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Long-term outcome after treatment of pulmonary atresia with ventricular septal defect: nationwide study of 109 patients born in 1970–2007

Anu K. Kaskinen*, Juha-Matti Happonen, Ilkka P. Mattila and Olli M. Pitkänen

Division of Pediatric Cardiology and Cardiac and Transplantation Surgery, Children's Hospital, University of Helsinki and Helsinki University Central Hospital, Helsinki, Finland

* Corresponding author. Pediatric Research Center, University of Helsinki and Helsinki University Central Hospital, Biomedicum Helsinki 2U E104b, 00029 HUS, Helsinki, Finland. Tel: +358-9-4711; fax: +358-9-47171977; e-mail: anu.kaskinen@helsinki.fi (A.K. Kaskinen).

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Abstract

OBJECTIVES: Treatment of pulmonary atresia with ventricular septal defect (PA + VSD) has evolved during recent decades, but it still remains challenging. This study evaluated 41-year experience of outcome, survival and treatment of PA + VSD patients.

METHODS: Patient records and angiograms of 109 patients with PA + VSD born in Finland between 1970 and 2007, and treated at the Children's Hospital, Helsinki University Central Hospital, were retrospectively analysed in this nationwide study.

RESULTS: Of the 109 patients, 66 (61%) had simple PA + VSD without major aortopulmonary collateral arteries (MAPCAs). Although we observed no difference in overall survival between those with or without MAPCAs, the patients without MAPCAs had better probability to achieve repair (64 vs 28%, $P < 0.0003$). Only 3 patients were treated by compassionate care. Overall survival was affected by the size of true central pulmonary arteries on the first angiogram ($P = 0.001$) and whether repair was achieved ($P < 0.0001$). After successful repair, the survival rate was 93% at 1 year, 91% from the second year, and functional capacity as assessed by New York Heart Association (NYHA) I–II remained in 85% of patients alive at the end of follow-up. Palliated patients at 1, 5, 10 and 20 years of age had Kaplan–Meier estimated survival rates of 55, 42, 34 and 20%, respectively. Patients who underwent repair attempts but were left palliated with right ventricle (RV)–pulmonary artery connection and septal fenestration had better survival than the rest of the palliated patients ($P = 0.001$). Further, the McGoon index improved after implementation of a systemic–pulmonary artery shunt in the overall PA + VSD population ($P < 0.0001$).

CONCLUSIONS: These findings show that achievement of repair and initial size of true central pulmonary arteries affect survival of patients with PA + VSD. Although the overall survival of patients with MAPCAs showed no difference compared with simple PA + VSD patients, they had a higher risk of remaining palliated. However, palliative surgery may have a role in treatment of PA + VSD because the size of pulmonary arteries increased after placement of systemic–pulmonary artery shunt. In addition, subtotal repair by a RV–pulmonary artery connection and septal fenestration improved survival over extracardiac palliation.

Keywords: Congenital heart defect • Incidence • McGoon index • Mortality • Pulmonary blood supply • Late results

CONGENITAL

INTRODUCTION

Pulmonary atresia with ventricular septal defect (PA + VSD) has an incidence between 4.2 and 10 per 100 000 live births [1–3]. Within this patient group, there is anatomical diversity: the size of central pulmonary arteries varies from diminutive/absent to reasonable, and pulmonary blood supply is derived either from native pulmonary arteries or major aortopulmonary collateral arteries (MAPCAs), or both. Unfortunately, the natural survival and survival in the early surgical era have been dismal. Patients with PA + VSD, with or without MAPCAs, have been described as having less than a 50% chance of being alive at 10 years of age [2]. PA + VSD patients with MAPCAs, instead, have had only a 40% chance being alive at 10 years of age, and a 20% chance being alive at the age of 30 [4].

Surgical treatment of PA + VSD aims at repair, consisting of VSD closure and reconstruction of a connection between the right ventricle (RV) and pulmonary arteries allowing antegrade pulmonary blood flow. However, problems may arise when the true pulmonary arteries are scanty and multiple MAPCAs exist. The treatment protocol at our institution prefers staged repair, whereas some institutions aim at primary repair despite anatomical factors [5]. As preparatory palliative surgery, we perform a systemic–pulmonary artery shunt to secure postnatal pulmonary circulation aiming at enlarging the native, often diminutive pulmonary arteries. If MAPCAs exist, they are either connected to pulmonary arteries (unifocalization) or

ligated and disconnected from the pulmonary circulation, depending on their importance to pulmonary blood supply.

Modern surgical strategies have had a positive influence on the naturally very poor survival rate of PA + VSD [5–8]. Studies with extensive follow-up demonstrating improved survival and increased rates of surgical repair, however, are scarce [7, 9]. Further, most studies concerning survival into adulthood have concentrated on only PA + VSD patients with MAPCAs [4, 10], and the data on the MAPCAs' effects on the survival of PA + VSD are controversial [9, 11–13].

The present retrospective nationwide study investigated long-term survival and factors affecting survival of PA + VSD patients, with and without MAPCAs, born in Finland from 1970 to 2007. In addition, the factors influencing achievement of repair were identified. Further, we evaluated morphology and growth of central pulmonary arteries, and source of pulmonary blood supply from angiograms.

