insufficient.[5] Recurrent changes in their health,[6] initiate new treatment demands. A mean length of a hospital stay after a change of the pulmonary valve was 5.7 days with a mean stay of 2.8 in the intensive care unit.[7] Patients treated with percutaneous pulmonary valve implantation went home 1 day after treatment.[7] In a limited number of studies investigating experiences in patients with congenital heart disease using qualitative methods, normalisation is documented to be a

central issue.[6 8–10] In a study of 11 patients treated for single ventricle physiology, the patients emphasised the limitations in their physical and social activities as a main problem. To compensate for the lack of physical performance they were adapting to alternative roles during physical activity and pursuing academic interests in order to obtain social recognition.[9] This finding was confirmed in a Norwegian study of 11 children with congenital heart disease,[8] referring to qualitative data. Authors concluded that children used different strategies to participate and to fulfil their first priority which is to be together with other children.[8] Repeated major surgeries may add to this challenge.[6] Percutaneous pulmonary valve implantation is a minimally invasive technique that rapidly has become an alternative option to surgery to restore pulmonary valve function.[4] In order to evaluate and understand the importance of this minimally invasive technique, we conducted qualitative interviews of patients and their next-of-kin. The aim was to investigate whether this treatment technique influenced individual perceived health and reduced some of the burden in their daily lives in the early rehabilitation phase after treatment.

METHODS

Design

A qualitative, explorative design was chosen to generate a deeper understanding of the experienced outcome for each individual. Data was collected through in-depth interviews with the patients and their next-of-kin.

The institution

Norway has a national healthcare system with a health assurance offering the same treatment to each individual, independent of income. The study was conducted at Oslo University Hospital, the only cardiac centre in Norway offering advanced surgical and interventional treatment to patients with congenital heart defects, serving the whole Norwegian population.

Participants

During a 2-year period 10 patients: 3 girls of median age 17 (10–30) and 7 boys of median age 18 (7–28) met the inclusion criteria and were treated with percutaneous pulmonary valve implantation. Patients were consecutively included in the study, and all informants spoke and understood Norwegian. The patients and their next-of-kin were included with informed consent. Inclusion was based on internationally accepted treatment criteria within this medical field, and a consensus set by the local team responsible for the patients. The selection criteria were also based on guidelines delineated by the producer of the device. The patients had previously in median undergone 3 (2–5) open heart surgeries.

Interviews

The study was based on in-depth, audio-taped interviews. To record experiences related to the intervention and the rehabilitation situation, all patients and their next-of-kin were interviewed between 3 and 6 months after the procedure. All interviews took place in a quiet room in the hospital, and lasted for approximately 1 h. We think that the number of participants was adequate for the research method because the in-depth interviews provided us with a large amount of information sufficient to detect patterns. The interview guide contained the following themes: (1) life satisfaction in the early rehabilitation period; (2) experiences of physical, psychological and social limitations; (3) family and friend network and (4) life perspectives. A semistructured interview guide guaranteed that predetermined issues were covered during the interview. In the interview we used open-ended questions. We started the interview with: "How are you? How did you experience your rehabilitation after your last treatment? How was the influence in every day living? These are examples of questions. Modifying the interview according to the patient's age was done mainly by following up of their answers. The children and teenagers needed more following up questions compared to the grown-ups in general. The main concern then was to try to get the patient to elaborate the experience in order to get as rich information as possible.

Concerning the interview of the next-of-kin, the questions were open and questioned in a way that explored her/his experiences on how the rehabilitation situation influenced their child, and their family life in daily living.

At the end of the interview the participants were asked if they had anything to add. All informants were given the opportunity to discuss their interview situation and to add other or related experiences.

Data analysis

The interviews were first transcribed verbatim and then analysed and reported separately. The process of analysis was based on a phenomenological approach according to a previously described methodology.[11] In brief, first, the whole interview was read to get a general impression. Second, the text was divided into units of meaning, in order to grasp the most probable interpretation. Third, the person's answer was read with the aim to be without prejudice and the theme that dominated a meaning unit was stated as simple as possible. Fourth, 'expressive units' related to the aim of the study were sought. These units were then condensed and coded. In the fifth step, the essential themes of the entire interview were tied together in a descriptive statement. The method thus involved condensation of the expressed meaning into a more essential formulation of the experience following the percutaneous pulmonary valve implantation.[11]

Data quality

To assure data quality, two researchers were present at each interview. One of the researchers led the interview and the other added supplementary questions when

necessary. Data analysis was performed mainly by two researchers to obtain the patients and next-of-kin's opinions. All researches were participating to strengthen accurate reflection, highlight differences and reach final consensus.

Ethical considerations

All participants were provided with oral and written information about the aim and the design of the study. One of the patients was mentally retarded and did not want to speak with the researcher. In this case we chose to include data from next-of-kin. Another patient had Di-George syndrome with some degree of retardation. He was interviewed with a modified interview guide according to an evaluation of his ability to answer.

RESULTS

Demographic and medical data are presented in table 1. The informants' experiences are grouped in two parts: patients' experiences (figure 1) and experiences of next-of-kin (figure 2).

Patients' experiences

The main finding evolving throughout the interviews was the significance of regaining independence and taking control of daily life shortly after the new interventional treatment. Second, the ability to fulfil everyday roles and to be in physical control shortly after treatment was emphasised as important by all patients. Third, renewed hope towards treatment and treatment options contributed to positive feelings towards future life.

Table 1 Demographic and medical data of 10 patients treated with percutaneous catheter-based implantation of artificial pulmonary valve

Gender	
Men	7
Women	3
Original diagnoses	
Tetralogy of Fallot, all variants*	6
Truncus arteriosus communis	3
Aorta stenosis, Ross-operated†	1
Right ventricle outlet	
Valve conduit	6
Homograft	3
Biological valve (Perimount)	1
	Median (range of variation)
Age (years)	17 (7–30)
Weight (kg)	66 (28–98)
Height (cm)	172 (132–177)

*One patient with pulmonary atresia and ventricular septal defect; known as an extreme variant of tetralogy of Fallot.
†By Ross-surgery the native pulmonary valve is moved into an aortic position; by this procedure an artificial outlet is implanted from right ventricle.

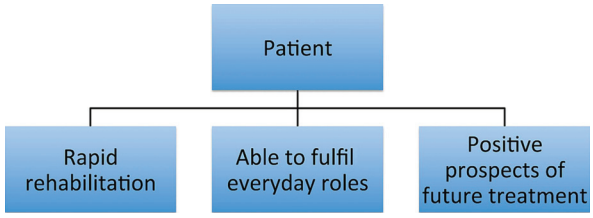

Figure 1 Experiences of patients. Main categories emerging from the interviews.

Rapid rehabilitation

The easier pathway during the two first days after treatment was highly regarded and addressed in different ways: "The rehabilitation period was different this time, I walked over to visit a friend the day after the percutaneous implantation and overall, my social life was hardly affected at all". The experience of no or minimal pain or discomfort in the early postoperative period was communicated and stated as an important issue by three patients: "Everything was normalized faster after this intervention. When they cut me open, it was like having all my ribs fractured. Now there was hardly pain at all". Another statement was: "I feel I tolerate less and less pain as time passes, so it is lovely to avoid surgery. I got my daily life back much faster this time".

Being able to fulfil everyday roles

The experience of regaining independence and taking control of life shortly after the intervention was praised. This meant resuming the ability to fulfil roles related to one's own expectations, for the children to 'hang out with friends' doing ordinary things. One of the girls expressed her view on her physical endurance and her thoughts about her role among peers: "No matter, I am always the one who is behind the others physically in class. But there is something I can do, I can help the others with schoolwork etc." Her main concern seemed to be her ability to join her peers and to be included socially by participating. One adult female patient described the psychological and emotional strain relief following this intervention experiencing the ability to attend socially and take care of her children shortly after

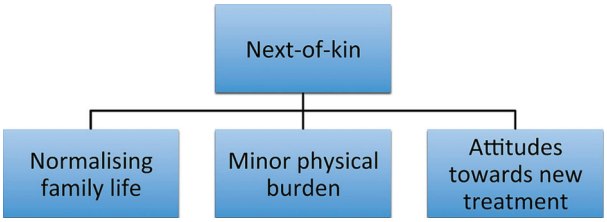

Figure 2 Experiences of next-of-kin. Main categories emerging from the interviews.

being discharged: "I started driving again much earlier this time, you are not supposed to do that when you have had an open-chest operation. Nor can you can lift heavy things for quite some time, as an example I was not able to lift up my own children when I wanted".

