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DISSERTATION

The Role of Subcoronary Implantation Technique in Children and Young Adults Undergoing Ross Operation

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ABBREVIATIONS

AoV: Aortic valve

AR: Aortic regurgitation

AS: Aortic stenosis

BSA: Body surface area

ECMO: Extracorporeal membrane oxygenation

EF: Ejection fraction

EFE: Endocardial fibro-elastosis

HLHS: Hypoplastic left heart syndrome

ICU: intensive care unit

IVS: Interventricular septum

IQR: interquartile range

LV/OT/O: Left ventricular outflow tract/ obstruction

MV: Mitral valve

NYHA: New York Heart Association

RV/OT/O: Right ventricular outflow tract/ obstruction

RV-PA: Right ventricle to pulmonary artery

STJ: Sino-tubular junction

ABSTRACT

Objectives: The aim of this work was to report our experience with the modified subcoronary autograft implantation in children and young adults and to furthermore discuss the outcomes and role of this technique in growing patients requiring Ross operation.

Methods: All patients who underwent modified subcoronary Ross/Ross-Konno operation at our institution were included. Early and late survival, morbidity, reinterventions, aortic valve function, and aortic root dimensions were observed in a retrospective manner.

Results: During the study interval from January 2013 to January 2019, a total of 50 patients received the modified subcoronary Ross/Ross-Konno operation. The median age at surgery was 6.3 years (interquartile range [IQR]: 1.4 - 13.6, 58% males), including ten infants (20%). During a median follow-up of 31.2 months (IQR: 14.4 - 51), there was one early and one late death with an overall survival at 5 years after surgery of 95%. The autograft had to be replaced in two patients, 11 and 15 months after their initial Ross operation. Freedoms from reoperation on the autograft and/or on the right ventricle to pulmonary artery conduit were 94% and 97% at 5 years, respectively. Freedom from aortic valve regurgitation > mild was 97% at 5 years. Aortic root diameters at all levels remained in normal ranges at last follow-up.

Conclusion: The modified subcoronary Ross/Ross-Konno operation in children and young adults showed excellent early and mid-term outcomes. Our modification of the autograft implantation technique proved to be reproducible. An even broader use of this technique in children might be advantageous in order to avoid situations when prosthetic supporting techniques are precluded due to somatic growth.

ZUSAMMENFASSUNG

Hintergrund: Das Ziel dieser Arbeit war es über unsere Erfahrungen mit der Modifikation der subkoronarer Implantation des Autograft bei Kindern und jungen Erwachsenen während einer Ross-Operation zu berichten. Weitergehend soll das Outcome sowie die Rolle dieser Modifikation in der Behandlung von Patienten während des körperlichen Wachstums soll diskutiert werden.

Methoden: In einer retrospektiven Studie an 50 von Januar 2013 bis Januar 2019 am Deutschen Herzzentrum Berlin konsekutiv mittels Ross/Ross-Konno-Operation in subkoronarer Modifikation behandelter Patienten, wurden die primären und sekundären Endpunkten wie Früh- und Spätmortalität, Morbidität, Reinterventionen, Funktion der Aortenklappe und der Dimensionen der Aortenwurzel analysiert.

Ergebnisse: Das mediane Alter bei der Operation betrug 6.3 Jahre (IQR: 1.4 – 13.6, 58% männlich), davon waren 10 Patienten in Säuglingsalter (20%). Innerhalb der medianen Beobachtungsdauer von 31.2 Monaten (IQR; 14.4-51) wurde bei frühem und spätem Todesereignis jeweils eines Patienten ein Gesamtüberleben von 95%, 5 Jahre nach der Operation beobachtet. Das Autograft musste bei zwei Patienten, 11 und 15 Monate nach initialer Ross-Operation ersetzt werden. Die Freiheiten von Reoperation am Autograft und am rechtventrikulären Ausflusstrakt waren 94% beziehungsweise 97%, nach 5 Jahren. Die Freiheit von einer mehr als milden Aortenklappeninsuffizienz betrug 97% nach 5 Jahren. Die Diameter der Aortenwurzel blieben bei der letzten Kontrolle auf allen Ebenen innerhalb der Normwerte stabil.

Schlussfolgerung: Die modifizierte subkoronare Ross/Ross-Konno-Operation bei Kindern und jungen Erwachsenen zeigte exzellente früh- und mittelfristige Ergebnisse.

Die vorgestellte Modifikation der Implantationstechnik des Autografts ist technisch reproduzierbar. Eine Ausweitung der Anwendung dieser im Erwachsenenalter validierten Technik auf das Kindesalter, könnte gerade in Hinblick auf die Erhaltung des Wachstumspotentials vorteilhaft sein.

SYNOPSIS

1. INTRODUCTION

1.1. Congenital aortic valve disease

In general, aortic valve (AoV) disease represents the most common valvular heart disease in the European population [1]. The disease is present across all ages; congenital lesions are present in the majority in children whereas degenerative valve disease is far more common in the adult population [1]. However, the coincidence of congenitally malformed dysfunctional AoVs and the early onset of degenerative changes of these valves can be observed. Congenital aortic valve stenosis (AS) can be found in approximately 3-6% of all congenital heart defects and is 3-times more frequent than aortic regurgitation [2][3]. Detailed understanding of the valve pathology and the mode of dysfunction are guiding the multimodal treatment options and timing [4]. Life-long reinterventions are common, leaving even the valve replacement with its limitations as a suboptimal temporary solution [5].

1.1.1. Aortic stenosis

1.1.1.1. Critical aortic stenosis of the neonate

Severe dysplasia of the aortic leaflets and/or hypoplasia of the aortic annulus lead to an increasing afterload for the left ventricle (LV). Patients with critical stenosis are developing signs of low-cardiac-output syndrome due to failure of the LV to provide adequate body perfusion. Without the contribution of the right ventricle (RV) to the systemic perfusion, via a patent arterial duct, inotropic support and subsequent surgical or catheter-based valvotomy, these neonates are at acute risk of severe multi-organ dysfunction and death. On the extreme end of the spectrum of the

disease, critical aortic stenosis can be associated with LV hypoplasia and/or obstruction of the left heart outflow (LVOTO) including a hypoplastic aortic arch and the hypoplastic left heart syndrome (HLHS) [6].

1.1.1.2. Aortic stenosis in older children and young adults

Less severe forms of AoV dysplasia with normal to borderline dimensions of the left heart structures are usually clinically well tolerated until the severity of the stenosis and/or the dysfunction of the LV become hemodynamically relevant. This can be usually diagnosed due to failure to thrive, syncopal episodes, systolic murmur, signs of LV hypertrophy and/or arrhythmia [7]. In adults, bicuspid aortic valve is frequently associated with the need for surgical or catheter-based interventions due to residual stenosis or regurgitation [8].

1.1.2. Aortic regurgitation

1.1.2.1. Primary aortic valve regurgitation

Native aortic regurgitation (AR) in the setting of a tricuspid AoV is a rare manifestation of AoV disease. Far more frequently AR is found in bicuspid AoVs, a combination of dysplastic leaflets, fused commissures or secondary changes due to high regurgitant volume are leading to development and progression of the disease [9]. Regurgitation of a quadricuspid AoV is not an uncommon problem [10].

1.1.2.2. Secondary aortic valve regurgitation

Secondary AR is usually caused by a combination of a congenital cardiac malformation and/or secondary changes due to an intervention or ongoing dysfunction. AR following a balloon dilatation for a stenotic AoV can be observed in 10-40% patients early after the intervention and during late follow-up [11]. Other

reasons for AR include: associated ventricular septal defect, subaortic stenosis, aortic root dilatation, sinus of Valsalva aneurysm/fistula or secondary scarring and valve destruction due to bacterial endocarditis or rheumatic changes [12].

1.2. Surgical anatomy of the aortic root

1.2.1. Normal anatomy

The aortic root connects the left ventricular outflow tract (LVOT) to the ascending aorta through the tricuspid aortic valve. The aortic leaflets are connected to ascending aorta at the level of the sino-tubular junction on one side, and to the fibrous skeleton of the heart and muscular outflow tract on the other side. The aortic root formed by the sinuses of Valsalva, the annulus and the aortic leaflets, is wedged inside the fibrous skeleton between the mitral and tricuspid valves posteriorly and the pulmonary valve anteriorly [13][14]. Although even in a normal AoV a slight interindividual difference in size and shape of the leaflets exists, a constant relationship between height and length at the free edges and at the attachments of the leaflets to the annulus are always preserved. The identical coapting surfaces of adjacent leaflets are mandatory for the competence of the valve [13].

1.2.2. Malformations of the aortic valve

1.2.2.1. Unicuspid aortic valve

An unicuspid AoV is characterized by congenitally fused dysplastic valvular tissue, which is functioning as one single leaflet with one or a non-developed commissure (unicommissural/non-commissural arrangement). The opening orifice is resembling an exclamation point of at least two fused commissures with an obtuse angle between fused leaflets at the commissure, an absent cleavage plane between

leaflets at the fusion point, and a raphe present at fused commissures [15]. The belly of the leaflets is poorly if developed. Combined AS and AR is the most common mode of dysfunction. In the general population, the occurrence of a unicuspid AoV is rare, in series of surgically explanted aortic valves the incidence reaches 5 % [16].

1.2.2.2. Bicuspid aortic valve

A bicuspid AoV can be found in 1-2 % of specimens examined by autopsy [14][17].The valve leaflets are often fused with one or more raphes. Depending on the symmetry of the leaflets and the geometry of the fusion, the valve orifice can be central or eccentric, with anterior-posterior or left-right configurations [13][18]. Similarly, to unicuspid valves, leaflets in bicuspid valve can develop both stenosis and regurgitation due to restriction or prolapse and/or severe calcification predominantly at the region of the raphe. Dilatation of the aorta due to an accompanying aortopathy is often described in patients with bicuspid valves. The progression of the aortic dilatation can be independent from the severity of the valve dysfunction [19].

1.3. Therapy

In children with congenital AoV disease, treatment is indicated if severe AS/AR, reduced LV function and/or relevant symptoms are present [4][20]. In adults with congenital heart disease, the indication criteria are modified according to the current guidelines of treatment of AoV disease in adults [21][22][23]. The intention to treat is to relieve the pressure and/or volume overload of the LV to prevent impairment of the systolic and diastolic left ventricular function and to prevent or reduce symptoms.

1.3.1. Medical therapy

Medical therapy in AS is not curative, but can be supportive for symptomatic patients, i.e. to stabilize the LV function or to improve the general patient's condition prior to intervention or surgery. In AR, medical therapy for afterload reduction can be carefully employed in selected patients. Endocarditis prophylaxis is mandatory in patients with implanted prosthetic materials and/or residual lesions after surgical or catheter-based intervention and in rheumatic valvular disease [24].

1.3.2. Balloon valvuloplasty

Balloon dilatation (valvuloplasty) can be effectively employed in the therapy of congenital AS. In many centers, critically ill neonates with severe LV dysfunction are predominantly treated by balloon dilatation as primary palliative procedure to postpone the surgery. Outside the neonatal period, for selected patients, satisfying results in terms of lowering the pressure gradient and reduction of the number of reoperations can be achieved [25][26]. In combined lesions with moderate AR balloon dilatation is contraindicated due to high risk of acute aggravation of the regurgitation [27]. Technically successful in utero valvuloplasty for aortic stenosis has been reported by experienced groups with promising effects on postnatal biventricular outcome [28].

1.3.3. Surgical strategies

In the multidisciplinary, life-long management of patients with aortic valve disease, the accurate timing, choice and execution of surgical treatment modalities play a tremendous role. Any surgical strategy in congenital AoV disease carries the burden of palliative procedure. Nevertheless, especially in growing patients, the primary attempt to relieve the AoV disease should be valve repair even at the cost of a

potentially suboptimal reconstructive result. As long as the LV function is well preserved and monitored, the definitive replacement can be usually postponed. The early and long-term prognosis is depending on different factors such as valve morphology, the mode of dysfunction, age at presentation, comorbidities, and the applied center-/operator-specific surgical technique [29].

1.3.3.1. Aortic valve repair

Valvotomy of the AoV uses the principle of dividing the fused commissures and thinning/shaving of the thickened leaflets under direct vision during a surgery on cardio-pulmonary bypass. In a normal-sized aortic annulus with tricuspid leaflet arrangement without the need for leaflet extensions, excellent early and long-term results can be achieved [30][31][32][33]. Complex repair techniques utilizing autologous or xenogeneic patch material for recreation of valve leaflets in order to create a bicuspid or tricuspid leaflet arrangement have shown excellent early results in terms of valve function and in postponing the valve replacement. However, compared to valvotomy, the long-term results are mixed [34][35]. Even if AoV replacement is inevitable, i.e. Ross operation, individualized staged approach utilizing subsequent surgical valvotomy during the growing age, consistent monitoring of the residuals and the preservation of optimal systolic and diastolic LV function shows promising results [36].

1.3.3.2. Aortic valve replacement

1.3.3.2.1. Prosthetic valve replacement

Valve replacement using *mechanical* prosthesis plays only a minor role in children and adolescents due to its lack of growth potential resulting in an increasing patient-prosthesis mismatch requiring repeated reoperations. An adult-sized prosthesis can

be implanted in very rare cases due to predominantly small aortic annulus in children. Another significant limitation is the life-long anticoagulation medication with significant implications for the quality of life and ongoing risk of thrombo-embolism and bleeding [37][38].