MATERIALS AND METHODS

Patients

This study comprised 109 PA + VSD patients, with or without MAPCAs, born in Finland from 1970 to 2007 and treated at the Children's Hospital, Helsinki University Central Hospital. The institution's ethics committee approved the study protocol.

Since 1995, all paediatric cardiac surgery in Finland has been centralized to our hospital. Even before this, all corrective surgeries and the vast majority of palliative surgeries for children with congenital heart defect were performed in our hospital. All PA + VSD patients born in Finland between 1995 and 2007—when the yearly birth rate in Finland was on average 58 000—were included in our study. Review of the cardiac surgical database and the medical records found 127 patients, 18 of whom were excluded, either because the presence of the right ventricular outflow tract changed their correct diagnosis to Tetralogy of Fallot ($n = 7$) or because PA + VSD was associated with other major cardiac abnormalities ($n = 11$), such as atrioventricular septal defect, atrioventricular discordance, transposition of the great arteries, double outlet RV, total anomalous pulmonary venous drainage or univentricular heart. Thus, the present study included 109 patients whose medical records, angiograms and operative reports were reviewed. In the PA + VSD population of our manuscript, antenatal diagnosis of PA + VSD was extremely rare ($n = 5$) and thus insignificant for our study (Table 1). Direct RV–left ventricle (RV/LV) systolic pressure ratio was measured at the end of the operation (data documented for 33 patients). During follow-up after repair, right ventricular pressure (RVP) was measured at cardiac catheterization (data available for 15 patients), or estimate of systolic RVP was determined by the maximal tricuspid valve regurgitation velocity on Doppler echocardiography (data available for 18 patients). The causes and dates of death were obtained from

Table 1: Patient characteristics

	Simple PA + VSD ($n = 66$)	PA + VSD + MAPCAs ($n = 43$)	P
Male gender, n (%)	33 (50)	26 (60)	0.28
Birth weight (kg)	2.86 ± 0.83	3.09 ± 0.73	0.15
Antenatal diagnosis, n (%)	5 (8)	0 (0)	0.07
Age at postnatal diagnosis (months)	0.94 ± 7.0	0.99 ± 2.0	0.96
Associated cardiac findings, n (%)[a]	27 (41)	17 (40)	0.89
Comorbidities, n (%)	24 (36)	15 (35)	0.88
22q11.2 deletion	3 (5)	9 (21)	0.01
Other genetic or significant syndrome[b]	14 (21)	1 (2)	0.004
Extracardiac anomaly[c]	7 (11)	5 (12)	0.87
Morphological characteristics			
Presence of pulmonary artery confluence[d], n (%)	66 (100)	31 (72)	<0.0001
Source of pulmonary circulation[d], n (%)			
True pulmonary arteries only	66 (100)		
MAPCAs only		16 (37)	
True pulmonary arteries and MAPCAs		27 (63)	
First available angiogram[e]			
McGoon index, median (IQR)	1.50 (1.11–1.77)	0.75 (0.09–1.09)	<0.0001
TNPAI, median (IQR)		150 (87–301)	
Lung segments supplied by native pulmonary arteries, mean ± SD	19.8 ± 0.9	5.4 ± 6.1	<0.0001
Lung segments supplied by MAPCAs, mean ± SD	0	11.6 ± 1.8	
Hypoperfused lung segments, mean ± SD	0.3 ± 1.0	1.7 ± 2.2	0.007
Preoperative angiogram prior to repair attempt[f]			
McGoon index, median (IQR)	1.78 (1.39–2.00)	1.41 (1.05–1.60)	0.005
Hypoperfused lung segments, mean ± SD	0.3 ± 1.1	1.8 ± 2.4	0.02

PA + VSD: pulmonary atresia with ventricular septal defect; MAPCA: major aortopulmonary collateral artery; TNPAI: total neopulmonary arterial index; IQR: interquartile range; SD: standard deviation; VACTERL: vertebral defects, anal atresia, cardiac defects, tracheo-oesophageal fistula, renal anomalies and limb anomalies.

[a]Right-sided aortic arch ($n = 27$), left superior vena cava ($n = 7$), atrial septal defect ($n = 5$), abnormal coronary arteries ($n = 4$).

[b]Lissencephaly ($n = 1$), Mayer-Rokitansky-Küster-Hauser syndrome ($n = 1$), Mucolipidosis II ($n = 1$), other genetic syndromes ($n = 4$), Trisomy 21 ($n = 2$), unconfirmed but strongly suspected other syndromes ($n = 4$) and VACTERL ($n = 2$).

[c]Cleft palate ($n = 1$), clubfoot ($n = 1$), duodenal atresia ($n = 1$), oesophageal atresia ($n = 1$), hearing loss ($n = 1$), hip dislocation with acetabular dysplasia ($n = 1$), polydactyly and face deformity ($n = 1$), testicular retention ($n = 1$) and urinary tract anomaly ($n = 4$).

[d]Data from angiogram or operation.

[e]$n = 79$ for first angiogram.

[f]$n = 62$ for preoperative angiogram prior to repair attempt.