Five of the boys (7), median age 18 years (7–28), in the study referred mainly to physical endurance when asked about improvements after the percutaneous intervention. This was unlike girls (3), median age 17 years (10–30), who emphasised the possibility of taking part socially as the main issue. Adults (2) commented on how fewer symptoms gave psychosocial benefits shortly after treatment. There was a gender difference on how patients described improvements after treatment and how these improvements influenced their daily lives.

Prospects of future treatment

Surgery was often referred to as a major trauma involving tissue matters. The experiences and future prospects of repeated major surgeries were associated with anxiety and insecurity. Renewed hope towards treatment options was stated "I think technology evolves in many areas and I don't think I have to be afraid." Another statement was: "It doesn't matter if they have to intervene once more, as long as they fix it I am happy." One of the adult patients said: "Not any special expectations, usually things work out. Things often take time—I have been in the system for some time and that is how it is in a way."

Experiences of close relatives

The main finding was the significance of normalisation. The normalisation of the psychological performance of their child led to a normalisation of their family life. Second, the minor physical burden with little pain was highlighted. Third, the positive attitude towards this new treatment and renewed hope towards treatment options in the future, were the main themes evolving throughout the interviews.

Normalising family life

All next-of-kin strongly expressed the importance of normalising everyday life. All parents expressed that they laid down a lot of resources both economically and timewise in order to normalise their childrens' lives and thereby trying to create a normal family situation. This seemed to be a part of a preventative health strategy concerning both their family and society: "It is obvious that if you miss out from school 3–4 weeks after treatment, you loose a lot of opportunities, both in school, among friends and in different ways. After surgery in 2006 our daughter was sort of switched out of her social life." Another statement was: "For the family's sake, the avoidance of spending a lot of time in hospital was of great importance. The organizing at home with siblings was easier after the percutaneous implantation." Nine (50%) of the parents stated in different ways that they would recommend the percutaneous option as it simplifies everyday life for the parents as well as the patient. One father expressed it like this: "Being a parent and having a job waiting for you, it is not uncomplicated to be away 2 till 4 weeks. We have extended days of incapacity as parents, still we do not want to use them if we don't have to. To get away with an intervention is 'worth gold'."

Minor physical burden

Minimal pain and an easy rehabilitation decreased the physical burden. Five parents stated that increased mobility, flexibility and almost non-existence of pain during the rehabilitation period, made the percutaneous implantation technique attractive. One parent stated "The rehabilitation phase is different. She went to see a friend the same day she was discharged from hospital. She had a bruise in her groin for a few days, that was all. She told herself that she would rather have 10–20 new bruises than one new open-chest operation." One father explained his experience after percutaneous pulmonary valve implantation in his daughter: "The relief of not having to see your daughter in pain and avoiding a stay in the intensive care unit, was a big relief. To see your child in such a situation is quite stressful for parents. I think this is the most important issue from my point of view. Another statement was: "After the percutaneous pulmonary valve implantation, she told it hurt a bit when walking the first day after the intervention, that was all."

Attitudes towards the new treatment

Despite a positive attitude, the next-of-kin visualised vulnerability and insecurity being a parent or close relative to a patient with a chronic disease requiring repeated surgeries and hospital stays. Conflicting thoughts of life and death when leaving their child in the operating theatre were described. Being among the first patients treated with this technique, parents and other next-of-kin were left in a situation of insecurity, hoping for a gentler pathway for their child. Three of the parents did not seem to be able to differ, or to know what to expect differently of these two treatment methods before the admission. The differences were first appreciated after the percutaneous pulmonary valve implantation was completed successfully. One couple of parents described their thoughts about the device equipment as follows: "When we saw the new device equipment, we thought the introduction cable looked massive and far to big to use. But then the doctor explained and showed us how it was done. Our daughter seemed calm and confident with the information he gave her, and we decided to put our trust in the medical team." Another couple explained how they felt when they first heard of the percutaneous pulmonary valve: "As long as it is a minor intervention, it is worth a try. If this had been more complicated, it would probably not have been wise to be among the first ones treated with this new intervention. Anything that makes things easier, is good." The value and need of trust to healthcare providers are

shown in the citing above with the parent's main focus on the wellbeing of their child.

DISCUSSION

This study demonstrates the impact of a chronic disabling disease requiring repeated surgeries on the patient's and next-of-kin's daily life and the priorities they have to make. Patients with congenital heart disease today have a longer life expectancy than before.[3] Along with the longer life expectancy comes frequent hospitalisations and repeated surgical interventions.[6]

Regular check-ups and unexpected complications can lengthen the hospitalisation duration.[12] Medical complications, ventricular failure and arrhythmias are common.[13] Many of these events may cause a temporary set-back in the patient's physical function, and thereby causing an interruption in the patient's and the next-of-kin's social life. With this background it is not surprising that the experience of regaining a functional role and returning to normal life 3 days after treatment was embraced as the most important asset of the percutaneous valve technique by the patients and the next-of-kin. The importance of regaining physical control as fast as possible after treatment, has previously been documented in other patients with congenital heart disease.[10]

Previous studies show that the patients with congenital heart disease try to compensate for the lack of physical performance by adapting to alternative roles during physical activity and pursuing academic interests in order to obtain social recognition.[8 9] In this context it is interesting that in the present study we found a difference between genders in their evaluation of the benefit of the minimal invasive technique. While the males emphasised the physical improvements as a major benefit, the females claimed the possibility of taking part in their social arenas as the most important consequence of the minimal invasive treatment.

Several studies indicate that patients with chronic cardiac disease are at risk of having poorer educational and vocational outcomes as compared with healthy young adults.[13–15] There may be many causes for this phenomenon. The interruption of the school year by repeated controls and treatments is obviously a factor, but some authors have also emphasised the effect on the cognitive function of having repeated open heart surgeries.[6 9]

An important consequence of the percutaneous technique as experienced by the patients was their ability to follow the school year. Another possible advantage of this technique is that the valve implantation is performed by venous insertion at the right side of the heart, thus not affecting the arterial side.[16] One would thus expect a lesser challenge of the cognitive function after treatment compared to open surgery including the use of extracorporeal circulation.

The transition from adolescence to adulthood is a major challenge. Peer support and social activities with close friends appear to be important for keeping up a normal maturation progress and handling challenges associated with adolescence.[6 8 9] In accordance with this several of the patients mentioned the importance of being able to visit their friends immediately after the treatment. Overgaard *et al* referring experiences of young adults with single ventricle physiology, state that respondents underscored the need for friends and resource persons to lift them out of their role as disabled cardiac patients and provide them with 'normal' life experiences.[9]

For the adult patients, the main benefit of the treatment was their ability to continue with and mastering their daily chores such as tending to their children, driving their car or maintaining their social life. They emphasised the psychological impact of not being able to do that after open heart surgery. Previous studies also demonstrate that family, education, career, friends and healthcare are rated among the most important domains to have an impact on quality of life for adult patients.[17 18] Social adjustment, academic progress, future employment as well as health insurance and life insurance are also major challenges for this group.[6 10 19 20]

For the parents and next-of-kin living in close relationship with a patient with congenital heart disease this is a challenge, thus the next-of-kin also emphasised the minimal disruption of the family life as a main benefit of the minimal invasive method. The family members were able to maintain an almost normal everyday life following the hospitalisation. The quick recovery with no stay in the intensive care unit after treatment was appreciated. The parents referred to these benefits as 'worth gold' for the family, but also for their own career and their relation with their employer, as they were able to go to work with little interruption. The striving for life normality is essential for this patient population. Normalisation seemed to be a management strategy of the patients and their family. Because of a minor interference on daily life, the minimal invasive technique was experienced as important for their strive for normality.

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Collaborators BA; MHA; HL; GD; EF.

Contributors BA, MHA, HL and EF made substantial contributions to the conception of the study. All authors contributed in the study design process. BA, MHA, GD and EF were responsible for data acquisition. BA and MHA made substantial contributions in the analysis data process, but all authors participated to strengthen accurate reflection, highlight differences, provided critical revisions for the content and approved the final version.

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In-hospital cost comparison between percutaneous pulmonary valve implantation and surgery

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Abstract

OBJECTIVES: Today, both surgical and percutaneous techniques are available for pulmonary valve implantation in patients with right ventricle outflow tract obstruction or insufficiency. In this controlled, non-randomized study the hospital costs per patient of the two treatment options were identified and compared.