Xenogeneic *biological* prothesis found a restricted use because of similar limitations with regard to patient-prosthesis mismatch, at least temporarily required anticoagulation and reoccurring reoperations/reinterventions due to rapid degeneration of the leaflets, and pannus formation [39].

1.3.3.2.2. Homograft valve replacement

The use of *cryopreserved* aortic homograft is currently restricted to special indications such as bacterial endocarditis of the aortic valve or for patients who are not considered for Ross operation and/or with contraindication for anticoagulation medication. The drawback of these implants is certainly the limited availability and the high reoperation rate due to failure and calcification especially in growing patients. The newly introduced *fresh decellularized* aortic homograft implanted in children and young adults shows encouraging early results [40][41].

1.3.3.2.3. Aortic neocuspidalization (Ozaki operation)

This technique involves the replacement of all aortic leaflets by custom-made leaflets manufactured from autologous or xenogeneic pericardium using pre-defined templates. After sizing of the aortic annulus, the fitting templates are used to trim the leaflets and a standardized implantation technique is used to recreate a tricuspid aortic valve [42]. The extensive experience in adult patients with adequate sized-annulus shows excellent mid-term results, however, the rationale for the use of this

technique in children and patients with limited annular size must be further investigate [43][44][45].

1.3.3.2.4. Ross operation

The Ross operation offers the unique opportunity to replace the aortic valve by the autologous pulmonary valve (autograft) and therefore preserving the growth potential of the valve and preventing the need of anticoagulation. The operation can be performed at any age and can be combined with a resection of the LVOTO and/or enlargement of the hypoplastic aortic annulus by Konno incision (aorto-ventriculoplasty) if necessary [46]. The potential drawbacks of Ross operation are technical complexity of the procedure and the double-valve involvement; the autologous pulmonary valve has to be replaced simultaneously by either a biological prosthesis (heterograft) or a homograft if available. Risk factors such as bicuspid aortic valve and/or connective tissue disorders, pure aortic regurgitation, age at operation and most probably the surgical technique of implantation of the autograft place the neo-aortic root at risk for late dilatation and failure [47][48]. Reinterventions on the RVOT are inevitable and not surprisingly the younger patients with smaller implanted valves are at higher risk [49]. The originally suggested *subcoronary* technique has been mostly abandoned due to its technical difficulty. In this modification, historically resembling the homograft aortic root replacement, the autograft is scalloped and implanted directly inside the native aortic root without excision and reimplantation of the coronary arteries. The external support by the native aortic tissue is preserved [50]. The most frequently used technique nowadays is the *free-root replacement* autograft implantation. In this case, the autograft is implanted as free-standing root, the coronary arteries are first excised from their origin in the native aorta, then the autograft is implanted as free-standing cylinder inside the aortic annulus. Subsequently, the coronary arteries are reimplanted and the autograft is anastomosed to the ascending aorta. This modification is technically

feasible, however, the autograft tissue lacks external support to withstand the systemic pressure load in the aortic position [51]. In adults, external prosthetic support called “root wrapping” can be used to protect the autograft; the autograft is first implanted inside a prosthetic tube-graft, such prepared autograft is then implanted as root replacement, followed by coronary reimplantation and aortic anastomosis [52].

1.4. Subcoronary Ross operation in children and young adults: rationale and hypothesis

Aortic root dilation and progressive autograft regurgitation leading to a significant reoperation rate, typically in the 2nd decade after the operation, constitute well-known limitations of unsupported *root replacement* autograft implantation both in children and adults [53][54]. Long-term result from pediatric series show, that especially older children and adolescents seem to be at higher risk [55]. External prosthetic supporting techniques may reduce these complications but are prone to hinder the growth of the aortic root and are therefore generally avoided in childhood [56]. In adults, these discouraging results have led some groups to re-introduce several supporting techniques, utilizing the autologous support of the native aortic tissue [57]. The originally suggested *subcoronary* autograft implantation technique showed excellent results, however, the feasibility and performance of this technique in patients with congenital aortic valve disease during growth remain unclear [58]. The major limitation for its use in this population seem to be the frequent mismatch between the autograft and the aortic annulus dimensions in congenital cohorts. We have introduced a modified *subcoronary* implantation technique in children and young adults to prove our concept of preventing late autograft failure. In addition to the original *subcoronary* technique, in cases of extremely mismatched aortic and

pulmonary valves, Konno incision was employed to enable the implantation or to better address the accompanying LVOTO and/or endocardial fibro-elastosis (EFE) [59]. The early results were promising, and this technique was adopted as preferable for Ross or Ross-Konno operation in our institution [60].

The hypothesis of this work was: The *subcoronary* implantation is a feasible and safe technique for Ross operation in children and young adults with congenital aortic valve lesions.

2. MATERIALS AND METHODS

2.1. Study design

A single-center, retrospective, non-controlled study was conducted. After institutional review board approval (EA2/080/20), informed consent for data analysis was obtained.

2.2. Patient population and baseline characteristics

Between January 2013 and January 2019, Ross/Ross-Konno operation was performed in a total of 84 patients at our institution. Out of these, *the subcoronary* modification was used in 50 patients (59%), who represent the substrate of this study. Baseline characteristics of these patients are shown in ***Table 1***. The median age at the time of the surgery was 6.3 years (IQR: 1.4 – 13.6). The study included ten infants (20%) and four neonates (8%).

2.3. Study endpoints

Primary study endpoints were death and AoV reoperation. Secondary outcome measures were AoV function, aortic dimensions, and RVOT reinterventions. In addition, the pressure gradient through the LVOT and the RVOT/conduit, LV function, major postoperative complications and the patient´s functional outcome were analyzed.

2.4. Clinical assessment

For all patients, preoperative and postoperative data were available. Medical records including pre- and postoperative clinical and echocardiographic assessment, surgical notes as well as outpatient reports were reviewed.

2.5. Echocardiographic analysis

Two independent investigators reviewed the echocardiographic data at our institution if imaging data were available. Otherwise, the outpatient reports were analyzed accordingly. The focus of these investigations was both the LV/RVOT as well as the AoV itself. The simplified Bernoulli equation was used to estimate the peak pressure gradient across the AoV [61]. Because of the use of Konno incision and the enlargement of the aortic annulus with patch material, we aimed to rule out any sort of aneurysm formation within the outflow tracts, and/or the occurrence of new aortic root distortion. The semi-quantitative method was used to evaluate grade of AR [62]. The aortic root dimensions were assessed preoperatively, postoperatively and at the last follow-up. Diameters at level of the annulus, the sinus of Valsalva, the sino-tubular junction (STJ), and the ascending aorta in long-axis view were measured [63]. The absolute dimensions were standardized to body surface area (BSA) and expressed in Z-scores [64]. Important increase in dimensions at any level was considered relevant if the Z-score exceeded > 2.

2.6. Surgical technique

We have introduced the surgical technique of modified *subcoronary* autograft implantation in children [59]. Since then, standardized technical steps were followed by three senior staff surgeons. The details of the currently used technique are illustrated by ***Figures 1-3***. For optimal exposure of the aortic root, aorta is opened using an inverted hockey-stick incision deep into the non-coronary sinus. Alternatively, complete transection of the aorta above the sino-tubular junction can be performed. The aortic leaflets are excised completely leaving only minimal tissue at

the original hinge-points. The coronary artery buttons are left in place within the native aortic root. The autograft can be harvested on beating heart to reduce myocardial ischemia time in case of good visualization. In young adults, however, we prefer to excise the autograft on arrested heart. It is of utmost importance to trim the autograft in a scalloped fashion; the subvalvular muscular skirt should not exceed 3-5 mm ***(Figure 1).*** In case of significant size-mismatch of the autograft and the aortic annulus (i.e. at least 5 mm difference in diameter), a Konno incision is performed between the left-right commissure of the native aortic valve. The incision is guided towards the RVOT, the portion of the interventricular septum at safe distance from conduction tissue. For enlargement of the Konno incision a pericardial patch of trapezoid shape is secured to the right side of the septum. If the aortic root is extremely hypoplastic, the non-coronary sinus can be enlarged by a second patch to maintain optimal geometry and function of the autograft. The autograft can be oriented with only minimal rotation, similar to the root replacement technique, with remnant of the infundibular muscle (i.e. non-facing sinus) towards the Konno incision. Alternatively, the autograft can be rotated by 180°, with one commissure anteriorly towards the Konno incision ***(Figure 2).*** For the implantation of the autograft two separate suture lines are used. The first (proximal) suture line runs at the subannular/annular level to secure the muscular skirt of the autograft inside the aortic annulus. The autograft sinuses are scalloped, leaving only 3-5 mm of tissue above the hinge-points and commissures. The second (distal) suture line is running truly at subcoronary level. Starting in the left coronary sinus at the most remote point. The non-coronary sinus is the last to be completed ***(Figures 1,2).***

If the use of pericardial patches can´t be avoided, the upper rim is cut sharp to meet at the sino-tubular junction and match the normal diameter of the ascending aorta

(Figure 3). For reconstruction of the RVOT a RV-PA conduit (biological valve or homograft) is implanted on beating heart in standard fashion.

2.7. Statistical analysis

Statistical analysis was performed by the author and by V. Weixler, MD, who also co-authored the referenced publication. GraphPad Prism software version 8.0.1 (GraphPad Software, Inc., San Diego, CA, USA) was used to create survival and event-free curves using Kaplan-Meier time-to-event models. P-values < 0.05 were considered statistically significant. Baseline characteristics, early and follow-up measures were presented as median with IQR for continuous variables and as frequency (%) of patients for categorical data.

3. RESULTS

3.1. Procedural characteristics

In the studied interval, the *subcoronary* implantation was used in combination with Konno incision in 42 cases (84%). The reason for the enlargement of the aortic root was a concomitant LVOTO and/or annular hypoplasia in 24 patients (48%). Limited Konno incision was performed in 18 patients, due to significant mismatch between the aortic and pulmonary annular dimensions to enable *subcoronary* implantation of the autograft. In case of Konno incision, to achieve an outflow tract diameter that was approximately 5 mm larger than normal-sized aortic annulus, the aortic annulus/LVOT was augmented with at least one patch of autologous pericardium in 33 cases (66%). To not jeopardize the geometry of the aortic root, an additional patch for the non-coronary sinus was used in 17 cases (34%). For RVOT reconstruction,

homograft (cryopreserved or decellularized – Espoir®, Corlife oHG, Hannover, Germany) or bovine jugular vein conduit (Contegra®, Medtronic Inc., Minneapolis, MN, USA) were used in the majority of cases (94%). The median conduit diameter was of 18 mm (IQR: 16 - 22 mm). A number of concomitant procedures was performed in 32 patients, including: LVOT/EFE resection (n=10), replacement of ascending aorta (n=9), mitral valve (MV) repair (n=4), aortic arch repair (n=2), and MV replacement (n=1) ***(Table 2).***

3.2. Early Postoperative Outcome

3.2.1. Survival

There was one death (2%) during the early postoperative period. This neonate was born with hypoplastic left heart complex, hypoplastic aortic arch and Turner syndrome, required Ross-Konno operation combined with aortic arch repair. Due to severely impaired LV function and low-cardiac-output, extracorporeal membrane oxygenation (ECMO) support was necessary directly after the operation. After 14 days on ECMO, weaning failed and the patient died due to multi-organ failure.

3.2.2. Clinical assessment

The clinical outcome was assessed based on review of the postoperative period and incidence of major complications such as unplanned reoperation, neurological deficit at discharge, permanent pacemaker implantation, acute kidney injury requiring dialysis and others [65]. The median duration of postoperative mechanical ventilation, intensive care unit (ICU) and total hospital stay were 17.8 hours, 1 and 7 days, respectively. Major postoperative complications occurred in five patients. Permanent pacemaker implantation was required in three patients with complete atrioventricular block following an extensive LVOT resection. One pericardial drainage of

hemorrhagic effusion and one chest re-opening due to low cardiac output syndrome were classified as unplanned reoperations. Anti-arrhythmic medication was necessary in two patients at discharge.

3.2.3. Echocardiographic analysis

Grade of AR at discharge was none-to-mild in 46 patients (93.8%) and moderate in three (6.2%). There was no severe AR detected. The dimensions of the aortic root and ascending aorta were assessed in the entire cohort and showed median AoV annulus Z-score of -0.4 (IQR: -1.9 to 0.9), median Sinus of Valsalva Z-score of -0.7 (IQR: -1.5 to 0.4), median STJ Z-score of 0.2 (IQR: -0.8 to 0.8), and median ascending aorta Z-score of 0.1 (IQR: -1.1 to 1.5). There was no relevant LVOTO detected; peak pressure gradients across the LVOT and/or AoV were below 10 mmHg in all patients. All peak pressure gradients across the RVOT and/or the RV-PA conduits were < 20 mmHg (median 7 mmHg, IQR: 3.6 - 11.6 mmHg). No unfavorable effects such as LVOTO/RVOTO or septal aneurysmal formation were found when a patch was used in the Konno incision. MV regurgitation was minimal (n=1), mild (n=2) and moderate (n=1) with no stenosis in four patients, who underwent concomitant MV repair. Nine (18.3%) patients showed mildly to moderately reduced LV systolic function (ejection fraction, EF: 30 - 50%). Early postoperative outcome measures are summarized in ***Table 3***.