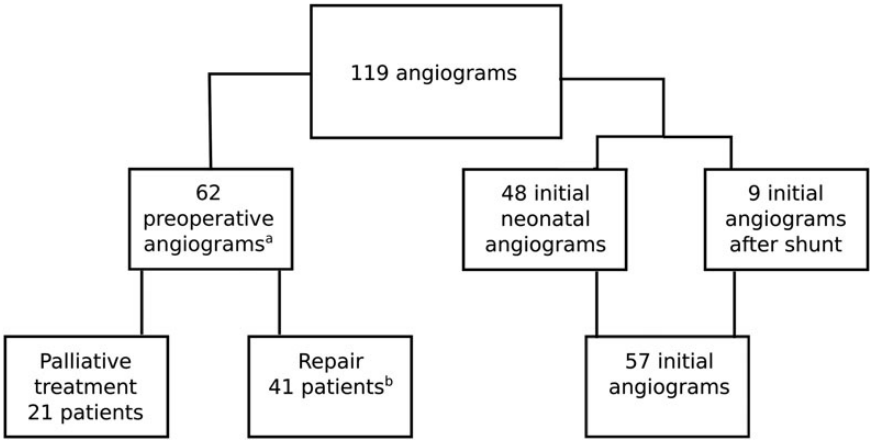

Figure 1: Flow diagram of analysed angiograms. Altogether 119 angiograms of 79 PA + VSD patients were analysed. Our treatment protocol has not included native angiograms, especially when the echocardiogram has been deemed sufficient. [a]Twenty-two patients had no angiogram prior to preoperative angiogram. [b]Preoperative angiogram on average 0.60 ± 0.80 years prior to repair. PA + VSD: pulmonary atresia with ventricular septal defect.

Statistics Finland. The last follow-up of all study patients was obtained from their patient records and Statistics Finland through December 2011.

Angiograms

Four physicians (including two paediatric cardiologists, one paediatric cardiac surgeon and one paediatric cardiology research fellow) analysed the first angiograms of 79 patients performed at the age of 4.9 (0.1–14.0) months, as well as preoperative angiograms prior to repair attempt when available (Fig. 1). Analysis of angiograms was either from nitrocellulose film ($n = 55$), videotape ($n = 36$) or from digital data ($n = 28$). Although angiograms at our institution have been performed according to clinical indications, the distribution of age at the first angiograms showed no difference between patients with or without MAPCAs, or between patients with or without later repair (data not shown).

The presence of pulmonary artery confluence, blood flow to each lung segment and the McGoon index were evaluated from each angiogram. In addition, from the first angiogram a total neopulmonary arterial index (TNPAI)—combined cross-sectional area of left and right pulmonary arteries at hilar level and of MAPCAs divided by the body surface area—was calculated for patients with MAPCAs. We interpreted MAPCAs connecting with native pulmonary arteries outside the lungs as insignificant. To calculate the McGoon index, the combined diameter of the left and right pulmonary arteries at hilar level was divided by the diameter of the descending aorta just above the diaphragm. All viewers independently measured the vessel sizes, and the average of these four measurements was used as a single datum. Finally, we compared cross-sectional area of the descending aorta indexed with body surface area between patients with or without MAPCAs and confirmed that the comparison revealed no statistical difference (data not shown). Accordingly, we deemed the McGoon index, systematically used at our institution to describe size of central pulmonary arteries an appropriate tool for the present study.

Surgical management

In our hospital surgical management aimed at repair, and a patient always underwent repair when the McGoon index was 1.5 or above. However, at repair a postoperative RV/LV systolic pressure ratio up to 85% was accepted if the patient was haemodynamically stable. Repair was typically staged consisting of a preparatory palliative procedure(s) and a later repair. Repair was defined as closure of septal defects, reconstruction of a connection between the RV and pulmonary arteries, and elimination of extra-cardiopulmonary blood supply. Often, as a preparatory palliative procedure, a systemic–pulmonary artery shunt (most often a modified Blalock–Taussig shunt) was created as an attempt to enlarge the native central branch pulmonary arteries. Any MAPCAs without adequate communication with the native pulmonary arteries were principally targeted for unifocalization. This was previously done through thoracotomy, but during the last 15 years, unifocalization has been performed through sternotomy. When echocardiogram has been deemed sufficient for evaluation of initial morphology, our treatment protocol has not included primary angiograms [14].

Statistical analysis

We compared qualitative variables (n with percentages) with the χ^2 test. Continuous variables [median with interquartile range (IQR), or mean ± standard deviation (SD), as appropriate] were compared with the t-test, Mann–Whitney U-test or Wilcoxon matched-pairs test, as appropriate. We estimated survival probabilities with the Kaplan–Meier method and compared them by log-rank analysis. We applied a univariable Cox proportional hazard model for regression analyses, and significant variables in the univariable model were used for the multivariable Cox proportional hazard model. The level of statistical significance was set at 0.05 for all analyses. Statistics were analysed with SPSS 21.0 (SPSS, Inc., Chicago, IL, USA).