METHODS: During the period of June 2011 until October 2014 cost data in 20 patients treated with the percutaneous technique and 14 patients treated with open surgery were consecutively included. Two methods for cost analysis were used, a retrospective average cost estimate (overhead costs) and a direct prospective detailed cost acquisition related to each individual patient (patient-specific costs).

RESULTS: The equipment cost, particularly the stents and valve itself was by far the main cost-driving factor in the percutaneous pulmonary valve group, representing 96% of the direct costs, whereas in the open surgery group the main costs derived from the postoperative care and particularly the stay in the intensive care department. The device-related cost in this group represented 13.5% of the direct costs. Length-of-stay-related costs in the percutaneous group were mean $3885 (1618) and mean $17 848 (5060) in the open surgery group. The difference in postoperative stay between the groups was statistically significant ($P \leq 0.001$).

CONCLUSIONS: Given the high postoperative cost in open surgery, the percutaneous procedure could be cost saving even with a device cost of more than five times the cost of the surgical device.

Keywords: Congenital pulmonary heart disease • Innovative techniques • Cost analysis • In-hospital costs

INTRODUCTION

Percutaneous pulmonary valve implantation is an alternative to open surgery in selected patients with pulmonary valve dysfunction [1]. The method involves overstenting the degenerated pulmonary valve with either a bovine jugular vein or a bovine pericardial valve [2, 3]. In Norway 62 patients have been treated so far, all of them in our hospital. Short- and midterm follow-ups have shown improved and sustained haemodynamics and an increase in exercise capacity, particularly in patients with predominant pulmonary stenosis [2, 4, 5]. Patients have reported positive experiences of the short rehabilitation time and the ability to normalize and taking part in their social life almost immediately after treatment [6]. However, there has been little detailed information on the impact of the percutaneous technique on the in-hospital costs. Thus, the purpose of this study was to identify the main cost-driving factors associated with the two techniques.

MATERIALS AND METHODS

Patients

All patients treated with pulmonary valve replacement percutaneously or surgically were recruited during a 3-year period and defined as a standard revision with no other intraoperative procedures. The inclusion was not randomized, as the percutaneous technique could not be applied in all patients, due to anatomical restrictions. The inclusion criteria were independent of procedure technique, based on international principles of treatment within

this medical field [7] and a consensus set by the local team responsible for the patients. The study was conducted at Oslo University Hospital, the only cardiac centre in Norway offering advanced surgical and interventional treatment to patients with congenital heart defects.

Treatment procedures

The choice of valve was based on what was deemed best for the individual patient. Thus, in both groups various valves were used. For percutaneous implantation the advantage of prestenting was acknowledged during the study period to minimize the risk of stent fractures [8–10]. Prestenting was therefore not an option in the first six patients. The interventional procedures were performed in an angiography room with a team of cardiologists, anaesthesiologists and specialist nurses. All procedures were performed in general anaesthesia. The induction was done with benzodiazepines and maintained with gas and fentanyl.

The costs for prestenting were defined as a part of the percutaneous pulmonary valve implantation procedure, even in the cases where the stents were implanted 1–3 months before percutaneous pulmonary valve implantation.

In the open surgery group, all surgical procedures were carried out in an operation theatre with a team of cardiac surgeons, cardiologists, anaesthesiologists, specialist nurses and a perfusionist. All surgeries were performed on standard extracorporeal circulation. Transoesophageal echocardiography was performed in most of the surgical patients. The anaesthesia was the same for both procedures.

Setting and location

In order to monitor the costs in detail the total admission time was divided into three phases: the pre-, per- and postoperative phase. In the patients admitted for pulmonary valve replacement by open surgery, the preoperative phase of the study was defined from the admission day before surgery until transferal to the operation theatre. The preoperative phase included laboratory tests, radiological imaging, echocardiography, information from the physiotherapist and a clinical evaluation by a senior surgeon in all surgical patients. The per-operative phase was defined as the time from admission to the operation theatre until transferal to postoperative care. The postoperative phase was defined as the duration at the postoperative care unit and at the general ward. In patients referred to a local hospital before discharge to home, the time spent at the general ward was defined as the time at our hospital in addition to the time at a local hospital. The first night at the general ward all patients spent in a 'step-down room' before they were placed in a two- or four-bed room.

In the patients treated with the percutaneous technique, the preoperative phase was defined from the admission day before the intervention until transferal to the catheterization suite. They were admitted to a ward either at the adult cardiology department or at the pediatric cardiology department where laboratory tests, radiological imaging, echocardiography and a clinical evaluation by a senior cardiologist were performed. The per-operative phase was defined from admission to the catheterization suite to transferal to postoperative care.

The postoperative phase was defined as the length of stay (LOS) from the arrival at the postoperative care unit until discharge from a hospital setting. This included a stay at the paediatric or adult cardiac ward at our hospital, as well as an eventual stay at a local hospital.

Cost analysis

In both treatment groups, two different methods were used for cost analysis. One method was based on data for the individual patient (direct costs) and one was based on the overhead costs (indirect costs), with the overhead costs ultimately also allocated to the individual patient [11, 12]. By the overhead cost method, costs were based on the average estimated cost of each hour at different wards at Oslo University Hospital, Rikshospitalet. These estimates were produced by the hospital account department and comprised costs as an estimated price for each examination (echocardiography, catheter laboratory procedure, radiologic imaging, surgical procedure, etc.) based on purchase cost divided by the number of procedures performed. These costs were allocated to clinical departments and further to the specific patients by predefined allocation keys [11, 13].

The direct cost method was based on direct registration of selected costs for each patient in both groups with the basic principle to relate as much as possible of the resources used as direct costs to the individual patient [12]. The following categories were used to describe the direct resource use in both types of treatment techniques; diagnostic- and laboratory tests, medication, disposables, blood products, echocardiography, radiological imaging, procedure costs and physiotherapy. Patient-specific costs and overhead costs are reported separately for each patient group. Cost associated with the stay in a local hospital was calculated by multiplying the daily Oslo University Hospital general ward costs by the number of days they stayed at the local hospital.

All interventions were evaluated as if operating under steady-state conditions based on the budget of 2013, whereas prices of disposables (direct costs) were obtained from the university hospital procurement system using negotiated prices for 2014. Prices were consequently converted from Norwegian crowns (NOK) to US dollars (US$) with the mean exchange rate for 2014 of 1 USD ($) = 6.3 NOK. All patient costs were covered by the Norwegian public insurance system [14].

Data analysis

Due to small sample sizes of the study, data were not normally distributed, thus a bootstrapping analysis was made for both data sets to allow comparison of arithmetic means concerning analysing the costs and LOS hours without making assumptions about the data distribution [15]. A P-value <0.05 was considered as statistically significant. Mean and standard deviation or median and range were presented for normally and non-normally distributed data, respectively. Number and percentage were given for categorical data. Continuous data were examined for significant departure from normality by using histogram and Kolmogorov–Smirnov's test. Scatter plot was used to investigate whether the relationship between two continuous variables was linear (Fig. 1).

Relationship and its strength between total LOS (hours) and age (years), total LOS and weight (kilograms) or total LOS and numbers of preoperations were assessed by non-parametric correlation analysis because of non-linear relationship, non-normally distributed data and small sample sizes. Bootstrapped 95% confidence