3.3. Follow-up

3.3.1. Survival

The median follow-up duration was 31.2 months (IQR: 14.4 - 51 months). One infant with combined AoV and MV lesions died late during the follow-up period. In this patient, aortic balloon valvuloplasty on day 3 of life resulted in reduction of the stenosis, however, urgent neonatal Ross-Konno operation and MV repair were necessary in the first week of life due to severe AR and reduced LV function. The postoperative recovery was complicated due to recurrent MV incompetence and severely impaired LV function. Subsequently, successful hybrid MV replacement by a custom-made stented bio-prosthesis was performed. The patient was discharged home with a satisfying initial surgical result concerning the LVOT and LV inflow, however elevated RV pressure as a consequence of postcapillary pulmonary hypertension pursued. Several months after discharge, the patient died of unknown cause. With respect to one early and one late death the overall survival at 5-years was 95.8% (95% CI: 84.3 - 98.9) (***Figure 4***).

3.3.2. Clinical assessment

According to New York Heart Association (NYHA) functional classification; 44 patients (96%) were in Class I, 2 patients were still in NYHA Class II, 26 and 47 months postoperatively. Valve-related events such as thromboembolism or bleeding were not observed. There were no signs of infective endocarditis neither on the autograft nor on the RV-PA conduit. Several patients were on medication; one patient was still receiving a ß-receptor antagonist for intermittent supraventricular arrhythmia. The three early implanted patients were still dependent on permanent pacemaker. The remaining patients were in stable sinus rhythm.

3.3.3. Echocardiographic analysis

The analysis of available data from the last echocardiography revealed that no

patient had AR greater than moderate. In one patient (2%), AR was greater than mild. Based on these finding, the freedom from AR greater than mild for the entire study period was estimated 97.4% (95% CI: 82.8 - 98.7) at 5 years (***Figure 4***). There was no significant aortic root dilatation observed, which could be documented by Z-scores for aortic annulus, sinus of Valsalva, STJ and ascending aorta. Their respective median values at all levels were in normal ranges; did not exceed -2.0 to 2.0 Z-score (aortic annulus: 1.5 [IQR: 0.1 - 2.7], sinus of Valsalva: 0.6 [IQR: 0 - 2.3], STJ: 0.7 [IQR: 0 - 1.4], and ascending aorta: 0.8 [IQR: 0 - 2]). Peak pressure gradient across the LVOT and/or AoV was lower than 10 mmHg in all patients. Neither distortion nor asymmetry of the aortic root or signs of aneurysm formation in the LVOT were detected. The median peak pressure gradient through the RVOT was 20 mmHg (IQR: 11 - 32mmHg). In the three patients, who received simultaneous MV repair and survived until follow-up, MV regurgitation grade was unchanged. LV systolic function was still mildly to moderately reduced in three patients. The echocardiographic follow-up data are summarized by ***Table 4***.

3.4. Reinterventions

3.4.1. Autograft

The autograft had to be re-operated in two patients, 11 and 15 months after the Ross operation, respectively. The indication for reoperation was severe AR due to cusp prolapse, although, the aortic root dimensions remained in normal range in both cases at the time of the redo-surgery. The autograft could not be repaired; both patients required a mechanical valve replacement by an adult-sized prosthesis. At the initial operation, both patients were considered as suboptimal Ross candidates, but due to a strong patient wish to avoid prosthetic valve replacement, the patients were offered the *subcoronary* modification. The risk factors for autograft failure were

initial severe AR, bicuspid AoV and aneurysm of the ascending aorta (Z-score: +7.9 and +2.3) in both. Due to enlarged aortic annulus, both patients received a pure Ross operation without the need for the Konno incision. In one patient, the annulus was downsized using an additional circular annuloplasty suture. These results are reflected by the freedom from autograft reoperation of 94.9% (95% CI: 81.1 - 98.7) at 5 years ***(Figure 4)***.

3.4.2. RV-PA conduit

Subvalvular muscular stenosis and early degeneration of a 16 mm bovine jugular vein conduit was the reason for RV-PA conduit reoperation 12 months after initial Ross operation in one patient. There were another five catheter-based reinterventions carried out, including two percutaneous homograft replacements (MelodyValve® - Medtronic Inc.) 14 and 23 months postoperatively. The freedom from RV-PA conduit reoperation was 97.4% (95% CI: 83.1 - 99.6) at 5 years ***(Figure 4)***, the freedom from RV-PA conduit reoperation/reintervention was 83.3% (95% CI: 66.1-92.3).

3.4.3. Mitral valve

Three out four patients who received a concomitant MV repair had no further MV reinterventions during follow-up. In one patient, subsequently a hybrid custom-made MV replacement was needed in the early postoperative course. Even though the patient unfortunately deceased of unknown cause, at last follow-up, 10 months after implantation, the valve showed acceptable function.

4. DISCUSSION

The aim of this work was to evaluate the role of the newly introduced modified *subcoronary* implantation technique for Ross operation in children and young adults. The rationale for the use of this technique in growing patients was the well-known risk of aortic root dilation after Ross operation using the root replacement technique and its possible impact on the development of late AR with autograft failure [66][67][68]. To avoid these serious drawbacks in long-term, various technical modifications to stabilize the aortic root were implemented in adults with satisfactory early and late results [69][70][71]. The use of prosthetic materials to support the autograft prerequisites adult-sized aortic dimensions. However, in children applied replacement techniques have to ensure adequate growth potential and simultaneously avoid extensive root dilation during a long period of adult life. The use of *subcoronary* modification is frequently avoided due to its limited technical versatility in a hypoplastic annulus, which is at the same time frequently associated with congenital aortic valve disease as demonstrated by the baseline characteristics of the studied cohort. An optimal solution for this controversy is lacking as yet [72][73][74]. In our recent experience, adding the Konno incision to the described technique of *subcoronary* autograft implantation, while preserving the rest of the native aortic root, offered a novel option of autologous support with native aortic tissue. In our hands, this was applicable to a wide age range of patients with congenital aortic valve disease, who were typically at high risk of autograft failure if the standard technique would be used. Our technique also addresses severe LVOTO, which is frequently associated with significant mismatch between the size of aortic annulus and pulmonary autograft. As a potential drawback, the frequent use of a Konno incision in this specific cohort of patients can be discussed, as patients

undergoing the Ross-Konno operation might be at higher risk of complications such as complete atrioventricular block and/or left ventricular dysfunction. However, in our series there were no technical or functional disadvantages of this approach within the studied period. The potential complications, were not more frequently observed in our series compared to others, using the root replacement technique [46][75]. Higher incidence of complications after Ross-Konno operation is probably more linked to the specific patient cohort in which the technique is usually used (i.e., infants with multilevel LVOTO and borderline LV dimensions) than to the use of the Konno incision itself in a different patient cohort. Another disadvantage of our technique could be the risk of potential distortion of the geometry of the aortic root because of the use of pericardial patches for enlargement of the annulus. Enlargement of the aortic sinus and/or annulus by patch material is a routine procedure for a number of indications and so far, we did not observe any distortion of the aortic root or of the outflow tracts, which could be related to the augmentation of the aortic root. Dilatation of the aortic root is another major concern in the long-term after any Ross operation. Although it is usually rather observed late, in our initial experience reported in this work, the aortic root diameters were stable during the follow-up period, which showed at least equivalent initial performance to the standard techniques. With respect to the autograft function; in all but two patients it was excellent. The failure of the autograft in these two cases might be explained by suboptimal patient selection and minor technical imperfections early in our experience with this new technique. As observed in adults, the *subcoronary* or inclusion techniques seem to protect the autograft from late dilation but do not completely prevent the occurrence of leaflet prolapse [76]. Although the described technique proved to stabilize the aortic annulus, well described risk factors such as preoperative bicuspid aortic valve regurgitation and severe dilation of the aortic root cannot be neglected. Looking closely at the

postoperative outcome, the morbidity was substantial, illustrating the complexity of the lesions especially in the infant subgroup [77]. Survival was nevertheless promising. The brief analysis of the durability of RV-PA conduits revealed comparable results as for other Ross/Ross-Konno techniques [49]. This limitation of any type of Ross operation in general might be eventually attenuated by the growing clinical experience with the use of fresh decellularized homograft in the pulmonary position [78]. We have aimed to prove the safety and reproducibility of our novel approach especially in the pediatric patient population. Our encouraging initial experience described in this work makes us and others look at future long-term studies of this cohort with hope. Whether or not, the expected positive effect on the durability of the autograft function in the long run can outweigh the potential risks of our modification remains to be investigated. There are several reasons to support this hypothesis. Among others above stated, the avoidance of coronary transfer seems to eliminate the risk of coronary artery related complications, moreover, if any valve-sparing reoperation is needed, mobilization of the coronary buttons should be facilitated by less scar formation. In spite of the frequently seen inevitable autograft reoperations after Ross operation in children and young adults, we believe that a standardized surgical protocol and careful patient selection proved our concept to be safe and reproducible. In particular, for surgeons used to perform Ross/Ross-Konno operation, our modification could become an important tool in their surgical armamentarium [79].

Limitations

The heterogeneity of the congenital cohort may have had an influence on the patient selection, timing of the procedure and outcome of this cohort as both the standard and the novel techniques were used in the parallel setting for a limited time-period

during the observed study interval. To assess the dilatation of the aortic root in a longitudinal fashion, further analysis e.g. progression of Z-scores using regression models would be appropriate, however, it was not performed due to a small sample size and limited follow-up period. Finally, the limited number of patients and short follow-up period precluding any robust statistical analysis are well-known limitations.

5. CONCLUSION

The current analysis proved the hypothesis of this work that the *subcoronary* implantation with or without the use of Konno incision is a feasible and safe technique for Ross operation in children and young adults with congenital aortic valve lesions. Especially in children during growth in whom prosthetic supporting techniques are precluded, the described modification may have an advantage over an unsupported autograft. Our modification proved to be applicable to a wide age range of patients with congenital AoV disease with or without LVOTO. Our initial results reported by this study indicate optimal autograft function, stable aortic root dimensions and no specific complications of this approach. It remains a challenge for our future proceedings to identify and prove the superior durability of the autograft in the long run.

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7. FIGURES

Figure 1: Trimming of the autograft leaving only 3-5 mm rim **(A)**. Operative view of the trimmed autograft (right ventricular aspect) **(B)**. Autograft is seated into the native aortic annulus **(C)**. Both proximal and distal suture lines are depicted schematically **(D)**.

(reproduced with permission from [60]).

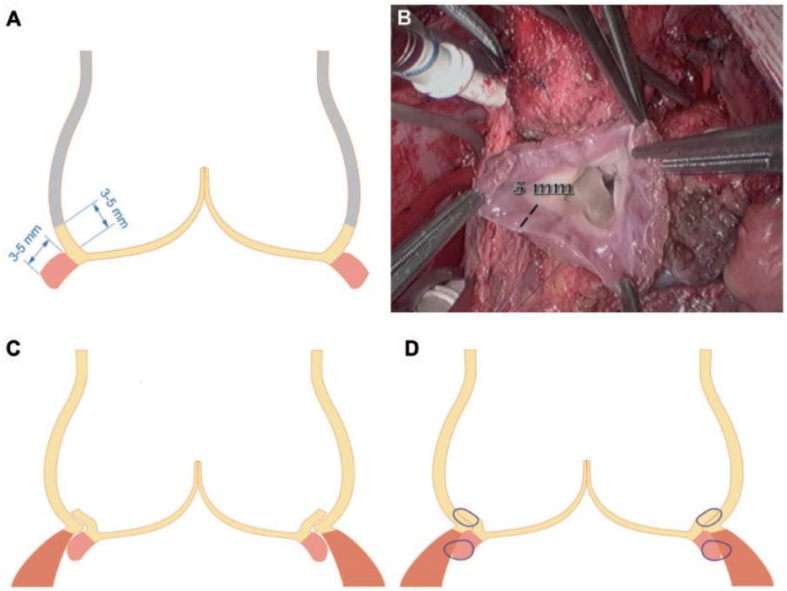

Figure 1: Trimming of the autograft leaving only a 3–5 mm rim (**A**). Operative view of the trimmed autograft (right ventricular aspect) (**B**). Autograft is seated into the native aortic annulus (**C**). Both proximal and distal suture lines are depicted schematically (**D**).

Figure 1: Trimming of the autograft leaving only a 3-5mm rim

Figure 2: Enlargement of the aortic annulus by pericardial patches (**A**: schematic and **B**: operative view, both from surgeon´s perspective). Two alternative options of the autograft orientation (**C, D**: schematic view from surgeon´s perspective). *LCA: left coronary artery, LVOT: left ventricular outflow tract, NCS: non-coronary sinus, RCA: right coronary artery.* (reproduced with permission from [60]).

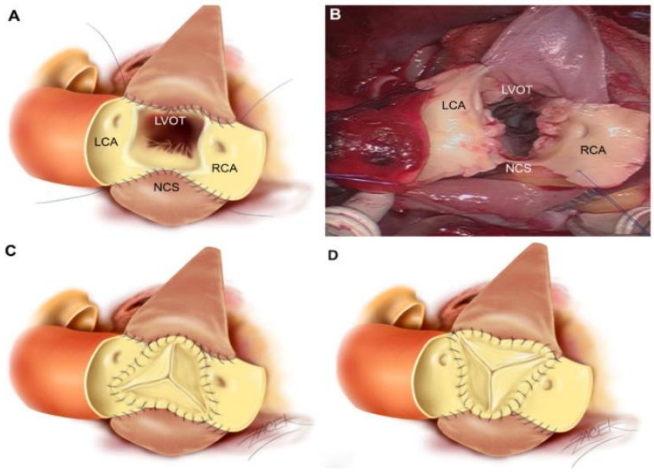

Figure 2: Enlargement of the aortic annulus by pericardial patches [(**A**) schematic and (**B**) operative view, both from surgeon's perspective]. Two alternative options of the autograft orientation [(**C** and **D**) schematic view from a surgeon's perspective]. LCA: left coronary artery; LVOT: left ventricular outflow tract; NCS: non-coronary sinus; RCA: right coronary artery.