RESULTS

Patients and morphology

From 1970 to 2007, 109 children with PA + VSD were born in Finland and treated at the Children's Hospital, Helsinki University Central Hospital. The incidence of PA + VSD, which could be determined reliably from 1995 to 2007, was 6.1 per 100 000 live

Table 2: Operations

	Simple PA + VSD (n = 66)	PA + VSD + MAPCAs (n = 43)	P
Repair	42 (64%)	12 (28%)	0.0003
1-stage repair	2 (3%)	3 (7%)	
Staged repair	40 (61%)	9 (21%)	
Preparatory procedures[a]			
RVOT patch	1	0	
RV–pulmonary artery conduit/homograft	2	2	
Systemic–pulmonary artery shunt	39	8	
Pulmonary artery branch reconstruction	2	0	
MAPCA unifocalization or ligation		8	
Palliative treatment only	24 (36%)	31 (72%)	0.001
RV–pulmonary artery connection with septal fenestration	4 (6%)	17 (39%)	<0.0001
RVOT patch	1	0	
RV–pulmonary artery conduit/homograft	3	17	
Other palliative procedures	20 (30%)	11 (26%)	0.83
Systemic–pulmonary artery shunt with or without pulmonary artery branch augmentation[b]	19	9	
MAPCA unifocalization		1	
MAPCA unifocalization with RVOT reconstruction		1	
Pulmonary artery valvulotomy	1	–	
Unoperated	–	3 (7%)	0.06

Data presented as n (%) or n.
PA + VSD: pulmonary atresia with ventricular septal defect; MAPCA: major aortopulmonary collateral artery; RVOT: right ventricular outflow tract; RV: right ventricle.
[a]Number of operations.
[b]Only shunt (n = 19), with pulmonary artery branch augmentation/MAPCA ligation (n = 9).

births. At the end of follow-up, 62 (57%) patients were alive with a median follow-up time of 18.0 years (range 4.04–41.77 years). For the overall study population, including patients who died during the follow-up, the median follow-up time was 11.4 years (range 0.01–41.77 years). Patient characteristics and morphological data from the angiograms are presented in Table 1.

At the primary angiogram prior to any surgery the patients with simple PA + VSD had a 73% higher McGoon index (P = 0.0002) and 15 more lung segments indicative of perfusion by native pulmonary arteries (P < 0.0001) than the patients with MAPCAs. Also, when all first angiograms were analysed, the patients with simple PA + VSD had a 99% higher (P < 0.0001) McGoon index and had 84% less hypoperfused lung segments (P = 0.007). At the preoperative angiogram prior to repair attempt, the patients with simple PA + VSD had a 27% higher McGoon index (P = 0.005) and 84% less hypoperfused lung segments (P = 0.02) than patients with MAPCAs. In patients receiving a systemic–pulmonary artery shunt during the time between the two angiograms, the McGoon index increased by 41% from 1.12 (0.76–1.47) to 1.58 (1.25–2.01) (P < 0.0001). In the PA + VSD + MAPCAs subgroup, the McGoon index improved by 103% from 0.77 (0.71–1.14) to 1.57 (1.23–1.68) (P = 0.002). No such increase in the McGoon index was seen in the 6 patients who had no systemic–pulmonary artery shunt during the time between the two angiograms (P = 0.23).

Surgical treatment

Repair was performed in 54 (50%) patients, of whom 49 (91%) had staged repair with on average 1.4 ± 0.6 preparatory palliative operations. Palliative treatment only was given to 55 (50%) patients (Table 2), of whom 21 (38%) underwent a repair attempt but were left with an open/fenestrated VSD (n = 16) or atrial septal defect (ASD) (n = 5). Ten patients (18%) were deemed unsuitable for repair for various reasons: 5 had no adequate response to systemic–pulmonary artery shunt and poor peripheral pulmonary blood supply including a patient destined for a heart–lung transplant in the future; 3 received compassionate care only; and in 2 the extracardiac comorbidities prevented any further cardiac surgery. Twenty-four (44%) patients, of whom 23 were palliated with a systemic–pulmonary artery shunt with (n = 4) or without (n = 19) MAPCA operation, died before their treatment strategy was chosen or a previously planned repair was achieved.

The patients with simple PA + VSD successfully underwent repair more often (P < 0.0003) and needed more seldom septal fenestration at the repair attempt (P < 0.0001) than the patients with PA + VSD + MAPCAs (Table 2). Patients with the McGoon index at or above 1.5 on the first angiogram (n = 25) were all repaired. In 48 patients, the McGoon index was at or above 1.0 on the first angiogram, and of these 36 (75%) were repaired. Of the 29 patients with the McGoon index less than 1.0 on the primary angiogram, only 7 (24%) could be repaired, but their McGoon index had increased 1.1 ± 0.3 units by the time of repair.