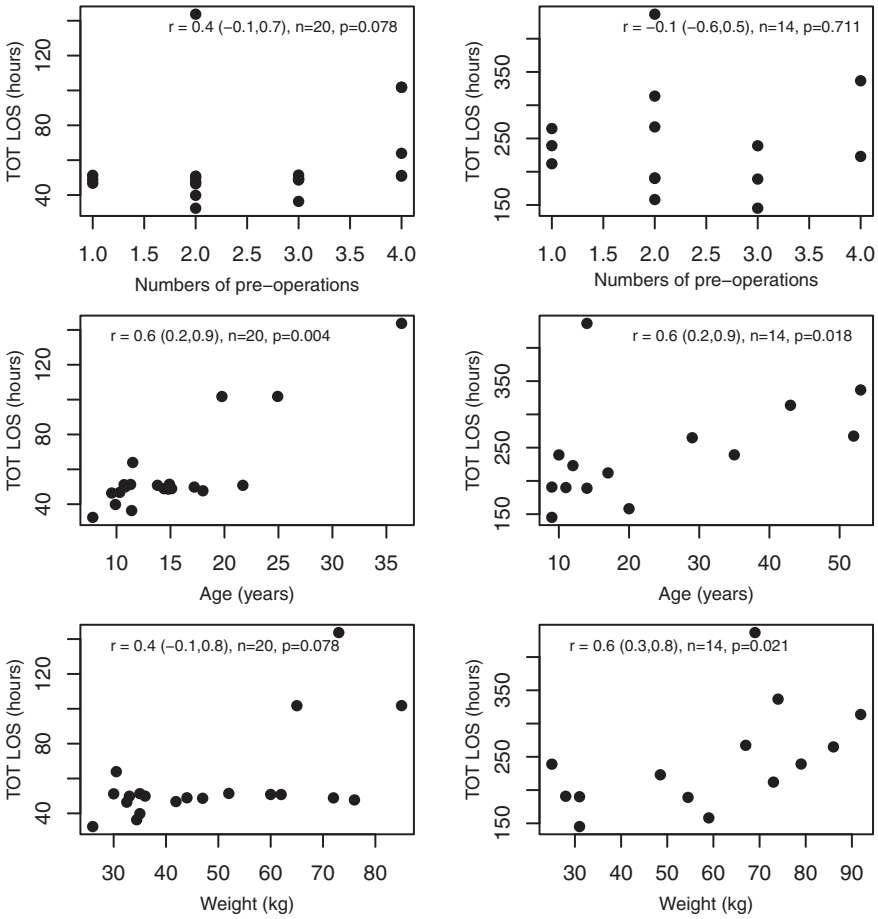

Figure 1: Scatterplots showing the relationship between total LOS and numbers of preoperations, total LOS (h) and age (years) and total LOS and weight (kg) or in the percutaneous pulmonary valve replacement group and the open surgery group.

interval (95% CI) for Spearman's correlation coefficient was based on 1000 replications and biased corrected and accelerated.

Analyses were performed in IBM Statistical Package for the Social Sciences 23 23.0.0.2 and the figures were created with R for Windows. The bootstrapping analyses were conducted in Microsoft Excel 2013.

RESULTS

Thirty-four patients were included in the study, 22 males and 12 females, aged 14 (8–36) years in the percutaneous group and 23 (9–53) years in the open surgery group (Table 1). In the 20 patients receiving percutaneous valve implantation, two of the patients were prestented 1 and 3 months before valve implantation, while nine patients were prestented during the implantation procedure. Median 1 (1–3) stents were used in these patients. Sixteen patients received a Medtronic Melody (Medtronic Inc., Minneapolis, MN, USA) valve and four patients an Edwards SAPIEN (Edwards Lifesciences, Irvine, CA, USA) valve. Of the 14 patients undergoing open surgery, 11 patients received a Carpentier-Edwards Perimount Magna (Edwards Lifesciences, Irvine, CA, USA) valve, two a Contegra bovine jugular valved conduit (Medtronic, Inc.), and one patient received a pulmonary homograft.

In the patients receiving percutaneous pulmonary valve implantation, the total length of hospital stay (LOS) was 58 (27) h and 243 (78) h in the patients treated by open surgery, thus total LOS cost was $3885 (1618) for the percutaneous pulmonary valve group and $17 848 (5060) for the open surgery patients.

The LOS cost (overhead costs) in the percutaneous pulmonary valve implantation group was $1337 (1239) for the prephase, $238 (57) for the per-operative phase and $2309 (1433) for postoperative phase (Table 2). Cost drivers (direct costs) in the preoperative phase of the percutaneous pulmonary valve implantation group were diagnostic tests as echocardiography and X-ray expenses at the costs of $562 (257). In the open surgery patients, the LOS in-hospital cost was $1329 (952) for the preoperative phase, $247 (68) for the per-operative phase and $16 273 (5034) for postoperative phase.

Cost drivers in the per-operative phase for the percutaneous pulmonary valve implantation group were related to the device cost and represented a cost (prestent + valve) of $30 629 (3712). Disposable items (monitoring equipment, introducer catheters and balloons) and drugs (anaesthetics, medication, fluids) represented a minor cost for these patients $1121 (566).

Cost drivers in the per-operative phase for the open surgery group were oesophagus echocardiography representing $104 (80) and the cost of the valve conduit $3814 (655), disposables (equipment needed to perform the open surgery, heart- and lung equipment, monitoring equipment) at the cost of $2267 (195), drugs and blood products representing $1985 (2146) (Table 3).

In the percutaneous pulmonary valve group, the patients stayed 3.3 (3.6) h at the postoperative unit at a cost of $876 (1087) and 26.8 h at the general ward at a cost of $1432 (972).

Table 1: Patient characteristics

Groups	Percutaneous pulmonary valve replacement (n = 20)	Open heart surgery pulmonary valve replacement (n = 14)	P-value
Female gender, n (%)	7 (35.0)	5 (35.7)	1.00
Age (years), median (range)	14. (8–36)	23 (9–53)	0.323
Weight (kg), median (range)	43.0 (26–85)	63.0 (25–92)	0.274
Number of previous surgeries, median (range)	2.5 (1–4)	2.0 (1–4)	0.416

Table 2: Total hospital length of stay, cost per phase based on overhead costs for percutaneous valve replacement and open surgery

	Groups				P-value	
	PPVI (n=20)		Open surgery (n=14)			
	LOS (h)	Costs	LOS (h)	Costs	LOS	Costs
Phases						
Preoperative phase						
Mean (SD)	25 (23)	1337 (1239)	32 (23)	1329 (952)	0.37	0.98
Median (range)	23 (4–117)	1215 (187–6247)	24 (15–99)	1007 (639–4075)		
Per-operative phase						
Mean (SD)	3 (1)	238 (57)	3 (1)	247 (68)	0.39	0.70
Median (range)	3 (2–5)	239 (154–428)	3 (2–5)	232 (160–410)		
Postoperative phase						
Mean (SD)	30 (19)	2309 (1433)	208 (65)	16 273 (5034)	<0.001	<0.001
Median (range)	24 (20–91)	1799 (1406–6604)	204 (119–361)	13 920 (9256–25 913)		
Total LOS						
Mean (SD)	58 (27)	3885 (1618)	243 (78)	17 848 (5060)	<0.001	<0.001
Median (range)	50 (32–144)	3223 (2244–8161)	231 (145–437)	16 347 (10 593–27 113)		

All costs are in USD ($) (2013).

Table 3: Direct costs for percutaneous valve replacement and open surgery

Item	Groups				P-value
	PPVI (n=20)		Open surgery (n=14)		
	Mean (SD)	Median (range)	Mean (SD)	Median (range)	
Disposables	1121 (566)	1044 (268–1940)	2267 (195)	2421 (250–2429)	<0.001
Device/valve- conduit replacement	30 629 (3712)	32 420 (23 750–35 229)	3814 (655)	3601 (3226–5736)	<0.001
Diagnostic tests	562 (257)	53 (231–1421)	2042 (522)	1854 (1365–2940)	<0.001
Drugs	8 (17)	78 (70–141)	1196 (293)	1215 (836–1878)	<0.001
Physiotherapy	0 (0)	0 (0)	137 (48)	135 (53–219)	
Laboratory tests	33 (8)	31 (20–56)	107 (23)	107 (60–154)	<0.001
Blood products	0 (0)	0 (0)	789 (1942)	0 (0–7222)	

All costs are in USD ($) (2013).

In the open surgery group, the patients stayed 33 (22) h in the intensive care unit at a cost of $8836 (5679). Diagnostic tests represented 10% of the costs in the postoperative phase. After discharge from the postoperative unit these patients stayed 68 h (79) in a local hospital at a cost of $2834 (3261) representing 16% of cost for in the postoperative phase for this group (Fig. 2).

The Spearman rank correlation analysis demonstrated a coefficient of 0.614 (P= 0.004) between age and LOS, whereas in the open surgery group the coefficient was 0.621 (P = 0.02) demonstrating a significant correlation between LOS and the patient's age in both groups.