Figure 2: Enlargement of the aortic annulus by pericardial patches

Figure 3: Final result after closure of the native aortic root (**A** - schematic and **B** - operative view). *Ao asc: aorta ascendens, RCA: right coronary artery, RVOT: right ventricular outflow tract, STJ: sino-tubular junction.* (reproduced with permission from [60]).

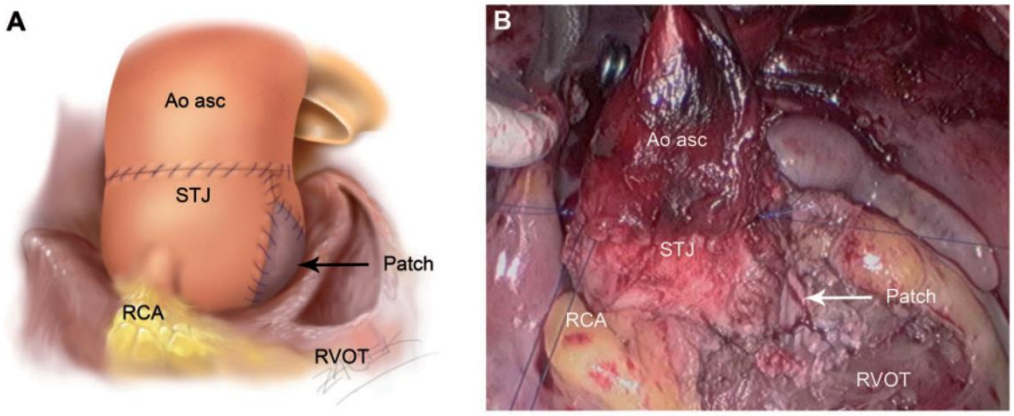

Figure 3: Final result after closure of the native aortic root [(**A**) schematic and (**B**) operative view]. Ao asc: aorta ascendens; RCA: right coronary artery; RVOT: right ventricular outflow tract; STJ: sinotubular junction.

Figure 3: Final result after closure of the native aortic root

Figure 4: Overall survival at 5 years **(A),** Freedom from aortic regurgitation greater than mild at 5 years **(B),** Freedom from autograft reoperation **(C)**, Freedom from RV-PA conduit reoperation **(D)**, both at 5 years of follow-up. *AoV: aortic valve, RV-PA: right ventricle to pulmonary artery.* (reproduced with permission from [60]).

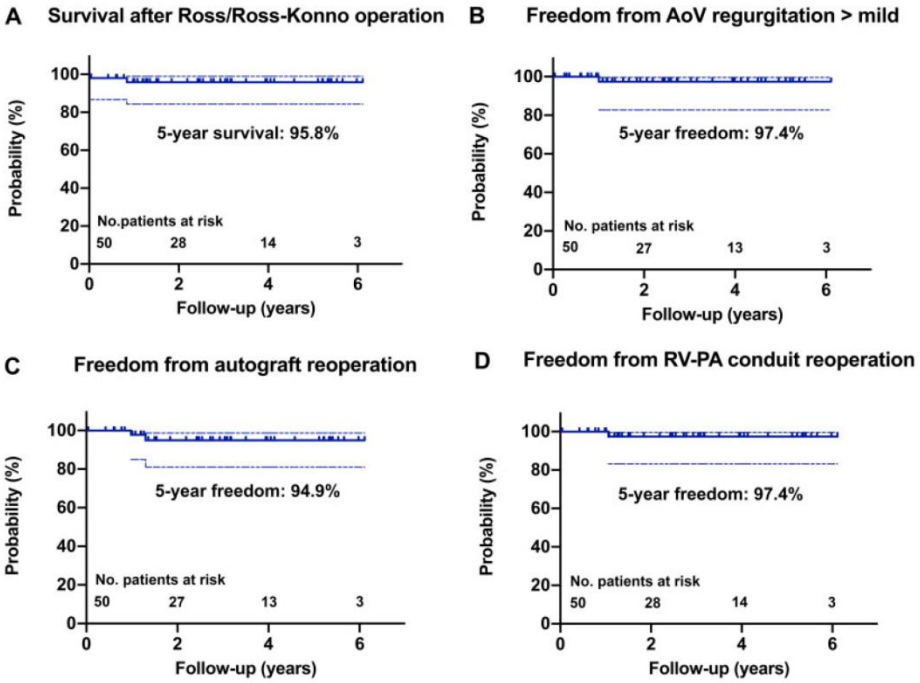

Figure 4: Overall survival at 5 years (**A**), freedom from aortic regurgitation greater than mild at 5 years (**B**), freedom from autograft reoperation (**C**), freedom from RV–PA conduit reoperation (**D**), both at 5 years of follow-up. AoV: aortic valve; RV–PA: right ventricle to pulmonary artery.

Figure 4: Overall survival at 5 years

8. TABLES

Table 1: Baseline characteristics

	n = 50
Age at surgery (years), median (IQR)	6.3 (1.4–13.6)
Age groups, *n* (%)	
<1 month	4 (8)
>1 month <1 year	6 (12)
>1 year <12 years	25 (50)
>12 years <18 years	7 (14)
>18 years	8 (16)
Sex, *n* (%)	
Male	29 (58)
Weight at surgery (kg), median (IQR)	18.3 (10.5–51.4)
BSA (m^2), median (IQR)	0.8 (0.5–1.5)
Indication for surgery, *n* (%)	
AS	20 (40)
AR	21 (42)
Combined	9 (18)
Intraoperative AoV morphology, *n* (%)	
Tricuspid	22 (43)
Bicuspid	15 (29.4)
Unicuspid	13 (25.5)
NYHA class, *n* (%)	
NYHA I	27 (55.6)
NYHA II	20 (40)
NYHA III	3 (4.4)
NYHA IV	0
Previous procedures, *n* (%)	
AoV balloon valvotomy	24 (49)
AoV repair	16 (31.4)
LV-EF, *n* (%)	
Normal (>50%)	46 (90.7)
Mild–moderately reduced (30–50%)	2 (4.7)
Severely reduced (<30%)	2 (4.7)
AoV annulus size (mm), median (IQR)	14 (10.8–19.3)
AoV annulus *Z*-score, median (IQR)	-0.09 (-1.9 to 1.4)
Sinus *Z*-score, median (IQR)	0 (-1.4 to 1)
STJ *Z*-score, median (IQR)	0.4 (-1 to 1.2)
Ascending aorta *Z*-score, median (IQR)	1.7 (-0.2 to 3.6)
LVOTO, *n* (%)	24 (48)
AoV peak gradient (mmHg), median (IQR)	55 (35.6–69.5)
AoV max. flow velocity (m/s), median (IQR)	3.7 (2.9–4.2)
LVEDD (mm), median (IQR)	48.5 (37.8–54)
LVEDD *Z*-score, median (IQR)	2.4 (1.3–3.8)
PV annulus size (mm), median (IQR)	17 (14–20)
PV annulus *Z*-score, median (IQR)	0.45 (-0.9 to 1.2)

AR: aortic regurgitation; AS: aortic stenosis; AoV: aortic valve; BSA: body surface area; IQR: interquartile range; LV-EF: left ventricular ejection fraction; LVEDD: left ventricular end-diastolic diameter; LVOTO: left ventricular outflow tract obstruction; NYHA: New York Heart Association; PV: pulmonary valve; STJ: sinotubular junction.

Table 1: Baseline characteristics (reproduced with permission from [60]).

Table 2: Procedural characteristics

	n = 50
Surgical technique, *n* (%)	
Ross	8 (16)
Ross–Konno	42 (84)
CPB time (min), median (IQR)	252.5 (210.8–297)
Aortic cross-clamp time (min), median (IQR)	144.5 (126.8–173.8)
Reperfusion time (min), median (IQR)	68 (55.8–86)
LVOT patch used, *n* (%)	33 (66)
RV–PA conduit diameter (mm), median (IQR)	18 (16–22)
Type of RV–PA conduit used, *n* (%)	
Cryopreserved aortic/pulmonary HG	12 (24)
Bovine jugular vein conduit (Contegra®)	33 (66)
Decellularized pulmonary HG (Espoir®)	2 (4)
Other biological valve substitutes	3 (6)
Concomitant surgery, *n* (%)	32 (64)
Replacement of ascending aorta	9 (17.6)
LVOT/EFE resection	10 (19.6)
MV repair	4 (7.8)
Aortic arch repair	2 (3.9)
Cardioplegia, *n* (%)	
Bretschneider	41 (81.6)
Blood	9 (18.4)
Intraoperative filtration, *n* (%)	13 (26.5)
Intraoperative transfusion, *n* (%)	23 (46)
Intraoperative ECMO implantation, *n* (%)	1 (2)

CPB: cardiopulmonary bypass; ECMO: extracorporeal membrane oxygenation; EFE: endocardial fibro-elastosis; HG: homograft; IQR: interquartile range; LVOT: left ventricular outflow tract; MV: mitral valve; RV–PA: right ventricle to pulmonary artery.

Table 2: Procedural characteristics (reproduced with permission from [60]).

Table 3: Early postoperative outcome

Early mortality, *n* (%)	1 (2)
Major complications, *n* (%)	
Delayed chest closure	3 (6)
Pacemaker implantation	3 (6)
Unplanned chest re-entry	2 (4)
Arrhythmia	2 (4)
Neurological complications	1 (2)
Acute kidney injury	1 (2)
ECMO	1 (2)
Ventilation time (h), median (IQR)	17.8 (13.2–43.2)
ICU stay (days), median (IQR)	1 (1–4)
Hospital stay (days), median (IQR)	7 (6–9.5)
Patients at discharge, *n* (%)	49 (98)
LV-EF, *n* (%)	
Normal (>50%)	40 (81.6)
Mild–moderately reduced (30–50%)	9 (18.3)
Severely reduced (<30%)	0
AoV regurgitation grade, *n* (%)	
None	9 (18.3)
Mild	37 (75.5)
Moderate	3 (6.2)
Severe	0
AoV annulus diameter (mm), median (IQR)	13 (9.9–16.5)
AoV annulus *Z*-score, median (IQR)	-0.4 (-1.9 to 0.9)
Sinus *Z*-score, median (IQR)	-0.7 (-1.5 to 0.4)
STJ *Z*-score, median (IQR)	0.2 (-0.8 to 0.8)
Ascending aorta *Z*-score, median (IQR)	0.1 (-1.1 to 1.5)
AoV max. flow velocity (m/s), median (IQR)	1.4 (1.2–1.8)
RV–PA conduit peak gradient (mmHg), median (IQR)	7 (3.6–11.6)
RV–PA max. flow velocity (m/s), median (IQR)	1.4 (0.9–1.7)
MV regurgitation grade, *n* (%)	
None	23 (46.9)
Mild	23 (46.9)
Moderate	3 (6.2)
Severe	0

AoV: aortic valve; ECMO: extracorporeal membrane oxygenation; ICU: intensive care unit; IQR: interquartile range; LV-EF: left ventricular ejection fraction; MV: mitral valve; RV–PA: right ventricle to pulmonary artery; STJ: sinotubular junction.

Table 3: Early postoperative outcome (reproduced with permission from [60]).

Table 4: Follow-up data

FU interval (months), median (IQR)	31.2 (14.4–51)
Age at FU (years), median (IQR)	8.2 (5.5–17.1)
Total mortality, *n* (%)	2 (4)
Reoperations/interventions, *n* (%)	
Balloon dilatation RV–PA conduit	3 (6)
Prosthetic AoV replacement	2 (4)
Percutaneous PV replacement	2 (4)
RVOTO resection	1 (2)
Patients at FU,[a] *n* (%)	46 (92)
Medication, *n* (%)	
β-Receptor antagonist	26 (52)
ACE-inhibitors	3 (6.5)
Aspirin	1 (2)
NYHA class, *n* (%)	
NYHA I	44 (95.6)
NYHA II	2 (4.3)
NYHA III–IV	0
LV-EF, *n* (%)	
Normal (>50%)	43 (93.4)
Mild–moderately reduced (30–50%)	3 (6.5)
Severely reduced (<30%)	0
AoV regurgitation, grade, *n* (%)	
None	31 (67.4)
Mild	14 (30.4)
Moderate	1 (2.2)
Severe	0
AoV annulus diameter (mm), median (IQR)	17.8 (15.3–20)
AoV annulus *Z*-score, median (IQR)	1.5 (0–2.3)
Sinus *Z*-score, median (IQR)	0.6 (0–2.3)
STJ *Z*-score, median (IQR)	0.7 (0–1.4)
Ascending aorta *Z*-score, median (IQR)	0.8 (0–2.5)
AoV max. flow velocity (m/s), median (IQR)	1.3 (1–1.8)
LVEDD (mm), median (IQR)	39.5 (33.3–47.8)
LVEDD *Z*-score, median (IQR)	0.2 (-0.3 to 1)
RV–PA conduit peak gradient (mmHg), median (IQR)	20 (11–32.2)
RV–PA max. flow velocity (m/s), median (IQR)	2.1 (1.6–2.6)
RV–PA conduit regurgitation grade, *n* (%)	
None	15 (32.6)
Mild	21 (45.7)
Moderate	10 (21.7)
Severe	0
MV regurgitation (grade), *n* (%)	
None	26 (57.8)
Mild	17 (35.5)
Moderate	3 (6.6)
Severe	0

[a]Patients after autograft reoperation or death excluded (100% follow-up for the remaining patients).