We found that patients reaching repair had a 63% higher McGoon index at the primary angiogram prior to any surgery (P = 0.002). In the presence of MAPCAs, the TNPAI index on the first angiogram showed no significant difference between patients reaching repair [263 (142–594), n = 4] and receiving palliative treatment only [133 (78–260), n = 19, P = 0.26]. Between patients who remained palliated with RV–pulmonary artery connection and septal fenestration and patients receiving other palliative treatments only, no difference in the McGoon index on the first angiogram existed (P = 0.43). Patients born between 1970 and 1994 had their first operation later (1.16 ± 2.05 vs 0.10 ± 0.23 years

Table 3: Univariable Cox regression analysis of selected variables for achievement of repair and mortality

	Achievement of repair		Mortality	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Demographic factors (*n* = 119)				
Later year of birth (per year)	1.03 (1.01–1.06)	0.02	1.00 (0.97–1.03)	0.75
Birth weight (per kg)	0.99 (0.71–1.38)	0.95	0.78 (0.55–1.11)	0.17
Associated cardiac findings	0.95 (0.55–1.63)	0.85	1.19 (0.67–2.11)	0.56
22q11.2 deletion	0.53 (0.21–1.33)	0.18	0.30 (0.07–1.22)	0.09
Other genetic or significant syndrome	2.20 (1.02–4.75)	0.04	1.42 (0.66–3.05)	0.36
Presence of pulmonary artery confluence	5.59 (1.35–23.12)	0.02	0.91 (0.39–2.15)	0.83
Presence of MAPCAs	0.18 (0.09–0.35)	<0.0001	1.10 (0.62–1.96)	0.74
Age at first operation (per year)	0.75 (0.60–0.94)	0.01	1.01 (0.86–1.18)	0.94
Achievement of repair			0.07 (0.03–0.17)	<0.0001
Data from first angiograms (*n* = 79)				
Number of lung segments supplied by true pulmonary arteries	1.15 (1.08–1.22)	<0.0001	0.97 (0.93–1.02)	0.25
Higher McGoon index (per 0.5 units)	1.85 (1.41–2.42)	0.0001	0.60 (0.45–0.82)	0.001
Higher TNPAI index (per 10 units)	1.00 (1.00–1.01)	0.61	1.00 (1.00–1.01)	0.67
Improvement of McGoon index (per 0.5 units)[a]	1.04 (0.84–1.29)	0.70	1.25 (0.82–1.90)	0.30

CI: confidence interval; HR: hazard ratio; MAPCA: major aortopulmonary collateral artery; TNPAI: Total Neopulmonary Arterial index.
[a]Data from 40 paired angiograms.

old, $P = 0.0002$) and were repaired later (4.80 ± 2.73 vs 1.41 ± 1.05 years old, $P < 0.0001$) than patients born between 1995 and 2007.

Table 3 presents the univariable analysis of selected factors for achievement of repair. In multivariable analysis, later birth year increased the probability of repair [hazard ratio (HR) 1.06, 95% confidence interval (CI) 1.02–1.10, $P = 0.008$]. In our study, the McGoon index and number of lung segments supplied by native pulmonary arteries at the first angiogram, as well as the presence of MAPCAs were interdependent factors. Thus, we excluded the latter two factors from the second multivariable analysis. In this multivariable analysis, only a higher McGoon index [HR 1.69, 95% CI 1.25–2.28, $P = 0.001$ (per 0.5 units)] increased the probability of repair.

Overall survival of the patient population and causes of death

The overall survival rate estimated with the Kaplan–Meier method at 1, 5, 10, 20 and 30 years of age was 73, 66, 60, 55 and 53%, respectively, and showed no difference between patients with or without MAPCAs ($P = 0.74$, Fig. 2). During follow-up, 47 (43%) patients died at the median age of 0.56 (0.08–4.60) years. Of all deaths, 28 (60%) occurred within 30 days from cardiac surgery. The underlying cause of death was congenital heart defect in all patients, except in one who had mucolipidosis II. The immediate cause of death was available for 25 patients, and only one of these patients died from shunt embolism.

Univariable analysis of selected factors for mortality is presented in Table 3. In this univariable analysis, a higher McGoon index at the first angiogram and achievement of repair improved survival. However, in multivariable analysis, achievement of repair was the sole factor improving survival (HR 0.12, 95% CI 0.03–0.39, $P = 0.001$). Accordingly, patients reaching repair had better Kaplan–Meier estimated survival from birth than palliated patients receiving only preparatory treatment both in simple PA + VSD ($P < 0.0001$) and in PA + VSD + MAPCAs ($P = 0.001$) (Fig. 2). Further, Kaplan–Meier estimated 20-year survival of the patients with a McGoon index below 1.0 on the first angiogram was 45% in contrast to 76 and 88% if the McGoon index exceeded 1.0 ($P = 0.02$) and 1.5 ($P = 0.006$), respectively (Fig. 3).

Outcome after repair

After repair, the Kaplan–Meier estimated survival rate was 93% at 1 year and 91% from the second year on. Of the 54 patients receiving repair, 4 (3 with simple PA + VSD and 1 with MAPCAs) died within 30 days from repair, and 1 with simple PA + VSD died of iatrogenic hypoglycaemia 2 years from repair. The surviving patients had a median of 18.6 (10.7–23.7) years of follow-up after repair and a mean New York Heart Association (NYHA) class of 1.3 ± 0.5 at the latest follow-up visit, which showed no difference between patients with or without MAPCAs ($P = 0.37$). At repair, the invasively determined mean RV/LV systolic pressure ratio was 0.53 ± 0.18. The latest available invasively determined RV/LV systolic pressure ratio was 0.48 ± 0.16, on average 9.0 ± 6.0 years after repair. The latest available echocardiographically estimated RV/LV systolic pressure ratio was recorded on average 13.7 ± 6.9 years after repair and was 0.30 ± 0.12.