DISCUSSION

The overhead cost method (indirect costs) developed at our hospital was based on a department-dependent fixed price for staying in a hospital ward during pre-, per- and postoperative phase

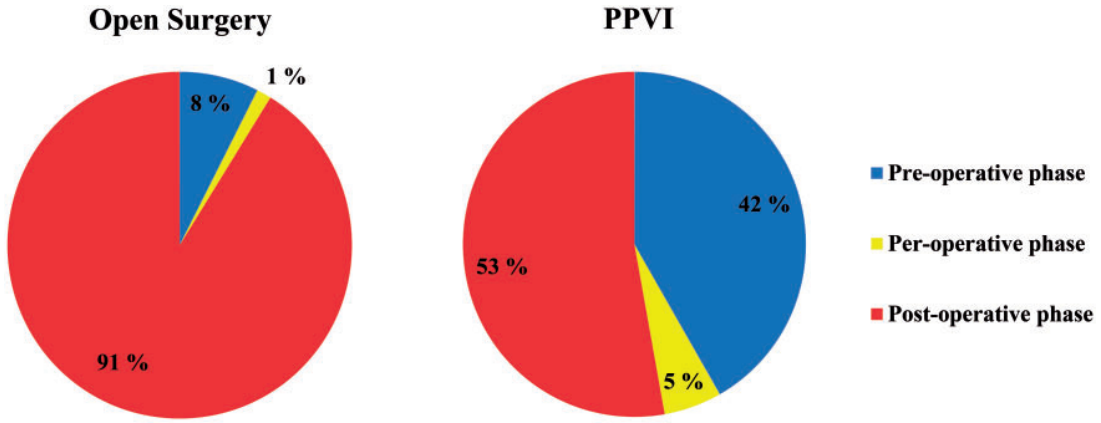

Figure 2: Overhead costs shown in percentages in the different in-hospital phases in the percutaneous pulmonary valve replacement group and the open surgery group. All costs are in USD ($).

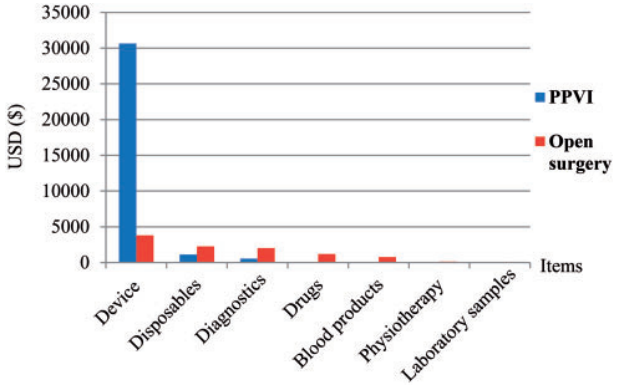

Figure 3: Direct costs in the percutaneous pulmonary valve replacement group and in the open surgery group. All costs are in USD ($).

after open surgery and a cardiac percutaneous intervention. As this method did not individualize the actual cost of the percutaneous valve and associated stents, the cost estimation by this method showed a difference in costs between the groups favouring the percutaneous technique. The major cause for this favourable outcome was the difference in LOS postoperatively. The overhead cost method was based on an average total cost for staying in a ward or intensive care unit calculated on the average of costs including diagnostics and treatment for all cardiac patients receiving surgery or percutaneous intervention. This method works well for monitoring costs of procedures that are well established and a well-known pathway.

The direct cost method (patient-specific cost) based on prospective detailed cost acquisition however, demonstrated a difference in costs favouring open surgery. The main reason for this was the price of the percutaneous valve (+equipment) representing 96% of total direct costs in this group. The direct cost method revealed reduced costs related to disposables, laboratory tests, diagnostic tests, drugs, physiotherapy and blood products for the percutaneous intervention group compared with open surgery, leaving the device cost as the singular cost-driving factor. The direct cost method revealed detailed information that was not exposed in the traditional overhead cost method. Thus the study showed that although the overhead cost method is well suited for monitoring established methods where the average cost will represent a more or less true picture of the costs, a direct cost method is necessary to identify the main cost drivers related to the new method when new methods and technologies are introduced [16] (Fig. 3).

The study further demonstrated that when compared with open surgery, percutaneous pulmonary valve implantation in Norway could be cost saving for hospitals even with a percutaneous device cost of more than five times the cost of the surgical device. As percutaneous techniques become more frequent and more companies enter the market a reduction in the device cost may be expected and thus give a more favourable in-hospital cost outcome [17, 18].

We defined prestenting as part of the routine percutaneous valve procedure when estimating costs, even if it was not needed in all patients. Patients with less rigid outflow tracts became candidates for the percutaneous technique, even outflow tracts with predominantly native tissue were prestented and transformed to become a rigid and safe landing zone for a percutaneous valve. Thus, the inclusion criteria for percutaneous valve replacement were slightly changed during the study.

In this study, the control group and the percutaneous valve group were not identical with respect to anatomical and pathological conditions as all patients where percutaneous valve implantation was possible received such treatment, whereas the control group comprised only patients where for various reasons percutaneous treatment was not possible. However, we chose not to perform a randomized trial as that would leave too few patients in each group. Even so, we believe that the present design gives a fairly accurate picture of the cost challenges of the percutaneous technique.

In this article, we did not address complications in each group as outcome variables for cost estimation.

Instead, LOS was used as basis. LOS reflects most minor and major complications from a cost analysis perspective.

Based on the overhead cost method (indirect costs) the open surgery group had major costs related to the stay in the intensive care unit, representing $8501 (5575) compared with the percutaneous pulmonary valve implantation group where the postoperative costs were $876 (1087). Costs were substantially influenced by a few patients in need of a longer in-hospital stay than most of the patients in both groups. These patients were adults above 40 years, indicating that surgical treatment in

grown-up congenital heart failure patients may be more costly than in children. This was also the case in patients treated with the percutaneous technique. The Spearman rank correlation analysis revealed a significant correlation between age and total LOS in both groups.

The percutaneous pulmonary valve replacement was significantly more costly than open surgery, even if the postoperative costs were significantly lower with the percutaneous technique. To get a full picture of the cost safety of the percutaneous technique, costs related to the first year after discharge should also be monitored.

In the study of Vergales *et al.* [18], doing a 5–10 year cost model, researchers found that percutaneous pulmonary valve implantation holds a significant cost advantage over the surgical approach, mainly because they estimated social cost savings in both groups in the analysis.

Because the sample size in our study population was small and not normally distributed we decided to perform bootstrapping along with parametric methods. Bootstrapping is a procedure to estimate the population distribution by using the information based on a number of resamples from the original sample. The bootstrap method creates a large number of datasets and computes the statistics on each of these datasets. We drew 1000 samples with replacement from the original sample and computed statistics (mean, median, SD, CI) for each bootstrap sample. Once we got a bootstrap samples created, we got distribution of the statistics.

The 95% bootstrap confidence interval is estimated by the cut-off values for the middle 95% of the bootstrap distribution. The mean of the bootstrap means was very close to the mean of the original sample. According to O'Hagan and Stevens [19], if parametric and bootstrap approaches show similar results, they should both be acceptable.

Strengths and limitations of the study

Strengths of our study are the prospective registration of data collection, allowing for the most precise level of microcosting as costs are recorded at the cost object level by counting every activity performed and transforming them into monetary units [16].

Limitations of the study were small patient populations influencing our statistical results. The results are not widely generalizable, as the data reflect the practice at a single centre, and the study is not randomized with a slightly different population in the study and the control group.

CONCLUSION

Although the mean device costs per patient were the main cost drivers in the patients receiving percutaneous pulmonary valve replacement, costs related to disposables, diagnostic tests and LOS in the intensive care unit and in the postoperative phase as a hole, were the main cost drivers in the patients receiving open heart pulmonary valve replacement. With a moderate reduction in the present device cost, the percutaneous technique may be cost saving from the hospital point of view as the technique holds the potential to reduce the postoperative costs significantly compared with open surgery.

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III

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Psychosocial and clinical outcomes of percutaneous versus surgical pulmonary valve implantation

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ABSTRACT

Objective This prospective non-randomised study was performed to compare the psychosocial function and clinical outcomes following surgical and percutaneous implantation of a pulmonary valve at 3 months and 1 year after treatment.

Methods All patients were consecutively admitted for treatment by either method from June 2011 to October 2014. The data of 20 patients treated with the percutaneous technique and 14 patients treated with open heart surgery were compared. Psychosocial function was measured by the Achenbach System of Empirically Based Assessment (ASEBA). We used linear mixed-effect models to investigate group changes between the psychosocial function and clinical data of 34 patients with congenital pulmonary valve disease.

Results A significant difference in favour of the percutaneous pulmonary valve implantation group was observed regarding the ASEBA scores, specifically in the Thought problems subscale at 1 year (p=0.015), Attention problems subscale at 3 months (p=0.016) and 1 year (p=0.007) after treatment. After adjustment for the right ventricle to pulmonary artery pressure gradient at 3 months, a significant change in the Attention problems subscale (p=0.038) was noted in the percutaneous group. The New York Heart Association functional score significantly improved in both groups. The measured right ventricle to pulmonary artery pressure gradient was reduced significantly in both groups at 1 year.