ACE: angiotensin-converting enzyme; AoV: aortic valve; FU: follow-up; IQR: interquartile range; LV-EF: left ventricular ejection fraction; LVEDD: left ventricular end-diastolic diameter; NYHA: New York Heart Association; MV: mitral valve; PV: pulmonary valve; RVOTO: right ventricular outflow tract obstruction; RV–PA: right ventricle to pulmonary artery; STJ: sinotubular junction.

Table 4: Follow-up data (reproduced with permission from (60)).

STATUTORY DECLARATION OF OWN CONTRIBUTION

“I, Peter Murin, by personally signing this document in lieu of an oath, hereby affirm that I prepared the submitted dissertation on the topic: *The role of subcoronary implantation technique in children and young adults undergoing Ross operation – Die Rolle der subkoronaren Implantationstechnik bei Kindern und jungen Erwachsenen im Rahmen der Ross-Operation*, independently and without the support of third parties, and that I used no other sources and aids than those stated.

All parts which are based on the publications or presentations of other authors, either in letter or in spirit, are specified as such in accordance with the citing guidelines. The sections on methodology (in particular regarding practical work, laboratory regulations, statistical processing) and results (in particular regarding figures, charts and tables) are exclusively my responsibility.

Furthermore, I declare that I have correctly marked all of the data, the analyses, and the conclusions generated from data obtained in collaboration with other persons, and that I have correctly marked my own contribution and the contributions of other persons (cf. declaration of contribution). I have correctly marked all texts or parts of texts that were generated in collaboration with other persons.

My contributions to any publications to this dissertation correspond to those stated in the below joint declaration made together with the supervisor. All publications created within the scope of the dissertation comply with the guidelines of the ICMJE (International Committee of Medical Journal Editors; www.icmje.org) on authorship. In addition, I declare that I shall comply with the regulations of Charité – Universitätsmedizin Berlin on ensuring good scientific practice.

I declare that I have not yet submitted this dissertation in identical or similar form to another Faculty.

The significance of this statutory declaration and the consequences of a false statutory declaration under criminal law (Sections 156, 161 of the German Criminal Code) are known to me.”

Date Signature

Declaration of own contribution to the top-journal publication

Peter Murin contributed the following to the below listed publication:

Conceptualization, data curation, formal analysis, investigation, methodology, software, validation, visualization, writing - original draft, writing - review & editing.

Publication:

Murin P, Weixler VHM, Moulla-Zeghouane J, Romanchenko O, Schleiger A, Lorenzen V, Sinzobahamvya N, Zacek P, Photiadis J, Cho M-Y. Subcoronary Ross/Ross–Konno operation in children and young adults: initial single-centre experience. Eur J Cardiothorac Surg. 2021 Jan 4;59(1):226–33.

Contribution:

Conceptualization: after thorough literature review and outcome analysis of the historical cohort treated by Ross operation at our center, Peter Murin, set out the concept of patient selection, standardization and refinement of the modified surgical technique to allow future retrospective study design and report of results of our current cohort.

Data curation, formal analysis, investigation, methodology: the application formalities for the waiver of ethical committee approval were written and prepared by Peter Murin. Peter Murin has personally elaborated, reviewed and submitted the age-specific patient consent forms as well as the age-specific study information bulletin. The curation of primary data from hospital reports as well as the criteria and methodology for the assessment of the follow-up investigations, together with the validation of the data were performed by Peter Murin. The statistical analysis and interpretation of the results was performed using the Graphpad Prism software used on limited license basis acquired by Peter Murin. The initial statistical testing and Kaplan-Meier estimates were performed under assistance by the second author of the publication; Viktoria Weixler MD, PhD. Peter Murin has validated the results and methods and contributed personally to the interpretation and visualization of the Tables 1, 2, 3, 4 and Figures 1, 2, 3, 4.

Visualization: the original graphical artwork performed by co-author; Pavel Zacek, was created from drafts, which were drawn by Peter Murin based on intra-operative snapshots from the video-material directed and recorded by Peter Murin, from a surgery, which was performed and/or assisted by the author. The original artwork was modified in co-operation with the artist and the final appearance as particular figure for the publication using labelling and legends was performed by Peter Murin.

Writing - original draft: the original draft was written by Peter Murin, reviewed and

commented by co-authors and the supervisor of this publication, Prof. Joachim Photiadis.

Writing – review & editing: the proposed changes were validated, reviewed and incorporated into the original draft by Peter Murin. The publication was prepared for submission to the journal and the revision of the manuscript as well as the subsequent re-submission, proof-editing and final approval were performed by the author.

The details of the proposed surgical modification as well as the findings from the above mentioned publication were presented by the author on national and prestigious international meetings.

Based on the retrospective analysis of the modified surgical technique, currently, Peter Murin is one of principal initiators of a congenital aortic valve database project to elucidate long-term outcome of various surgical techniques used in children and young adults with congenital aortic valve disease.

_____

Signature, date and stamp of first supervising university professor / lecturer

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Signature of doctoral candidate

EXTRACT FROM THE JOURNAL SUMMARY LIST

Journal Data Filtered By: **Selected JCR Year: 2018** Selected Editions: SCIE,SSCI
Selected Categories: **"SURGERY"** Selected Category Scheme: WoS
Journal count: 203 Journals

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
1	JAMA Surgery	6,432	10.668	0.034070
2	ANNALS OF SURGERY	50,355	9.476	0.066690
3	JOURNAL OF HEART AND LUNG TRANSPLANTATION	12,436	8.578	0.027310
4	JOURNAL OF NEUROLOGY NEUROSURGERY AND PSYCHIATRY	29,660	8.272	0.030730
5	AMERICAN JOURNAL OF TRANSPLANTATION	24,285	7.163	0.050970
6	ENDOSCOPY	10,604	6.381	0.016780
7	AMERICAN JOURNAL OF SURGICAL PATHOLOGY	21,132	6.155	0.023430
8	BRITISH JOURNAL OF SURGERY	23,178	5.586	0.028920
9	JOURNAL OF THORACIC AND CARDIOVASCULAR SURGERY	29,599	5.261	0.036950
10	JOURNAL OF BONE AND JOINT SURGERYAMERICAN VOLUME	46,190	4.716	0.042700
11	NEUROSURGERY	29,096	4.605	0.020730
12	TRANSPLANTATION	24,971	4.593	0.032780
13	JOURNAL OF THE AMERICAN COLLEGE OF SURGEONS	16,806	4.450	0.031030
14	ARTHROSCOPY-THE JOURNAL OF ARTHROSCOPIC AND RELATED SURGERY	17,057	4.433	0.021140

15	Bone & Joint Journal	5,865	4.301	0.024380
16	LIVER TRANSPLANTATION	10,513	4.159	0.013840
17	CLINICAL ORTHOPAEDICS AND RELATED RESEARCH	38,592	4.154	0.036010
18	JOURNAL OF NEUROSURGERY	36,001	4.130	0.027880
19	DISEASES OF THE COLON & RECTUM	13,467	4.087	0.012990
20	PLASTIC AND RECONSTRUCTIVE SURGERY	35,448	3.946	0.032890
21	Journal of NeuroInterventional Surgery	4,407	3.925	0.011860
22	ANNALS OF THORACIC SURGERY	36,145	3.919	0.040630
23	Hepatobiliary Surgery and Nutrition	719	3.911	0.002230
24	EUROPEAN JOURNAL OF CARDIO-THORACIC SURGERY	17,156	3.847	0.026410
25	World Journal of Emergency Surgery	1,217	3.798	0.002700
26	Surgery for Obesity and Related Diseases	6,229	3.758	0.014270
27	ANNALS OF SURGICAL ONCOLOGY	28,017	3.681	0.050930
28	EUROPEAN JOURNAL OF VASCULAR AND ENDOVASCULAR SURGERY	9,293	3.642	0.012760
29	Digestive Endoscopy	2,548	3.640	0.006320
30	OBESITY SURGERY	12,860	3.603	0.019200
31	TRANSPLANT INTERNATIONAL	4,868	3.526	0.009180
32	JAMA Otolaryngology-Head & Neck Surgery	2,855	3.502	0.012700
33	Aesthetic Surgery Journal	3,384	3.480	0.006110

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Subcoronary Ross/Ross–Konno operation in children and young adults: initial single-centre experience

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Key question

Is the subcoronary Ross/Ross-Konno operation a feasible option for growing patients?

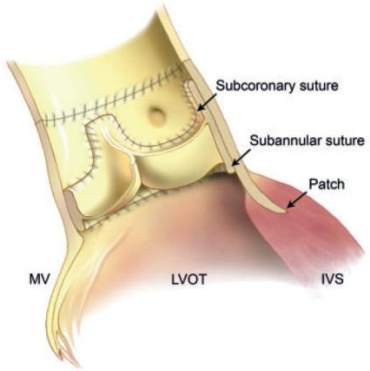
Key finding(s)

Our modification can be performed in children with encouraging early results and stable autograft function at 5 years.

Take-home message

Subcoronary implantation retains the advantage of autologous support together with the growth potential and avoidance of prosthetic material.

Proximal "subannular" and distal "subcoronary" suture lines after autograft implantation in the native aortic root. The Konno incision is enlarged by an anterior pericardial patch.



IVS: Interventricular septum, LVOT: Left ventricular outflow tract, MV: Mitral valve.

Abstract

OBJECTIVES: We sought to evaluate the outcome after modified subcoronary Ross/Ross–Konno operation in children and young adults.

METHODS: Between January 2013 and January 2019, a total of 50 patients with median age of 6.3 years (range 0.02–36.5 years, 58% males), including 10 infants (20%), received modified subcoronary Ross/Ross–Konno operation at our institution. Survival, morbidity, reinterventions, aortic valve function and aortic root dimensions were analysed.

RESULTS: At a median follow-up of 31.2 months (range 14.4–51 months), there were 1 early death and 1 late death, both in the infant group. The overall survival at 5 years after the operation was 95%. Two patients needed aortic valve replacement, 11 and 15 months after their Ross operation. At 5 years, freedoms from reoperation on the autograft and on the right ventricle to pulmonary artery conduit were

94% and 97%, respectively. Freedom from aortic valve regurgitation greater than mild was 97% at 5 years. Median dimensions of the aortic root at all levels remained in normal range at last visit. Forty-four patients (95%) were in New York Heart Association class I with normal left ventricular function.

CONCLUSIONS: The initial experience with the subcoronary Ross/Ross–Konno operation in children and young adults showed excellent outcome. The mortality and morbidity among infants remain significant. The described technique is reproducible and might be advantageous in situations when prosthetic supporting techniques interfere with somatic growth.

Keywords: Ross operation • Ross–Konno operation • Subcoronary implantation • Autograft • Aortic root • Congenital heart disease

ABBREVIATIONS

AoV	Aortic valve
CI	Confidence interval
ECMO	Extracorporeal membrane oxygenation
LV	Left ventricular
LVOT	Left ventricular outflow tract
LVOTO	Left ventricular outflow tract obstruction
MV	Mitral valve
NYHA	New York Heart Association
RVOT	Right ventricular outflow tract
RV-PA	Right ventricle to pulmonary artery

INTRODUCTION

Since its first introduction by Donald Ross [1], the original subcoronary autograft implantation technique was rarely used in young patients with congenital aortic valve (AoV) lesions. The technically less challenging and more feasible aortic root replacement technique was used instead almost universally among the paediatric population. However, progressive autograft regurgitation and/or aortic root dilation leading to a significant reoperation rate constitute well-known limitations [2–4]. External prosthetic supporting techniques may compromise the growth of the aortic root and are generally avoided in childhood. The discouraging results on late autograft failure after aortic root replacement techniques have led some groups to reintroduce the subcoronary autograft implantation technique in adults [5–7]. The feasibility and performance of this technique in patients with congenital AoV disease during growth remain unclear. We introduced a modified subcoronary implantation technique in children and young adults. Konno incision was used initially in patients with predominant aortic stenosis, left ventricular outflow tract obstruction (LVOTO) and severe aortic to pulmonary annular mismatched dimensions to accommodate the autograft in subcoronary fashion and/or to better address the endocardial fibro-elastosis [8]. The early results were promising, and this technique proved to be safe and reproducible. We adopted the subcoronary technique as preferable for Ross or Ross–Konno operation in patients with congenital AoV lesions. This study presents our initial experience with the subcoronary implantation technique.

PATIENTS AND METHODS

Study population

After institutional review board approval (EA2/080/20), the informed consent was obtained and this single-centre, retrospective study was conducted. Between January 2013 and January 2019, Ross/Ross–Konno operation was performed on 84 patients at our institution. Out of these, subcoronary modification was used in 50 patients (59%), who represent the substrate of this study. The baseline characteristics are shown in Table 1. The median age at the time of the surgery was 6.3 years (range 0.02–36.5 years). The study included 10 infants (20%) and 4 neonates (8%).