After repair, 33 (61%) patients had surgery or catheter-based reinterventions, and the Kaplan–Meier estimated rate of freedom from reintervention at 1, 5, 10 and 20 years after repair was 86, 76, 57 and 33%, respectively. Ten patients had altogether 17 catheter interventions, and 28 patients had surgery including 28 conduit replacements, 7 pulmonary artery branch augmentations, 3 aortic valve replacements and 2 residual MAPCA operations. Univariable analysis of the selected factors for reintervention after repair is reported in Table 4. However, in multivariable analysis, only a perioperative RV/LV systolic pressure ratio above 50% increased the probability of surgery or catheter-based reintervention (HR 3.86, 95% CI 1.07–13.93, $P = 0.04$).

Outcome of patients with palliative treatment only

Of the palliated patients, 52 had on average 2.0 ± 1.3 operations, and 4 patients with RV–pulmonary artery connection and septal

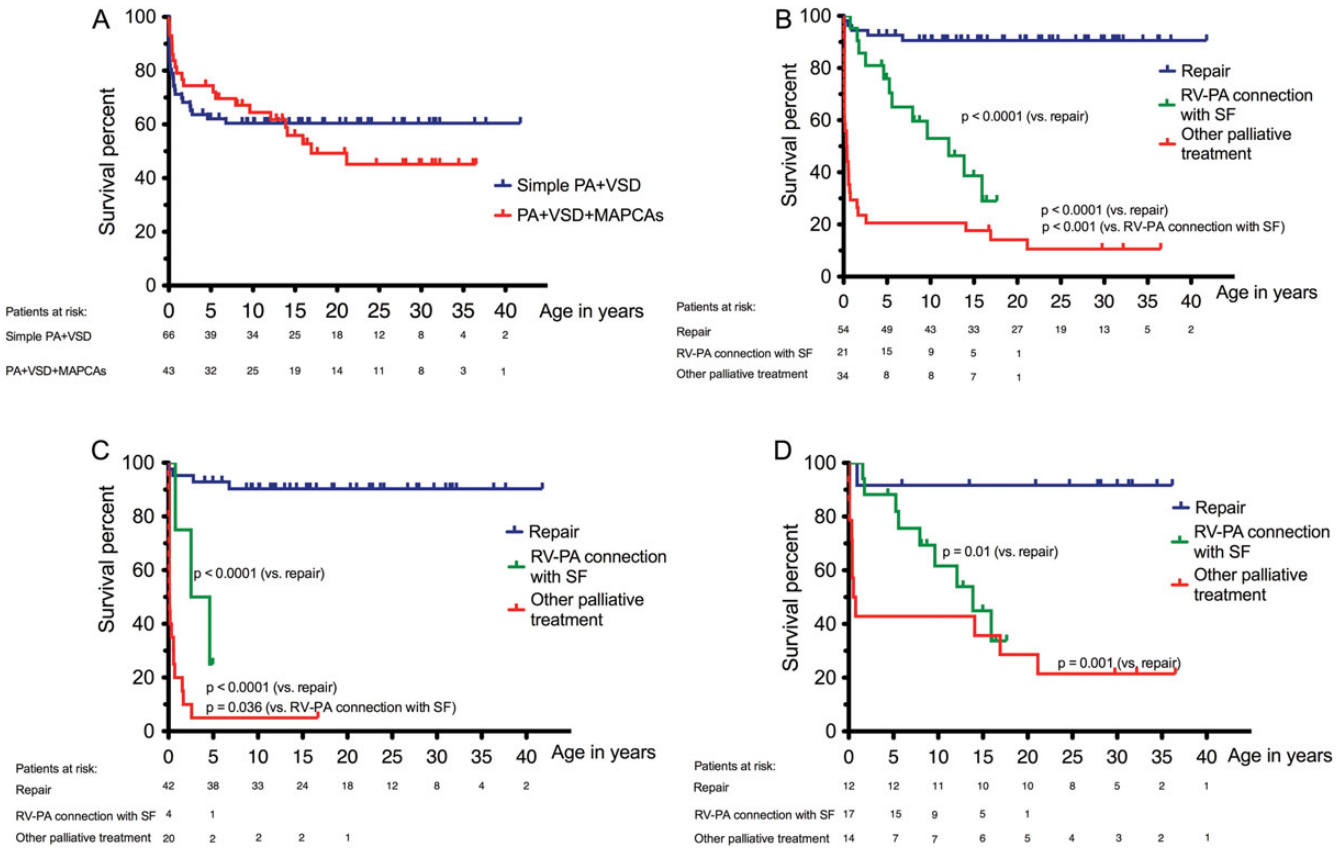

Figure 2: Comparison of survival from birth between patients with simple PA + VSD and PA + VSD + MAPCAs (**A**). Survival from birth in overall study population (**B**), in patients with simple PA + VSD (**C**) and in patients with PA + VSD + MAPCAs (**D**). Comparisons between repaired patients, patients palliated with a RV–pulmonary artery connection with SF and patients with other palliative treatment only. PA + VSD: pulmonary atresia with ventricular septal defect; MAPCA: major aortopulmonary collateral artery; RV–PA: right ventricle–pulmonary artery; SF: septal fenestration; MAPCA: major aortopulmonary collateral artery.