Conclusions Both methods led to significant clinical improvement. Thought and attention problems such as intrusive behaviour significantly decreased only in patients who underwent the percutaneous procedure. Complications as reintervention, bleeding and arrhythmia were only observed in the open surgery group.

Key questions

What is already known about this subject?

- Both treatment techniques are associated with good clinical outcomes. An easy rehabilitation and rapid life normalisation are described as positive experiences in the percutaneous pulmonary valve implantation group. However, the psychosocial outcome between the two treatment groups after treatment remains unknown.

What does this study add?

- In the percutaneous pulmonary valve group, a significant improvement was observed in subscales within psychosocial function. No significant improvements were observed in the open surgery group.

How might this impact on clinical practice?

- Subscales within psychosocial function was in favour of the percutaneous pulmonary valve implantation group 3 months and 1 year after treatment. However, future studies involving a larger sample population and longer-term follow-up are warranted to confirm our results.

INTRODUCTION

Percutaneous pulmonary valve implantation (PPVI) for selected patients with right ventricle outflow tract (RVOT) obstruction or insufficiency was introduced in 2000 as a complementary technique to surgical pulmonary valve replacement.[1–6] Device-related and technique-related improvements[7] have resulted in expanded performance of PPVI with increasingly more patient groups being accepted for treatment.[8] Long-term follow-up results have indicated improved and sustained haemodynamics after the procedure.[1 9 10] Patients have reported positive impacts on psychosocial function and normalisation of life after treatment.[11 12] Surgical valve replacement is a successful procedure with low mortality. However, repeated sternotomy is a predictor of prolonged hospitalisation and may increase the risk of complications.[13] Inattention, hyperactivity and poor school performance are described in children with complex heart disease.[14–16] Possible causes include underlying neurobehavioural impairment, genetic and epigenetic factors, surgical and interventional procedures, cerebral microembolisation, cerebral hypoperfusion, anaesthesia exposure, an inflammatory response, or simply psychological and physical strain caused by repeated surgeries.[14 16–18] A strategy for prevention

and lifelong perspective is important in modern healthcare, hence to alleviate neurodevelopmental and neurovascular risk factors is crucial.[16 19] The possible impact of PPVI on patients' psychosocial function should not be underestimated. When evaluating new treatments, patient-reported outcomes are important in estimating the psychosocial results of therapy.[20] Knowledge is limited regarding the relationship between patient-reported outcomes addressing psychosocial function and clinical data in patients who have undergone PPVI or open heart surgery. We aimed to compare the short-term and intermediate-term clinical and psychosocial outcomes after percutaneous and surgical techniques.

A priori, we hypothesised that (1) a significant improvement in clinical and psychosocial outcomes would occur in both treatment groups and (2) a difference in patient-reported outcomes would be noted between the two groups at 3 months and would be in favour of the PPVI group.

METHODS

Design

A single-centre, prospective case–control study.

Setting

All Norwegian patients eligible for surgical or interventional treatment for RVOT dysfunction are centralised to one centre at Oslo University Hospital. Recruitment was performed by sending an information letter to patients and/or their closest relatives before they arrived at the hospital. Informed consent was given by the patient for patients >18 years of age and by the parents/closest relatives for younger patients. A team of four thoracic surgeons and one interventional cardiologist working in close collaboration performed all RVOT procedures. A procedural strategy reflecting international guidelines[21] was planned for both paediatric and adult patients, using the same criteria for both procedures.

Patients

Thirty-four consecutive patients were included in the study in the period of June 2011 to October 2014 (20 in the PPVI group and 14 in the open surgery group); 23 of these patients were children (15 in the PPVI group and 8 in the open surgery group). The inclusion was not randomised because the percutaneous technique could not be applied in all patients due to mechanical restrictions.

The inclusion criteria were independent of procedure technique, based on international principles of treatment within the field[22] and a consensus set by the local treatment team. The exclusion criteria were aggressive endocarditis, conduit of >22 mm and no circumferential foreign material. All included patients had information on their former surgery (conduit type and size), clinical indication and gradient of their stenosis (as measured by echocardiography, cardiac MRI or catheterisation). All patients in both groups required pulmonary valve replacement secondary to a failed surgical procedure to repair the RVOT.

Interventions

Percutaneous intervention group

Pre-stenting performed up to 3 months before the procedure was considered part of the PPVI procedure. The vascular access route for the percutaneous pulmonary valve was either transfemoral or transjugular. Cardiac catheterisation with assessment of the right heart and pulmonary and aortic pressures preceded each implantation. According to the standard procedure, all patients underwent angiographic coronary visualisation during pulmonary artery balloon inflation to evaluate the potential risk of coronary compression by implantation of the percutaneous valve.

Open surgery group

The surgical valves were implanted after a midline sternotomy, either directly under a patch or in a Gore-Tex conduit. After preparation of the necessary mediastinal structures, bicaval and ascending aortic cannulation was performed. Cardiopulmonary bypass was initiated, and the patient was cooled to a temperature of 32°C. The aorta was then cross-clamped, and St. Thomas crystalline cardioplegia was delivered. Appropriate exposure and preparation of the RVOT was performed, and a valve was implanted in the pulmonary position using a standard technique. When necessary, a Gore-Tex patch was placed for enlargement of the RVOT. After rewarming and reperfusion, the patient was weaned from cardiopulmonary bypass and the wound was closed in a standard fashion.

Treatment

Anaesthesia and monitoring were standardised for both treatment groups. Induction was performed with benzodiazepines and maintained with gas and fentanyl. All patients in the PPVI group were extubated before leaving the angiographic suite. The patients in the open surgery group were transferred to the intensive care unit after surgery[23] and extubated when their haemodynamics and respiratory status were stable. Chest tubes were routinely removed on postoperative day 1.

Analgesia

Analgesics were administered according to established protocols. At the start of the operation, a single dose of fentanyl was administered intravenously, whereas paracetamol and ketorolac were administered at the end of anaesthesia. In the open surgery group, at the start of the postoperative phase on day 0, paracetamol was administered according to a fixed protocol with ketorolac/morphine intravenously as needed. From postoperative day 1, the patients received oral paracetamol. Ketorolac and additional analgesia were thereafter administered as needed.

Study outcomes

Patient-reported outcomes (psychosocial function) were assessed using the Achenbach System of Empirically Based Assessment (ASEBA) and New York Heart Association (NYHA) functional class. The clinical outcomes were mortality, reintervention or reoperation, complications such a stent fracture and arrhythmia, the right ventricle to pulmonary artery pressure gradient and the degree of pulmonary regurgitation measured before and after treatment.

Patient-reported outcomes

Psychosocial function

The ASEBA[24] was used to assess psychosocial function before treatment and twice postoperatively in both groups. This is a generic, comprehensive, self-administered outcome measure of social functioning. It comprises 112 items that are used to measure symptoms in eight subscales: Anxiety/Depression, Withdrawal, Social complaints, Thought problems, Attention problems, Intrusive behaviour, Aggressive behaviour and Delinquent behaviour. Items are scored on a 3-point scale, and lower scores indicate poorer functioning.[24 25] The Youth Self-Report questionnaire targets patients aged 11 to 18 years, while the Adult Self-Report questionnaire targets patients aged 18 to 59 years; each questionnaire was used as appropriate. The questionnaire was administered to all patients aged >11 years. The timing of data collection was based on the time intervals that were expected to maximise the treatment benefit and intermediate results. All patients were instructed to complete the questionnaire according to their perceived status of well-being at that time.

Changes in the NYHA classification of heart failure were measured through a self-reported questionnaire collected before treatment and twice postoperatively (3 months and 1 year).[26]

Clinical outcomes

The following data were collected before treatment and twice postoperatively (3 months and 1 year) in both groups: change in the measured right ventricle to pulmonary artery pressure gradient and the degree of pulmonary regurgitation. The right ventricle to pulmonary artery gradient pressure was measured in millimetres of mercury, while the pulmonary regurgitation was graded in five levels (0–4) defined as none, trace, mild, severe and free.[21]

Statistical analysis

Differences between two independent proportions were tested by Fisher's exact test or the χ^2 test and differences between two independent samples means were tested by the Mann-Whitney U test. Within-group changes from the preoperative period to 3 months and 1 year postoperatively were examined by the Wilcoxon signed-rank test for pulmonary stenosis, pulmonary regurgitation and NYHA classification. Otherwise, a mixed-effect linear regression model was used to fit multiple data points per patient, whereas the outcome variable was the psychosocial function score, the NYHA classification, cardiac function and length of stay. In the mixed model, patient identification was a random variable while time and group with interaction time×group were treated as fixed variables. The crude and adjusted mean changes from baseline to 3 months and 1 year, SD and p values were calculated for each group. The p values were not adjusted for multiple outcomes, and significance was set at $p < 0.05$.