Clinical and echocardiographic assessment

Medical records including preoperative data, surgical notes, postoperative clinical and echocardiographic assessment, as well as outpatient reports, were reviewed. Postoperative clinical and echocardiographic follow-up data were available for all patients. The median follow-up duration was 31.2 months (range 14.4–51 months). The primary end points were death and any AoV reoperation. AoV function, aortic root dimensions and right ventricular outflow tract (RVOT) reinterventions were secondary outcome measures. In addition, the pressure gradient through the left ventricular outflow tract (LVOT) and the conduit, left ventricular (LV) function, arrhythmias and the patient's functional outcome were recorded. The echocardiographic data were reviewed by 2 independent investigators at our institution. The peak pressure gradient (ΔPmax) in mmHg was calculated using the simplified Bernoulli equation ($\Delta P\text{max} = 4\text{Vmax}^2$, where Vmax is the peak instantaneous transvalvular Doppler velocity) [9]. Special attention was paid to rule out any aneurysm formation within the outflow tracts, or occurrence of any new aortic root distortion. AoV regurgitation was graded analogous to the semi-quantitative method described by Perry *et al.* [10]. Measurement of the aortic root dimensions were performed at the level of the annulus, the sinus of Valsalva, the sinotubular junction and the ascending aorta in long-axis view [11]. The dimensions were assessed preoperatively, postoperatively and at the last follow-up, standardized to body surface area and expressed in *Z*-scores [12]. Dilation on any level was considered significant if the *Z*-score exceeded 2.

Operative technique

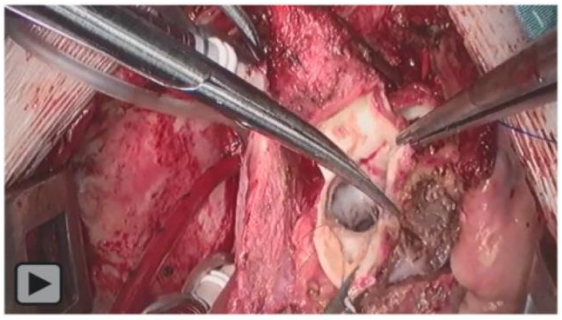
The modified surgical technique of subcoronary autograft implantation was introduced in 2013 [8]. Standardized technical steps were followed by 3 senior staff surgeons. The details of the currently used technique are described in the Supplementary Material (Video 1) and illustrated by Figs 1–3. A Konno incision was used in 42 cases (84%). This was needed in case of a concomitant LVOTO and/or annular hypoplasia in 24 patients (48%). In the remaining 18 patients, due to significant mismatch between the aortic and pulmonary annular dimensions, a limited

Table 1: Baseline characteristics

	$n = 50$
Age at surgery (years), median (IQR)	6.3 (1.4–13.6)
Age groups, *n* (%)	
<1 month	4 (8)
>1 month <1 year	6 (12)
>1 year <12 years	25 (50)
>12 years <18 years	7 (14)
>18 years	8 (16)
Sex, *n* (%)	
Male	29 (58)
Weight at surgery (kg), median (IQR)	18.3 (10.5–51.4)
BSA (m^2), median (IQR)	0.8 (0.5–1.5)
Indication for surgery, *n* (%)	
AS	20 (40)
AR	21 (42)
Combined	9 (18)
Intraoperative AoV morphology, *n* (%)	
Tricuspid	22 (43)
Bicuspid	15 (29.4)
Unicuspid	13 (25.5)
NYHA class, *n* (%)	
NYHA I	27 (55.6)
NYHA II	20 (40)
NYHA III	3 (4.4)
NYHA IV	0
Previous procedures, *n* (%)	
AoV balloon valvotomy	24 (49)
AoV repair	16 (31.4)
LV-EF, *n* (%)	
Normal (>50%)	46 (90.7)
Mild–moderately reduced (30–50%)	2 (4.7)
Severely reduced (<30%)	2 (4.7)
AoV annulus size (mm), median (IQR)	14 (10.8–19.3)
AoV annulus *Z*-score, median (IQR)	-0.09 (-1.9 to 1.4)
Sinus *Z*-score, median (IQR)	0 (-1.4 to 1)
STJ *Z*-score, median (IQR)	0.4 (-1 to 1.2)
Ascending aorta *Z*-score, median (IQR)	1.7 (-0.2 to 3.6)
LVOTO, *n* (%)	24 (48)
AoV peak gradient (mmHg), median (IQR)	55 (35.6–69.5)
AoV max. flow velocity (m/s), median (IQR)	3.7 (2.9–4.2)
LVEDD (mm), median (IQR)	48.5 (37.8–54)
LVEDD *Z*-score, median (IQR)	2.4 (1.3–3.8)
PV annulus size (mm), median (IQR)	17 (14–20)
PV annulus *Z*-score, median (IQR)	0.45 (-0.9 to 1.2)

AR: aortic regurgitation; AS: aortic stenosis; AoV: aortic valve; BSA: body surface area; IQR: interquartile range; LV-EF: left ventricular ejection fraction; LVEDD: left ventricular end-diastolic diameter; LVOTO: left ventricular outflow tract obstruction; NYHA: New York Heart Association; PV: pulmonary valve; STJ: sinotubular junction.

Konno incision was performed to enable subcoronary implantation. The aortic annulus/LVOT was augmented with at least 1 patch of autologous pericardium in 33 cases (66%), to achieve an outflow tract diameter that was ~5 mm larger than normal-sized aortic annulus. An additional patch for the non-coronary sinus was used in 17 cases (34%). The RVOT was reconstructed using a homograft (cryopreserved or decellularized—Espoir®, Corlife oHG, Hannover, Germany) or bovine jugular vein conduit (Contegra®, Medtronic Inc., Minneapolis, MN, USA) in the majority of cases (94%), with a median conduit diameter of 18 mm (range 16–22 mm). Concomitant procedures were performed in 32 patients, including LVOT/endocardial fibroelastosis resection ($n = 10$), replacement of ascending aorta ($n = 9$), mitral valve (MV) repair ($n = 4$), aortic arch repair ($n = 2$) and MV replacement ($n = 1$). Main procedural characteristics are given in Table 2.



Video 1: Sizing and enlargement of the aortic annulus, autograft implantation, closure of the aorta and final result (see Supplementary Material).

Statistical analysis

Baseline characteristics, early and follow-up measures are presented as median (interquartile range) for continuous variables and as frequency (%) of patients for categorical data. Survival and event-free curves were analysed using Kaplan–Meier time-to-event models. Statistical analysis was performed using GraphPad Prism software version 8.0.1 (GraphPad Software, Inc., San Diego, CA, USA). *P*-values <0.05 were considered statistically significant.

RESULTS

Early results

Survival. There was 1 early death (2%). This neonate, who was born with hypoplastic left heart complex, hypoplastic aortic arch and Turner syndrome, required extracorporeal membrane oxygenation (ECMO) support after the Ross–Konno operation. After 14 days on ECMO, weaning failed and the patient died due to multi-organ failure as a sequela of severe LV dysfunction.

Clinical outcome. The median duration of postoperative mechanical ventilation, intensive care unit and total hospital stay were 17.8 (h), 1 and 7 (days), respectively. Major postoperative complications occurred in 5 patients [13]. Three patients with complete atrioventricular block following an extensive LVOT resection required permanent pacemaker implantation. Two unplanned reoperations occurred, of which one was drainage of haemorrhagic effusion and one a chest reopening due to low cardiac output syndrome. Anti-arrhythmic medication was necessary for 2 patients at discharge.

Echocardiographic assessment. At discharge, the AoV regurgitation was graded as none-to-mild in 46 patients (93.8%) and moderate in 3 (6.2%) patients, with no severe AoV regurgitation. Median AoV annulus *Z*-score at discharge was -0.4 (range -1.9 to +0.9) in the entire cohort. Peak pressure gradients across the LVOT and/or AoV were below 10 mmHg in all patients. All peak pressure gradients across the RVOT and/or the right ventricle to pulmonary artery (RV–PA) conduits were <20 mmHg (median 7 mmHg, range 3.6–11.6 mmHg). There was no evidence

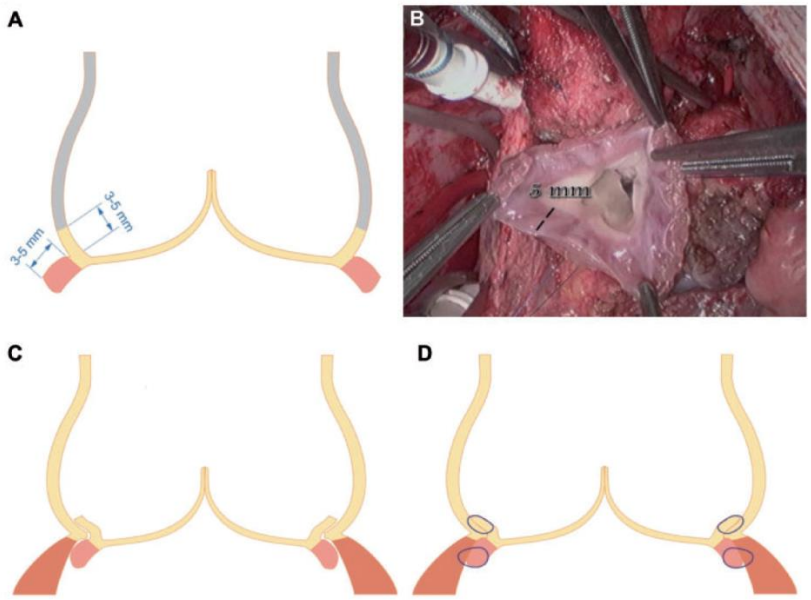


Figure 1: Trimming of the autograft leaving only a 3–5 mm rim (**A**). Operative view of the trimmed autograft (right ventricular aspect) (**B**). Autograft is seated into the native aortic annulus (**C**). Both proximal and distal suture lines are depicted schematically (**D**).

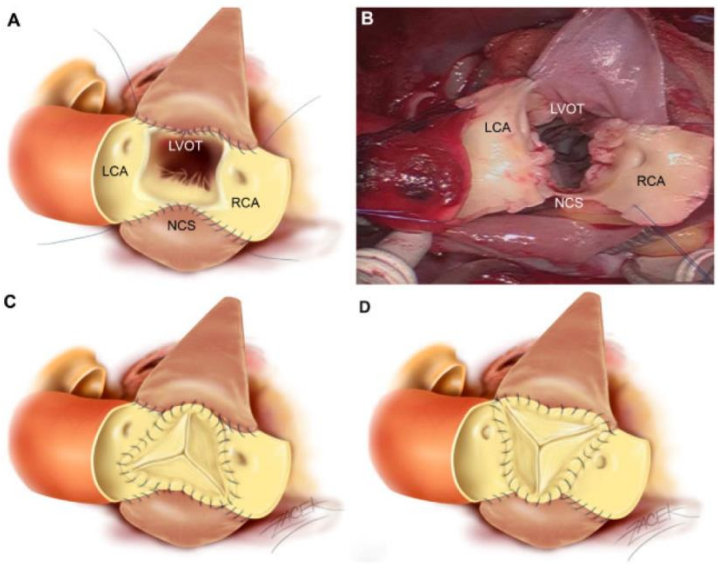


Figure 2: Enlargement of the aortic annulus by pericardial patches [(**A**) schematic and (**B**) operative view, both from surgeon's perspective]. Two alternative options of the autograft orientation [(**C** and **D**) schematic view from a surgeon's perspective]. LCA: left coronary artery; LVOT: left ventricular outflow tract; NCS: non-coronary sinus; RCA: right coronary artery.

of patch-related LVOTO/RVOT obstruction or septal aneurysmal formation. In 4 patients, who underwent concomitant MV repair, MV regurgitation was minimal ($n = 1$), mild ($n = 2$) and moderate ($n = 1$) with no stenosis. Nine (18.3%) patients showed mildly to moderately reduced LV systolic function (ejection fraction: 30–50%). Early postoperative outcome is summarized in Table 3.

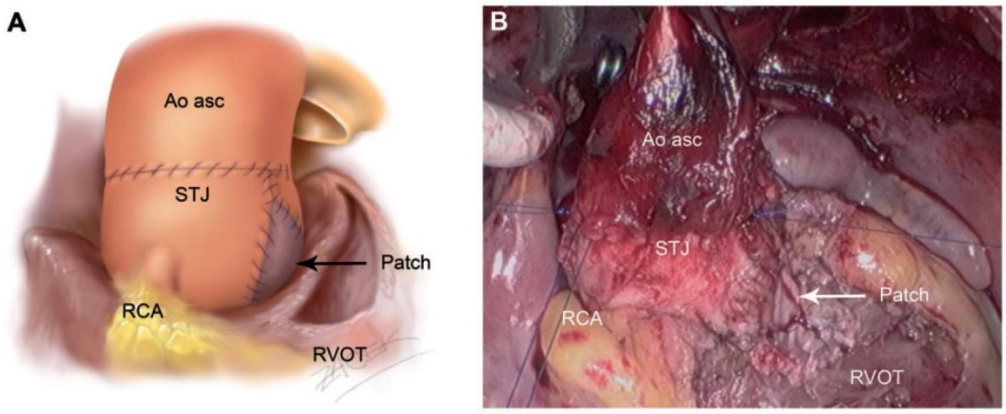


Figure 3: Final result after closure of the native aortic root [(**A**) schematic and (**B**) operative view]. Ao asc: aorta ascendens; RCA: right coronary artery; RVOT: right ventricular outflow tract; STJ: sinotubular junction.