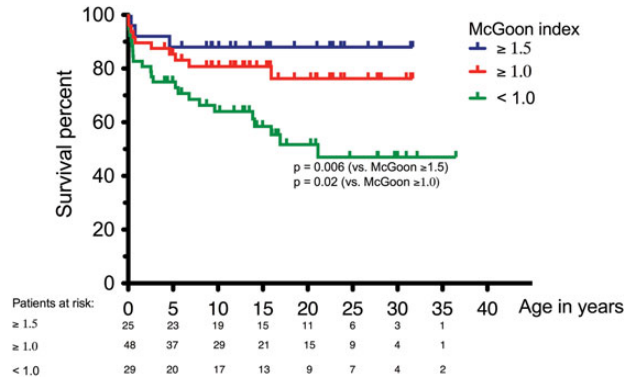

Figure 3: Comparison of survival from birth between patients with a McGoon index ≥1.5, ≥1.0 and <1.0 on the first available angiogram.

fenestration had on average 2.3 ± 1.9 catheter-based interventions. Patients receiving palliative treatment only had a Kaplan–Meier estimated survival rate at 1, 5, 10, 20 and 30 years of age of 55, 42, 34, 20 and 15%, respectively. Of the 55 palliated patients, 24 died within 30 days from cardiac surgery, 17 patients died on average 3.2 ± 4.8 years from the last cardiac surgery and 1 patient not operated on died at 0.42 years of age. Survival of the palliated patients was better if MAPCAs were present ($P < 0.0001$) but was not affected by the size of MAPCAs assessed by TNPAI ($P = 0.89$). At the end of follow-up, 2 (8%) patients with simple PA + VSD and

Table 4: Univariable Cox regression analysis of selected factors for surgery or catheter-based reintervention after repair

	HR (95% CI)	*P*
Demographic factors		
Birth year (per year)	1.02 (0.98–1.06)	0.46
Associated cardiac findings	0.81 (0.39–1.66)	0.56
22q11.2 deletion	1.53 (0.46–5.11)	0.49
Other genetic or significant syndrome	0.74 (0.26–2.11)	0.57
Presence of MAPCAs	1.92 (0.88–4.17)	0.10
Presence of pulmonary artery confluence	0.12 (0.02–0.58)	0.008
Perioperative RV/LV systolic pressure at repair >50%[a]	2.73 (1.01–7.39)	0.04
Age at repair (per year)	0.91 (0.79–1.06)	0.24
Age at first operation (per year)	1.37 (1.08–1.75)	0.01
Anatomic data from preoperative angiograms prior to repair ($n = 41$)		
Lung segments supplied by true pulmonary arteries	0.92 (0.79–1.07)	0.25
McGoon index (per 0.5 units)	0.57 (0.36–0.88)	0.01
Improvement of the McGoon index (per 0.5 units)[b]	1.12 (0.62–2.00)	0.71

CI: confidence interval; HR: hazard ratio; MAPCA: major aortopulmonary collateral artery; RV/LV: right ventricle/left ventricle.
[a]Data available for 33 patients.
[b]Data from 22 paired angiograms.

11 (35%) patients with MAPCAs were alive. Surviving patients had a mean NYHA class of 1.7 ± 0.9 at the latest follow-up visit.

DISCUSSION

In this study, comprehensively representing the nationwide patient population without a selection bias, we found that survival of patients with PA + VSD is influenced by initial size of true central PAs and whether repair is attained. Our results showed that the presence of MAPCAs was insignificant for overall survival. In addition, since central pulmonary arteries enlarge after implementation of a systemic–pulmonary artery shunt, palliative surgery also may have an impact on survival of PA + VSD patients.

According to our study, the incidence of PA + VSD in Finland is 6.1 per 100 000 live births, which is in line with incidence rates reported [1–3]. Our study demonstrated 10-, 20- and 30-year overall survival rates of 60, 55 and 53%, respectively. These rates, consistent with Dinarevic *et al.* [11] or only somewhat lower than those by Amark *et al.* [7] with similar follow-up periods, confirmed that the modern survival rates are better than survival rates in studies from earlier study periods [2, 4]. Although we could not demonstrate birth year affecting survival in our series, we did find that later year of birth increased the probability of repair, which is consistent with the findings of the previous study of Amark *et al.* [7].

In our study, the repair rate was 64% in the patients with simple PA + VSD, compared with 28% of the patients with MAPCAs. Furthermore, our finding—that presence of pulmonary artery confluence, higher McGoon index and more lung segments supplied by true pulmonary arteries increased the probability of repair—supports a more complex anatomy as a risk factor for remaining palliated [12]. A previous study with follow-up to 1989 showed lower repair rates than our study—46% in the patients with simple PA + VSD and 16% in the patients with MAPCAs [12]. However, our repair rates are somewhat lower than in previous reports with follow-up to 1999 or later, which have shown repair rates of 80–87% in simple PA + VSD patients, and 40–60% in patients with MAPCAs [7, 9, 15]. We believe that this disparity may reflect institutional differences in the selection criteria for a repair attempt. After repair, both the early and late survival rates of our series were acceptable and superior or comparable with previous series with 10–32 years of follow-up [7, 9, 11, 16]. Additionally, our patients after repair had good functional capacity, as well as reasonable RV/LV systolic pressure ratios, which according to the measurements decreased over the follow-up years. However, repaired patients had frequent reinterventions, which were associated with a RV/LV systolic pressure ratio of over 50% at repair, smaller central pulmonary arteries prior to repair, lack of initial pulmonary artery confluence and later timing of the first operation.