Statistical analyses were performed with IBM Statistical Package for the Social Sciences (SPSS).

RESULTS

Patient characteristics

The two groups were comparable with regard to baseline characteristics: gender, age, body weight and number of previous open heart surgeries. However, the groups differed significantly with respect to valvular disease: stenosis was the main disorder in the PPVI group, while pulmonary regurgitation or combined disease were the main disorders in the open surgery group. Among the 20 patients in the PPVI group, 16 received a Medtronic Melody valve (Medtronic, Minneapolis, Minnesota, USA) and 4 received an Edwards SAPIEN valve (Edwards Lifesciences, Irvine, California, USA).[23] Two of the patients underwent pre-stenting 1 and 3 months prior to valve implantation, while nine patients underwent pre-stenting during the implantation procedure. A median of 1 (range, 1–3) pre-stent was used. Of the 14 patients in the open surgery group, 11 received a Carpentier-Edwards Perimount Magna valve (Edwards Lifesciences), 2 received a Contegra bovine jugular valved conduit (Medtronic) and 1 received a pulmonary homograft (table 1).

Clinical endpoints

In the PPVI group, no procedure was cancelled because of unfavourable coronary localisation. High-pressure pre-dilatation of the pulmonary valve was performed in 13 patients (65%), and high-pressure post-dilatation was performed in 8 patients (40%).

Baseline clinical data showed a statistical difference between groups. Concerning pulmonary stenosis, there was a statistical finding showing more patients in the PPVI group diagnosed with pulmonary stenosis and a mixed lesion compared with the open surgery group.

The measured right ventricle to pulmonary artery pressure gradient was reduced significantly in the percutaneous pulmonary valve group from baseline 67 (10–96) mm Hg to 19 (11–30) at 3 months ($p<0.001$), and at 1 year 19 (9–56) ($p<0.001$) after treatment. In the surgery group, the change in measured right ventricle to pulmonary artery pressure gradient was not significant at 3 months, but at 1 year after treatment, the gradient was reduced to 20 (7–36) ($p=0.010$). In the percutaneous group, NYHA class function was reduced from baseline 2 (1–4) to 1 (1–2) after 3 months ($p=0.021$). After 1 year,

Table 1 Patient characteristics and baseline data

	Percutaneous pulmonary valve replacement (n=20)	Open heart surgery pulmonary valve replacement (n=14)	P values
Female sex	7 (35.0)	5 (35.7)	1.00
Age (years)	14 (8–36)	23 (9–53)	0.323
Weight (kg)	43.0 (26–85)	63.0 (25–92)	0.274
No of previous open heart surgeries	2.5 (1–4)	2.0 (1–4)	0.416
Diagnosis			
Tetralogy of Fallot, all variants	8 (40)	11 (79)	**0.038**
Pulmonary atresia, VSD	5 (25)	2 (14)	0.378
Truncus arteriosus communis	3 (15)	1 (7)	0.627
TGA, PS, VSD	4 (20)	0 (0)	0.126
RV-to-PA pressure/lesion			
Predominant PS[1]	15 (75)	2 (14)	**0.001**
Predominant PR[2]	4 (20)	6 (43)	0.252
Mixed lesion[3]	1 (5)	6 (43)	**0.012**
RVOT			
Native or patch-extended RVOT	4 (20)	4 (28)	0.689
Homograft RV-to-PA conduit	4 (20)	2 (14)	1.000
Contegra RV-to-PA conduit	1 (5)	1 (7)	1.000
Bioprosthesis (eg, Hancock, Carpentier-Edwards)	10 (50)	1 (7)	**0.011**
Other (GoreTex valve re-construction)	1 (5)	6 (43)	**0.012**

Data are presented as n (%) or median (range).
[1]PS, pre-echo peak RVOT velocity/gradient ≥50 mm Hg.
[2]PR, pre-echo peak RVOT velocity/gradient <50 mm Hg.
[3]Mixed lesion, mild stenosis and more than moderate insufficiency.
Bold numbers are statistical significant values.
PA, pulmonary artery; PS, pulmonary stenosis; RV, right ventricle; RVOT, right ventricular outflow tract; TGA, transposition of the great arteries; VSD, ventricular septal defect.

the functional NYHA class was still significant 1 (1–3) (p value=0.034).

In the surgery group, NYHA class function was significantly reduced from baseline 2 (1–3) to 3 months 1 (1–2) (p=0.004), and the improvement was not significant at 1 year.

Pulmonary regurgitation level was reduced significantly in the percutaneous group from baseline 3 (0–4) to 3 months 0 (0–2) (p<0.001), at 1 year the improvement sustained significant at 0 (0–2) (p=0.003). In the surgery group, the pulmonary regurgitation level was reduced significantly from baseline 4 (0–4) to 3 months 1 (0–2). One year after treatment, the level sustained significant at 1 (0–2) (p=0.003) (table 2).

No acute adverse events occurred in the PPVI group. One patient in the open surgery group underwent a reoperation and needed blood transfusion because of bleeding. Another patient required pacemaker implantation after surgery because of a permanent heart block. One patient in this group developed ventricular tachycardia before surgery and therefore received an implantable cardioverter defibrillator after surgery (table 3).

Psychosocial function

Baseline data were comparable between the groups. In the PPVI group, a significant improvement was observed in the Thought problems subscale from baseline to 1 year postoperatively (p=0.015), the Attention problems subscale at 3 months (p=0.016) and 1 year (p=0.007) after treatment. No significant improvements were observed in the open surgery group. No significant differences in psychosocial function before and after treatment were observed between the two groups.

Psychosocial function was assessed only in patients aged >11 years; this contributed to missing data in this study because the response rate for the ASEBA scores was only 63% (table 4).

Association between clinical and psychosocial outcomes

In the PPVI group, a significant association was found between the right ventricle to pulmonary artery gradient pressure and psychosocial function with respect to the Anxiety/Depression subscale at 3 months postoperatively (4.19) (p=0.038). This association was not significant in the same treatment group at 1 year postoperatively (3.66)

Table 2 Changes in clinical outcomes within groups from baseline to 3 months and 1 year after treatment

	Percutaneous pulmonary valve replacement (n=20)	Missing numbers	P values*	Open heart surgery pulmonary valve replacement (n=14)	Missing numbers	P values*
Pulmonary stenosis (mm Hg)						
Baseline	67 (10–96)	0		40 (12–112)	0	
3 months postoperatively	19 (11–30)	0	**<0.001**	14 (5–36)	5	0.123
12 months postoperatively	19 (9–56)	1	**<0.001**	20 (7–36)	0	**0.010**
Pulmonary regurgitation (levels 0–4)**						
Baseline	3 (0–4)	0		4 (0–4)	0	
3 months postoperatively	0 (0–2)	0	**0.007**	1 (0–2)	3	**0.001**
12 months postoperatively	0 (0–2)	1	**0.003**	1 (0–2)	0	**0.003**
NYHA classification (levels 1–4)						
Preoperatively	2 (1–4)	0		2 (1–3)	0	
3 months postoperatively	1 (1–2)	3	**0.021**	1 (1–2)	1	**0.004**
12 months postoperatively	1 (1–3)	11	**0.034**	1 (1–3)	7	0.102

Data are presented as median (range).
*Wilcoxon signed-rank test. The p values were not adjusted for multiple testing.
**Levels 0–4: 0, none; 1, trace; 2, mild; 3, severe; and 4, free.
NYHA, New York Heart Association.
Bold numbers are statistical significant values.

(p=0.058). No significant association of psychosocial function with the length of stay, pulmonary regurgitation or NYHA classification of heart failure was found between the two groups.