Table 2: Procedural characteristics

	n = 50
Surgical technique, *n* (%)	
Ross	8 (16)
Ross–Konno	42 (84)
CPB time (min), median (IQR)	252.5 (210.8–297)
Aortic cross-clamp time (min), median (IQR)	144.5 (126.8–173.8)
Reperfusion time (min), median (IQR)	68 (55.8–86)
LVOT patch used, *n* (%)	33 (66)
RV–PA conduit diameter (mm), median (IQR)	18 (16–22)
Type of RV–PA conduit used, *n* (%)	
Cryopreserved aortic/pulmonary HG	12 (24)
Bovine jugular vein conduit (Contegra®)	33 (66)
Decellularized pulmonary HG (Espoir®)	2 (4)
Other biological valve substitutes	3 (6)
Concomitant surgery, *n* (%)	32 (64)
Replacement of ascending aorta	9 (17.6)
LVOT/EFE resection	10 (19.6)
MV repair	4 (7.8)
Aortic arch repair	2 (3.9)
Cardioplegia, *n* (%)	
Bretschneider	41 (81.6)
Blood	9 (18.4)
Intraoperative filtration, *n* (%)	13 (26.5)
Intraoperative transfusion, *n* (%)	23 (46)
Intraoperative ECMO implantation, *n* (%)	1 (2)

CPB: cardiopulmonary bypass; ECMO: extracorporeal membrane oxygenation; EFE: endocardial fibro-elastosis; HG: homograft; IQR: interquartile range; LVOT: left ventricular outflow tract; MV: mitral valve; RV–PA: right ventricle to pulmonary artery.

Table 3: Early postoperative outcome

Early mortality, *n* (%)	1 (2)
Major complications, *n* (%)	
Delayed chest closure	3 (6)
Pacemaker implantation	3 (6)
Unplanned chest re-entry	2 (4)
Arrhythmia	2 (4)
Neurological complications	1 (2)
Acute kidney injury	1 (2)
ECMO	1 (2)
Ventilation time (h), median (IQR)	17.8 (13.2–43.2)
ICU stay (days), median (IQR)	1 (1–4)
Hospital stay (days), median (IQR)	7 (6–9.5)
Patients at discharge, *n* (%)	49 (98)
LV-EF, *n* (%)	
Normal (>50%)	40 (81.6)
Mild–moderately reduced (30–50%)	9 (18.3)
Severely reduced (<30%)	0
AoV regurgitation grade, *n* (%)	
None	9 (18.3)
Mild	37 (75.5)
Moderate	3 (6.2)
Severe	0
AoV annulus diameter (mm), median (IQR)	13 (9.9–16.5)
AoV annulus *Z*-score, median (IQR)	-0.4 (-1.9 to 0.9)
Sinus *Z*-score, median (IQR)	-0.7 (-1.5 to 0.4)
STJ *Z*-score, median (IQR)	0.2 (-0.8 to 0.8)
Ascending aorta *Z*-score, median (IQR)	0.1 (-1.1 to 1.5)
AoV max. flow velocity (m/s), median (IQR)	1.4 (1.2–1.8)
RV–PA conduit peak gradient (mmHg), median (IQR)	7 (3.6–11.6)
RV–PA max. flow velocity (m/s), median (IQR)	1.4 (0.9–1.7)
MV regurgitation grade, *n* (%)	
None	23 (46.9)
Mild	23 (46.9)
Moderate	3 (6.2)
Severe	0

AoV: aortic valve; ECMO: extracorporeal membrane oxygenation; ICU: intensive care unit; IQR: interquartile range; LV-EF: left ventricular ejection fraction; MV: mitral valve; RV–PA: right ventricle to pulmonary artery; STJ: sinotubular junction.

Follow-up

Survival. One late death occurred in an infant with combined AoV and MV lesions. Aortic balloon valvuloplasty on day 3 of life resulted in reduction of the stenosis; however, severe AoV regurgitation developed. The recovery after urgent neonatal Ross–Konno operation and MV repair was complicated due to recurrent MV incompetence and severely impaired LV function. A successful hybrid MV replacement by a custom-made stented bio-prosthesis was performed. Despite a satisfying initial surgical result concerning the LVOT and the autograft, the patient died several months after discharge of unknown cause. Overall survival at 5 years was 95.8% [95% confidence interval (CI) 84.3–98.9] (Fig. 4).

Clinical outcome. No valve-related complications such as thromboembolic or bleeding events were observed during the follow-up period. There were no signs of infective endocarditis either on the autograft or on the RV–PA conduit. One patient was still on a β-receptor antagonist for intermittent supraventricular arrhythmia and 3 patients were still dependent on permanent pacemaker. The remaining patients had stable sinus rhythm. Forty-four patients (96%) were in New York Heart Association (NYHA) class I, 2 patients were still in NYHA class II, 26 and 47 months, respectively, postoperatively.

Echocardiographic assessment. At the last available echocardiography, AoV regurgitation greater than mild was detected in 1 patient (2%). No patient had AoV regurgitation greater than moderate. Freedom from aortic regurgitation greater than mild for the entire study period was 97.4% (95% CI 82.8–98.7) at 5 years (Fig. 4). No significant aortic root dilatation was observed. Respective median *Z*-scores for aortic annulus, sinus of Valsalva, sinotubular junction and ascending aorta were 1.5 (range 0.1–2.7), 0.6 (range 0–2.3), 0.7 (range 0–1.4) and 0.8 (range 0–2). All peak pressure gradients across the LVOT and/or AoV were <10 mmHg. There was no evidence of distortion or asymmetry of the aortic root. No signs of aneurysm formation in the LVOT were detected. The median peak pressure gradient through the RVOT was 20 mmHg (range 11–32 mmHg). There was no evidence of subvalvular obstruction or aneurysm formation in the region of the Konno incision. The MV regurgitation grade of the 3 remaining patients after simultaneous MV repair was unchanged. LV systolic function was still mildly to moderately reduced in 3 patients (Table 4).

Reinterventions

Autograft. Two patients required autograft reoperation, 11 and 15 months after the Ross operation, respectively. Freedom from autograft reoperation was 94.9% (95% CI 81.1–98.7) at 5 years (Fig. 4). These 2 patients, 1 young adult and 1 adolescent, presented initially with severe AoV regurgitation, bicuspid AoV and aneurysm of the ascending aorta (*Z*-score: +7.9 and +2.3). Both were considered as suboptimal Ross candidates, but due to a strong patient wish to avoid prosthetic valve replacement, the patients were offered the subcoronary modification. In both, the Konno incision and enlargement of the aortic root were not necessary. In 1 patient, the annulus was downsized using an additional circular annuloplasty suture. The indication for reoperation (mechanical replacement) was severe AoV regurgitation due to cusp prolapse, and the aortic root dimensions remained in normal range in both cases at the time of the redo.

Right ventricle to pulmonary artery conduit. One patient needed RV–PA conduit reoperation 12 months after the initial Ross operation due to a subvalvular muscular stenosis and early degeneration of a 16-mm bovine jugular vein conduit. Another 5 transcatheteral reinterventions were carried out, including 2 percutaneous homograft replacements (MelodyValve®–Medtronic Inc.) 14 and 23 months postoperatively. Freedom from RV–PA conduit reoperation was 97.4% (95% CI 83.1–99.6) at 5 years (Fig. 4), and the combined freedom from RV–PA conduit reoperation/reintervention was 83.3% (95% CI 66.1–92.3).

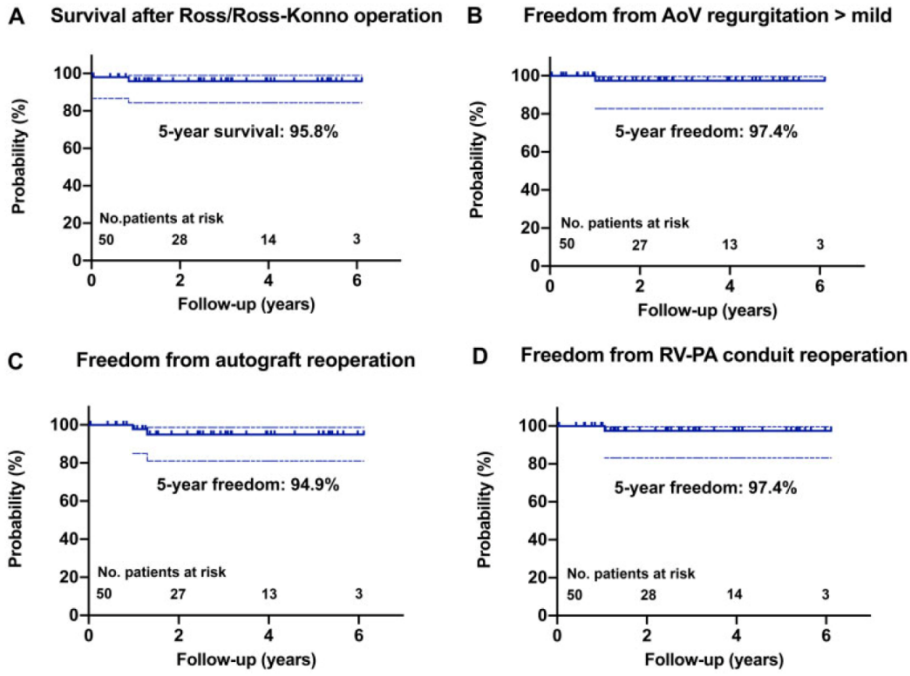


Figure 4: Overall survival at 5 years (**A**), freedom from aortic regurgitation greater than mild at 5 years (**B**), freedom from autograft reoperation (**C**), freedom from RV–PA conduit reoperation (**D**), both at 5 years of follow-up. AoV: aortic valve; RV–PA: right ventricle to pulmonary artery.

Table 4: Follow-up data

FU interval (months), median (IQR)	31.2 (14.4–51)
Age at FU (years), median (IQR)	8.2 (5.5–17.1)
Total mortality, *n* (%)	2 (4)
Reoperations/interventions, *n* (%)	
Balloon dilatation RV–PA conduit	3 (6)
Prosthetic AoV replacement	2 (4)
Percutaneous PV replacement	2 (4)
RVOTO resection	1 (2)
Patients at FU,[a] *n* (%)	46 (92)
Medication, *n* (%)	
β-Receptor antagonist	26 (52)
ACE-inhibitors	3 (6.5)
Aspirin	1 (2)
NYHA class, *n* (%)	
NYHA I	44 (95.6)
NYHA II	2 (4.3)
NYHA III–IV	0
LV-EF, *n* (%)	
Normal (>50%)	43 (93.4)
Mild–moderately reduced (30–50%)	3 (6.5)
Severely reduced (<30%)	0
AoV regurgitation, grade, *n* (%)	
None	31 (67.4)
Mild	14 (30.4)
Moderate	1 (2.2)
Severe	0
AoV annulus diameter (mm), median (IQR)	17.8 (15.3–20)
AoV annulus *Z*-score, median (IQR)	1.5 (0–2.3)
Sinus *Z*-score, median (IQR)	0.6 (0–2.3)
STJ *Z*-score, median (IQR)	0.7 (0–1.4)
Ascending aorta *Z*-score, median (IQR)	0.8 (0–2.5)
AoV max. flow velocity (m/s), median (IQR)	1.3 (1–1.8)
LVEDD (mm), median (IQR)	39.5 (33.3–47.8)
LVEDD *Z*-score, median (IQR)	0.2 (-0.3 to 1)
RV–PA conduit peak gradient (mmHg), median (IQR)	20 (11–32.2)
RV–PA max. flow velocity (m/s), median (IQR)	2.1 (1.6–2.6)
RV–PA conduit regurgitation grade, *n* (%)	
None	15 (32.6)
Mild	21 (45.7)
Moderate	10 (21.7)
Severe	0
MV regurgitation (grade), *n* (%)	
None	26 (57.8)
Mild	17 (35.5)
Moderate	3 (6.6)
Severe	0

[a]Patients after autograft reoperation or death excluded (100% follow-up for the remaining patients).

ACE: angiotensin-converting enzyme; AoV: aortic valve; FU: follow-up; IQR: interquartile range; LV-EF: left ventricular ejection fraction; LVEDD: left ventricular end-diastolic diameter; NYHA: New York Heart Association; MV: mitral valve; PV: pulmonary valve; RVOTO: right ventricular outflow tract obstruction; RV–PA: right ventricle to pulmonary artery; STJ: sinotubular junction.

Mitral valve. One hybrid custom-made MV replacement was successfully performed in the early postoperative course. At last follow-up, 10 months after implantation, the valve showed acceptable function. There were no further MV reinterventions during follow-up.