The patients in our study whose surgical treatment was limited to palliative treatment only had a 20% chance of reaching the age of 20 years, which was poorer than reported earlier [9]. Our finding—that patients who underwent a repair attempt but were left with an RV–pulmonary artery connection and septal fenestration had poorer survival than patients who achieved repair—supports failure to close VSD at repair as a risk factor for mortality [9, 17, 18]. However, despite remaining in a palliated state, the latter patients had significantly better survival than patients remaining with extracardiopulmonary blood supply. Of the palliated patients, those with MAPCAs had better survival and underwent a repair attempt with septal fenestration more often than patients without MAPCAs, who were more likely to receive extracardiac procedures only. This finding may explain why, in our study, in contrast to Cho *et al.* [9], the palliated patients had better survival in the presence of MAPCAs. Therefore, despite failure to achieve intracardiac repair, palliative surgery aiming at establishment of an RV–pulmonary artery connection should have a role in the treatment of PA + VSD.

In previous reports, achievement of repair has either improved or has lacked influence on survival of patients with PA + VSD + MAPCAs [10, 13]. In our series, both in patients without and with MAPCAs, achievement of repair was the most significant factor affecting survival. As the size of the native pulmonary arteries is very important for both survival and achievement of repair, we believe that their initial assessment is crucial. The lesser effect of MAPCAs on survival, however, may have at least partly be related to the lower repair rate compared with previous studies, and positive influence of MAPCAs on the survival of palliated patients.

After palliation with a systemic–pulmonary artery shunt, native central pulmonary arteries enlarged. This is consistent with previous studies demonstrating that even diminutive central pulmonary arteries enlarge in response to a systemic–pulmonary artery shunt [10, 19, 20]. Further, the timing of the first operation, which often was a creation of systemic–pulmonary artery shunt, changed towards earlier during the follow-up in our study. Since delayed creation of the systemic–pulmonary artery shunt may predispose native diminutive pulmonary arteries to scarce blood flow and increase the susceptibility of pulmonary arteries to atrophy [8], the change to an earlier improvement of flow and shear stress may have prevented stenosis and atrophy of the diminutive pulmonary arteries. Thus, in addition to improved preoperative treatment and centralization of all paediatric cardiac surgery in Finland to our hospital, the advanced timing of the first operation may have resulted in increased probability of repair in PA + VSD patients born in a later birth year.

With respect to central pulmonary arteries and pulmonary blood supply, the patients with MAPCAs in our study had smaller central pulmonary arteries with fewer lung segments supplied by native pulmonary arteries than patients without MAPCAs at the primary angiogram prior to any surgery. Besides, MAPCAs may have a poor growth potential and may not support development of biologically competent pulmonary circulation [10, 21, 22]. We found that patients with MAPCAs had less lung segments indicative of perfusion than patients without MAPCAs, which supports the finding that MAPCAs have a tendency to stenose [10]. Since this difference in the number of perfused lung segments occurred already in the first angiograms, we suggest that the competition between the collateral-dependent and the ductal-dependent pulmonary blood supply may affect the growth of the native pulmonary arteries already during the foetal period. Since the presence of MAPCAs has a significant influence on the chance of eventual repair of PA + VSD, it would be important to demonstrate their presence by ultrasound examination antenatally [23].

Limitations

The long follow-up extending 41 years from 1970 is an important merit of our study. However, in retrospective studies with extensive follow-up the effect of continuously evolving conservative, operative and interventional therapies in pre-, peri- and postoperative care on morbidity and mortality may be difficult to analyse precisely since many factors affecting survival are interrelated. Inadequate diagnostics of the genetic syndromes in the earlier era of our study obscured thorough evaluation of whether

the 22q11.2 deletion syndrome had an effect on mortality. In our study, 22q11.2 deletion was confirmed in only 11% of the patients, compared with up to 34% reported [24]. Although the size of the central pulmonary arteries and the source of blood flow to each lung segment could be assessed from angiograms, the evidence of the systemic–pulmonary artery shunt's ability to promote growth of intrapulmonary peripheral vessels remained undocumented [25].

CONCLUSIONS

In the present retrospective study extending from 1970 to 2011, the initial size of true central pulmonary arteries significantly affected the probability of repair and, together with eventual repair, influenced the survival of PA + VSD. In our experience, staged repair yields excellent survival with low operative mortality and good functional capacity. Palliative surgery remains an important treatment option of PA + VSD, since after the systemic–pulmonary artery shunt the size of pulmonary arteries increased, and patients palliated with an RV–pulmonary artery connection despite shunting at the septal level had better survival than the rest of the palliated patients. Pathobiology has a role in antenatal development of the pulmonary arteries and survival of PA + VSD patients. Therefore, careful evaluation of the source of pulmonary circulation, the size of pulmonary arteries, medical counselling of the parents and centralization of invasive care of this challenging patient group is crucial to improving outcomes.

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