DISCUSSION

In both groups, a significant improvement in clinical endpoints was found at 3 months; however, only in the percutaneous group improvements sustained significant

Table 3 Procedural and clinical variables

	Percutaneous pulmonary valve replacement (n=20)	Open heart surgery pulmonary valve replacement (n=14)	P values
Preoperative and postoperative variables			
Vascular access route			
Transfemoral	16 (80)		
Transjugular	4 (12)		
Procedural time (h)	3.05±0.69	2.79±0.70	
Postoperative respirator time (min)	0 (0–0)	240 (65–1005)	
Length of stay (h)	58±27	243±78	**<0.001**
Postoperative bleeding (mL)[1]	0 (0–0)	650 (285–3840)	
Postoperative transfusion (mL)[2]	0 (0–0)	550 (0–7690)	
Stent fractures within 1 year postoperatively	0		
Endocarditis within 1 year postoperatively	0	0	
Pacemaker within the same hospital stay	0	1	
ICD within the same hospital stay	0	1	
Reinterventions	0	1	

Data are presented as n, n (%), mean±SD or median (range).
[1]Day 1 postoperatively.
[2]Transfusions given day 1 postoperatively: erythrocyte concentrate (SAG), fresh frozen plasma (Octaplas), thrombocytes, blood from the heart and lung machine.
ICD, implantable cardioverter defibrillator.
Bold numbers are statistical significant values.

Table 4 Change in psychosocial function in both treatment groups within the different subscales from baseline to 1 year after treatment

Psychosocial function subscales 1–8	Percutaneous pulmonary valve replacement n=15** n=1 (baseline) n=2 (3 months) n=5 (1 year)	Change	P values*	Open heart surgery pulmonary valve replacement n=10** n=0 (baseline) n=1 (3 months) n=2 (1 year)	Change	P values*
1. Anxiety/depression						
Baseline	53.86±5.35			52.90±3.84		
3 months postoperatively	54.25±6.17	−0.23	0.853	50.78±1.99	−2.01	0.151
1 year postoperatively	52.36±5.07	−1.01	0.433	51.25±2.19	−1.91	0.190
2. Withdrawal						
Baseline	55.64±5.85			53.50±6.02		
3 months postoperatively	54.25±6.52	−1.05	0.310	52.78±5.21	−0.62	0.589
1 year postoperatively	51.91±4.53	−1.80	0.092	52.25±5.57	−1.48	0.218
3. Social complaints						
Baseline	54.71±5.92			53.80±4.32		
3 months postoperatively	53.48±6.36	−1.01	0.451	50.44±0.53	−2.43	0.108
1 year postoperatively	52.00±3.40	−2.09	0.131	52.38±4.84	−1.62	0.304
4. Thought problems						
Baseline	56.07±6.96			52.30±3.50		
3 months postoperatively	56.33±10.59	−0.98	0.565	52.22±4.02	−0.17	0.929
1 year postoperatively	50.45±1.21	−4.42	**0.015**	53.00±8.08	0.64	0.750
5. Attention problems						
Baseline	55.21±6.96			53.20±5.53		
3 months postoperatively	52.92±5.25	−2.49	**0.016**	52.11±5.60	−0.49	0.673
1 year postoperatively	51.91±4.39	−2.89	**0.007**	52.38±4.41	−1.36	0.261
6. Intrusive behaviour						
Baseline	53.71±4.18			51.70±2.26		
3 months postoperatively	55.42±7.73	1.29	0.291	51.33±2.35	−0.26	0.850
1 year postoperatively	51.27±2.24	−2.15	0.087	50.75±1.39	−0.85	0.553
7. Aggressive behaviour						
Baseline	52.43±3.46			52.10±3.51		
3 months postoperatively	52.08±3.60	−0.22	0.772	51.22±2.05	−0.89	0.291
1 year postoperatively	50.45±0.69	−1.06	0.171	50.25±0.46	−0.59	0.069
8. Delinquent behaviour						
Baseline	52.14±3.18			52.30±5.40		
3 months postoperatively	53.25±8.66	−0.60	0.470	51.89±4.28	−0.47	0.613
1 year postoperatively	50.18±0.40	−1.48	0.084	50.25±0.71	−0.88	0.357

Subscale changes are presented as mean±SD. T-score changes from baseline to 3 months and 1 year are presented in descriptive statistics. Negative numbers postoperatively indicated improvement from baseline within each group.
**Numbers of patients were less in each treatment group because only children aged >11 years were included.
n (baseline), n (3 months) and n (1 year) are given for missing data at different time points.
*P value and changes were analysed using a linear-effects model.
Bold numbers are statistical significant changes.

at 1 year concerning the right ventriculo-arterial gradient and the NYHA class. A difference in patient-reported outcomes was found between the groups, a significant improvement in psychosocial endpoints was observed within the PPVI group at 3 months concerning Thought problems, and in subscale Attention problems at 3 months and 1 year after treatment. No such finding was observed either at 3 months or 1 year after treatment in the open surgery group. A significant association was also found between the right ventricle to pulmonary artery

gradient pressure and psychosocial function with respect to the Anxiety/Depression subscale at 3 months postoperatively in the PPVI group. Psychosocial function in patients with congenital heart disease may be attributed to numerous factors such as age, genetics and altered cerebral perfusion in utero.[15] Open heart surgery with extracorporeal circulation may add to these factors in challenging psychosocial function. This may explain why the patients treated by the percutaneous catheter technique experienced an improvement in psychosocial function, not seen in the surgical patients.[16] In a previous paper from the present study covering the economic effects of the herein-described treatment methods, we demonstrated that the mean length of hospital stay in the open surgery group was significantly longer than in the PPVI group.[23] This may have also affected the patients' reported experience.

Adults with complex congenital heart disease have an increased risk of cumulative challenges associated with significant morbidity and an increased risk of mortality when they reach the age of 50 years.[27] These patients have an increased risk of anxiety, depression and social cognition issues, resulting in challenges in educational attainment, employment and social and emotional issues.[16]

Surgery is a more comprehensive treatment than the percutaneous technique and therefore has higher physical and psychological risks. Dos *et al*[13] described arrhythmias, respiratory complications and renal dysfunction as the most common early postoperative events following surgery in older patients with multiple sternotomies at highest risk for prolonged hospitalisation.[13] Interventional techniques are evolving, and more patients are likely to be treated percutaneously in the future. This may impact long-term quality of life in these patients.

We previously reported positive patient experiences following PPVI. A short hospital stay, easy rehabilitation and rapid life normalisation were common positive experiences.[11] The patients may have adapted and changed expectations accordingly. A near-normal life expectancy[28] in later life may also become a challenging issue for these patients.

The self-reported NYHA classification of heart failure sustained significant at 1 year only in the PPVI group, indicating less symptoms and a rehabilitation in favour of the percutaneously treated patients.

The self-reported NYHA classification is not necessarily only related to the initial diagnosis but can also be related to the assessment of perceived health.[29] A significant correlation among heart function, the degree of pulmonary stenosis and psychosocial outcomes with respect to the Anxiety/Depression subscale was observed in favour of the percutaneous treatment at 3 months (p=0.038). This finding may indicate that the reduction in the right ventricle to pulmonary artery gradient pressure was a result of reductions in anxiety and depression after treatment.

This was not a randomised study, and the groups differed with respect to type of pulmonary valve lesion. Patients with predominantly valve stenosis were offered PPVI, while most patients in the surgery group had pulmonary regurgitation caused by mixed underlying diseases. Therefore, we cannot rule out the possibility that differences in diseases may have impacted the psychosocial outcomes.

CONCLUSION

Both methods led to significant clinical improvement. A significant reduction in thought and attention problems such as intrusive behaviour was observed in patients who underwent the percutaneous procedure. After adjusting for the right ventricle to pulmonary artery gradient pressure, the attention problems significantly decreased in the PPVI group. A significant improvement in the NYHA functional score was observed in both groups. Complications such as reintervention, bleeding and arrhythmia were only observed in the open heart surgery group.

Strengths and limitations of the study

This was a prospective study with follow-up data. Self-reporting contributes to a more comprehensive assessment, which is an advantage over the established objective measures of illness severity. We used a well-established and validated instrument to measure psychosocial function and self-reported data. Increasingly more studies are showing that the NYHA functional class is a complementary classification to the level of disease severity because it involves the self-reporting of symptoms defined by the patient.[29] Our findings should be interpreted cautiously. The most important limitation is the small sample size and missing data, which could have increased the probability of type 2 errors. Our study population, which mainly comprised teenagers, was probably influenced by the amount of missing data. This vulnerable patient population is asked to participate in considerable ongoing research, probably influencing the willingness to communicate or share experiences. Our population also exhibited large age differences. The instrument used to assess psychosocial function included only children aged >11 years, resulting in a response rate of 63% for the ASEBA scores.

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