DISCUSSION

Aortic root dilation after the Ross operation using the root replacement technique and its possible impact on the development of late aortic regurgitation with autograft failure are extensively described in the literature [14–17]. Various technical modifications to stabilize the aortic root were implemented in adults with satisfactory early and late results [18–20]. However, in children, applied replacement techniques have to ensure adequate growth potential and simultaneously avoid extensive root dilation. An optimal solution is lacking as yet [21–23]. The described technique of subcoronary autograft implantation offers autologous support with native aortic tissue and is applicable to a wide age range of patients with congenital AoV disease. This technique also addresses severe LVOTO, which is frequently associated with significant mismatch between the size of aortic annulus and pulmonary autograft. The use of a Konno incision in this specific cohort of patients was high; however, there were no technical or functional disadvantages of this approach within the studied period. The potential complications were not more frequently observed in our series compared to others, using the root replacement technique [24, 25]. So far, we did not observe any distortion of the aortic root or of the outflow tracts, which could be related to the augmentation of the aortic root. The aortic root diameters were stable during the follow-up period. The autograft function was excellent in all but 2 patients. This might be explained by suboptimal patient selection and minor technical imperfections early in our experience with the new technique. As observed in adults, the subcoronary or inclusion techniques seem to protect the autograft from late dilation, but do not completely prevent the occurrence of leaflet prolapse [26]. Although the described technique proved to stabilize the aortic annulus, well-described risk factors such as bicuspid AoV regurgitation and severe dilation of the aortic root cannot be neglected. Postoperative morbidity was substantial, illustrating the complexity of the lesions, especially in the infant subgroup [27]. Survival was nevertheless promising. The durability of RV–PA conduits should be the same as for other Ross/Ross–Konno techniques [28]. The growing clinical experience with the use of decellularized homografts may alleviate this chronic drawback of the Ross operation [29]. Whether the expected positive effect on the durability of the autograft function in the long run can outweigh the potential risks of our modification remains to be investigated. Avoidance of coronary transfer seems to eliminate the risk of coronary artery-related problems; moreover, if any valve-sparing reoperation is needed, mobilization of the coronary buttons should be facilitated by less scar formation. Based on our initial experience with this method, a standardized surgical protocol and careful patient selection proved our concept to be safe and reproducible. This new modification could become an important tool for experienced surgeons in high-volume centres with routine in congenital Ross/Ross–Konno surgery.

Limitations

The presented surgical modification was inspired by other groups mainly operating on adults; thus, the heterogeneity of the congenital cohort may have had an influence on the patient selection, timing of the procedure and outcome of this cohort. Further analysis, e.g. progression of *Z*-scores using regression models, was not performed due to a small sample size and limited follow-up period. Finally, the limited number of patients and short follow-up period precluding any robust statistical analysis are well-known limitations of any initial report of surgical modifications.

CONCLUSION

The described modification may have an advantage over an unsupported autograft, especially in children in whom prosthetic supporting techniques are precluded. It is applicable to a wide age range of patients with congenital AoV disease with or without LVOTO. Our initial results indicate optimal autograft function, stable aortic root dimensions and no specific complications of this approach. However, the superior durability of the autograft in the long run remains to be proven.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

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Conflict of interest: none declared.

Author contributions

Peter Murin: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Software; Validation; Visualization; Writing—original draft; Writing—review & editing. **Viktoria H.M. Weixler:** Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Software; Validation; Writing—review & editing. **Jasmin Moulla-Zeghouane:** Data curation. **Olga Romanchenko:** Data curation. **Anastasia Schleiger:** Data curation. **Victoria Lorenzen:** Data curation. **Nicodème Sinzobahamvya:** Formal analysis; Investigation; Methodology; Supervision; Validation. **Pavel Zacek:** Visualization. **Joachim Photiadis:** Project administration; Resources; Supervision; Writing—review & editing. **Mi-Young Cho:** Conceptualization; Supervision.

Reviewer information

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CURRICULUM VITAE

Due to data protection regulations my curriculum vitae will not be published in the electronical version of this work.

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

COMPLETE LIST OF PUBLICATIONS

Books:

1. ***Surgical Management of Congenital Heart Disease I***
   Complex Transposition of Great Arteries, Right and Left Ventricular Outflow Tract Obstruction, Ebstein´s Anomaly - Video Manual.

   Hraška Viktor, **Murín Peter**
   Springer Verlag 2012, XVI, 206p. 271 illus. in color. With 2 DVD´s. eBook. ISBN 978-3-642-24168-0

2. ***Surgical Management of Congenital Heart Disease II***
   Single Ventricle and Hypoplastic Left Heart Syndrome, Aortic Arch Anomalies, Septal Defects and Anomalies in Pulmonary Venous Return, Anomalies of Thoracic Arteries and Veins - Video Manual.

   Hraška Viktor, **Murín Peter**
   Springer Verlag 2015, 305p. 290 illus. in color. With 3 DVD´s. eBook. ISBN: 978-3-662-44069-8

Chapters:

Hraška V., Murín P. (2016) Anatomic Correction of Corrected Transposition of the Great Arteries with Ventricular Septal Defect and Obstruction of the Left Ventricular Outflow Tract. In: Lacour-Gayet F., Bove E., Hraška V., Morell V., Spray T. (eds.) Surgery of Conotruncal Anomalies. Springer, Cham

Murín P. (2021) Valvular Aortic Stenosis, Subvalvular Aortic Stenosis, Supravalvular Aortic Stenosis, Tetralogy of Fallot - Pulmonary Atresia/ Stenosis with VSD, Ebsteins´ Anomaly. In: Ennker T, Falk V, Photiadis J, Starck C, Weymann. (eds.) Referenz: Herzchirurgie. Thieme-Verlag, Stuttgart (ahead of print)

Original articles:

1. ***Pulmonary artery augmentation using decellularized equine pericardium (Matrix Patch™): initial single-center experience***
   Murin P, Weixler VHM, Kuschnerus K, Romanchenko O, Lorenzen V, Nordmeyer J, Cho MY, Sigler M, Photiadis J.
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2. ***Long-Term Outcomes of Patients Undergoing the Ross Procedure.***
   Aboud A, Charitos EI, Fujita B, Stierle U, Reil JC, Voth V, Liebrich M, Andreas M, Holubec T, Bening C, Albert M, Fila P, Ondrasek J, **Murin P**, Lange R, Reichenspurner H, Franke U, Gorski A, Moritz A, Laufer G, Hemmer W, Sievers HH, Ensminger S.

J Am Coll Cardiol. 2021 Mar 23;77(11):1412-1422. doi: 10.1016/j.jacc.2021.01.034.

3. ***Can Left Atrioventricular Valve Reduction Index (LAVRI) Predict the Surgical Strategy for Repair of Atrioventricular Septal Defect?***
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   Pediatr Cardiol. 2021 Feb 12. doi: 10.1007/s00246-021-02558-5. PMID: 33580286

4. ***Fast-track extubation after cardiac surgery in infants: Tug-of-war between performance and reimbursement?***
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6. ***Reimbursement After Congenital Heart Surgery in Germany: Impact of Early Postoperative Extubation.***
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7. ***Asanguineous Cardiopulmonary Bypass in Infants: Impact on Postoperative Mortality and Morbidity.***
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8. ***Adult congenital open-heart surgery: emergence of a new mortality score.***
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   Eur J Cardiothorac Surg. 2020 Jul 1;58(1):171-176. doi: 10.1093/ejcts/ezaa024.

9. ***ADAPT-treated pericardium for aortic valve reconstruction in congenital heart disease: histological analysis of a series of human explants.***
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20. Chirurgische Therapie angeborener Herzfehler bei Neugeborenen. Derzeitige Indikationen und Ergebnisse am Deutschen Kinderherzzentrum, Sankt Augustin
Nobili F, Sinzobahamvya N, Photiadis J, Arenz C, **Murín P**, Hraška V, Asfour B.
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24. Ross-Konno operation in children.
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25. Stentless full root bioprosthesis in surgery for complex aortic valve-ascending aortic disease: a single center experience of over 300 patients.
Dapunt OE, Easo J, Hölzl PP, **Murín P**, Südkamp M, Horst M, Natour E.
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Guidelines:

1. **DGPK-Guideline: Ebstein´s anomaly.**
   Nagdyman N, Hummel J, Steinmetz M, **Murin P**, Cleuziou J.
   AWMF 2021

2. **DGPK-Guideline: Congenitally corrected transposition of great arteries (ccTGA).**
   Paul T, Rickers C, **Murin P.**
   AWMF 04/2021

3. **DGPK-Guideline: Valvular aortic stenosis.**
   Michel-Behnke I, **Murin P**, Sarikouch S.
   AWMF 11/2020

4. **DGPK-Guideline: Acute heart failure and mechanical circulatory support.**
   Michel-Behnke I, Thul J, **Murin P**, Miera O.
   AWMF 02/2020

5. **DGPK-Guideline: Transplantation of the heart in children and adults with CHD.**
   Kozlik-Feldmann R, Ulrich S, zu Knyphausen E, Dubowy O, **Murin P**, Dorka R.
   AWMF 11/2019

6. **DGPK-Guideline: Supravalvular aortic stenosis.**

Bertram H, Dähnert I, **Murin P**.
AWMF 11/2018

7. **DGPK-Guideline: Subvalvular aortic stenosis.**
   Bertram H, **Murin P**, Dähnert I.
   AWMF 11/2017

Invited lectures:

1. ***Surgical management of DORV***
   DGTHG-DGPK-Joint Session, Annual Meeting 2021

2. ***CON: Aortic valve repair***
   DGTHG-DGPK-Joint Session, Annual Meeting 2021

3. ***How do I prevent neo-aortic root dilatation - Subcoronary Ross operation***
   Deep Dive Session: Neo-aortic dilatation after Ross operation, STS Annual Meeting 2021, New York, USA

4. ***Cone repair as a part of 1 and ½ ventricle repair for severe forms of Ebstein´s Anomaly***
   Focus session - Ebstein´s Anomaly. 33rd EACTS Annual Meeting, October 2019, Lissbon, Portugal

5. ***How do I perform the Subcoronary Ross/Ross-Konno procedure?***
   Management of valvular disease. EACTS Skill Course, October 2018, Bergamo, Italy

6. ***Fenestrated VSD closure – really needed?***
   Murín P. Lange-Symposium, October 2018, Berlin, Germany

Abstracts/ Presentations:

1. ***Pulmonary artery augmentation using decellularized equine pericardium (Matrix Patch™): Initial single-center experience***
   Murin P. Abstract session: Research, Novel materials and techniques. 34th EACTS Annual Meeting, October 2020, Barcelona, Spain

2. ***Fast-track extubation after cardiac surgery in infants: Tug-of-war between performance and reimbursement?***
   Murin P, Weixler V, Romanchenko O, Schulz A, Redlin M, Cho MY, Sinzobahamvya N, Miera O, Kuppe H, Berger F, Photiadis J.
   100th AATS Annual Meeting, May 2020, New York, USA

3. ***Modified Ross-Konno procedure in children: Subcoronary implantation technique with Konno incision for annular and subannular hypoplasia***
   Murín P, Sinzobahamvya N, Schulz A, Lorenzen V, Ovroutski S, Berger F, Photiadis J, Cho M-Y
   31st EACTS Annual Meeting, September 2017, Vienna, Austria

4. ***Truncal Half Turn and Senning Operation: Anatomical Correction of Congenitally Corrected Transposition of Great Arteries (IDD) with Pulmonary Stenosis, Ventricular Septal Defect, Situs Inversus, and Levocardia***
   Murín P, Photiadis J.
   52nd Annual Meeting of the Society of Thoracic Surgeons, Jan 2016, Phoenix, USA

5. ***Truncus Arteriosus Communis with Interrupted Aortic Arch Repair: Complete Body Perfusion and Anteposition of the Pulmonary Arteries***
   Murín P, Hraška V.
   50th Annual Meeting of the Society of Thoracic Surgeons, Jan 2014, Orlando, USA

6. ***Arterial Switch Operation in Complex Transposition with Criss-cross Heart, Multiple Ventricular Septal Defects, Straddling of Tricuspid Valve, and Pulmonary Stenosis***
   Murín P, Hraška V.
   49th Annual Meeting of the Society of Thoracic Surgeons, Jan 2013, Los Angeles, USA

7. ***Yasui Operation***
   Murín P, Photiadis J, Asfour B, Hraška V.
   46th Annual Meeting of the Society of Thoracic Surgeons, Jan 2010, Fort Lauderdale, USA

8. ***Translocation of the pulmonary arteries: Effective technique for reduction of tracheobronchial compression***
   Murín P, Hesse C, Haun Ch, Arenz C, Asfour B, Hraška V.
   Jahrestagung der Deutschen Gesellschaft für Pädiatrische Kardiologie, 2014, Weimar

9. ***Effectiveness of mitral valve repair in congenital mitral valve malformation in infancy***
   Murín P, Sata S, Arenz C, Haun Ch, Asfour B, Hraška V.
   Jahrestagung der Deutschen Gesellschaft für Pädiatrische Kardiologie, Weimar 2014

10. ***Management of neonates with ventricular septal defects with aortic arch anomalies***
    Murín P, Arenz C, Haun Ch, Hraška V, Asfour B.
    Jahrestagung der Deutschen Gesellschaft für Pädiatrische Kardiologie, Weimar 2014

11. ***Ebstein's Anomaly: Midterm results of surgical therapy***
    Murín P, Sata S, Haun C, Sinzobahamvya N, Schneider M, Schindler E, Hraška V, Asfour B.
    Jahrestagung der Deutschen Gesellschaft für Pädiatrische Kardiologie, Weimar 2013

12. ***Atrioventricular Septal Defect with Aortic Arch Obstruction: 17-years of single center experience***
    Murín P, Sata S, Asfour B, Hraška V.
    Jahrestagung der Deutschen Gesellschaft für Pädiatrische Kardiologie, Weimar 2013

13. ***Surgery for mitral valve malformation in children***
    Murín P, Sata S, Sinzobahamvya N, Photiadis J, Haun C, Asfour B, Hraška V.
    Jahrestagung der Deutschen Gesellschaft für Pädiatrische Kardiologie, Weimar 2012

14. ***Long-term problems associated with Ross-Konno procedure***
    Murín P, Aszyk P, Thiel C, Sinzobahamvya N, Photiadis J, Arenz C, Haun C, Asfour B, Hraška V.
    Jahrestagung der Deutschen Gesellschaft für Pädiatrische Kardiologie, Weimar 2011

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