A retrospective study: Long term prognosis in adults with PA-VSD-MAPCAs

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ABSTRACT

Background: Pulmonary Atresia, Ventricular Deptal Defect, and Major Aortopulmonary Collateral Arteries (PA-VSD-MAPCAs) is a congenital cyanotic heart defect with poor prognosis. Due to its complex and highly variable anatomy, the best treatment plan is not clear. We aimed (1) to investigate the survival of PA-VSD-MAPCAs patients according to the underlying original anatomy and treatment strategy, and (2) to evaluate life expectancy between patients with or without severe hypoplastic native pulmonary arteries (NPAs) after surgical versus non-surgical treatment.
Methods: A prospectively established database of 169 PA-VSD-MAPCAs patients treated and followed up at University Hospitals Leuven was accessed. Patients were divided into three groups according to the treatment strategy. Kaplan-Meier survival curves were plotted, and Log Rank tests were used for comparison.
Results: The overall mean survival for patients with PA-VSD-MAPCAs was 38.5 years (95%-CI: 33.1–43.9). Patients with complete intracardiac repair had the longest mean survival of 43.8 years (95%-CI: 38.1–49.6) versus the other groups ($p < 0.001$). A longer mean event-free survival time was found in patients with normal, well-developed NPAs ($p = 0.047$). Finally, patients with poorly developed or absent NPAs had worse survival rates when a surgical approach was followed. Systemic-pulmonary shunt placement or unifocalisation had limited effect on prognosis in the absence of total repair ($p = 0.167$).
Conclusions: Patients with PA-VSD-MAPCAs who underwent complete intracardiac repair and/or with well-developed native pulmonary arteries had the best prognosis. Our analyzed data suggest that incomplete surgical repair resulted in survival rates comparable to those seen with a non-surgical approach.

1. Introduction

PA-VSD-MAPCAs stands for Pulmonary (valve) Atresia, Ventricular Septal Defect and Major Aortopulmonary Collateral Arteries. This is a complex cyanotic congenital heart defect with an incidence of approximately 7 per 100,000 live births and accounts for about 2.5% of all congenital heart defects [1–4]. It is considered the most extreme type of tetralogy of Fallot, in which patients have pulmonary valve atresia, a VSD, and an overriding aorta. In some patients the pulmonary circulation is partially or completely supplied by MAPCAs [2,4,5]. In about one third, this congenital defect occurs in the context of the 22q11.2 deletion syndrome [2,4,6].

Patients with PA-VSD-MAPCAs can be classified according to pulmonary perfusion and the size of the central pulmonary arteries [3,4,7]. In type A, the pulmonary blood supply is completely dependent on the native pulmonary arteries (NPAs) and there are no MAPCAs. This type has the best prognosis. In type B, both the NPAs (often hypoplastic) and the MAPCAs are responsible for pulmonary perfusion. Finally, in type C (20–40%) the pulmonary blood supply is entirely provided by the MAPCAs. These patients have no NPAs and have the worst prognosis [2,7]. The development of the pulmonary circulation depends on the size of the arterial duct: the larger the duct before birth, the better the

development of the NPAs [4].

Treatment differs according to the type of PA-VSD-MAPCAs. But due to the complex and highly variable anatomy, there is no overall consensus on the best strategy [2,4,8,9]. In type A, patients are usually directly treated by an intracardiac repair (VSD closure + conduit from the right ventricle (RV) to the pulmonary arteries) [4,10]. Also in type B, patients are completely repaired if feasible. A first step is a complete bilateral unifocalisation [1]. To facilitate focalisation, growth of the hypoplastic NPAs is first stimulated by creating antegrade blood flow via a systemic-pulmonary shunt, such as a Waterston or a Blalock-Taussig shunt [1–3,11]. Unifocalisation may be performed in one or more stages and is determined by the presence or absence of stenoses in the MAPCAs and the predicted RV/left ventricle (LV) pressure ratio [8]. After completion of bilateral unifocalisation, intracardiac repair is performed. However, if the predicted RV/LV pressure ratio is >0.5 (with a mean pulmonary artery (PA) pressure > 25 mmHg), the VSD is left open [2,8]. In type C a full recovery of the pulmonary circulation is almost not possible. These patients are helped by promoting blood flow through the MAPCAs by balloon dilatations and stents placements when significant stenoses are present. Full recovery can only be achieved by repeated peripheral PA reconstructions, where it sometimes remains impossible to close the VSD afterwards [2]. When the VSD cannot be closed, it is associated with potential complications such as increasing cyanosis, segmental pulmonary hypertension, haemoptysis, heart failure, arrhythmia and sudden cardiac death, endocarditis, and paradoxical embolism [4,12].

In addition, surgery itself is also associated with potential complications, such as residual RV outflow tract obstruction, early restenosis in the pulmonary circulation, significant pulmonary valve regurgitation, endocarditis, arrhythmia and sudden cardiac death [4,12]. Postoperative respiratory complications may also occur and increase the risk of prolonged postoperative respiratory failure. After unifocalisation, about half of the patients develop reperfusion pulmonary oedema, and postoperative bronchospasm might occur [4].

Because of the complexity of this disease, we were interested in outcome. As such, the first aim of this study was to evaluate and compare the survival of patients with PA-VSD-MAPCAs according to their underlying anatomy and treatment strategy. Secondly, we wanted to evaluate the life expectancy of patients with no or severely hypoplastic NPAs after surgical treatment versus a non-surgical, conservative approach.

2. Methodology

2.1. Patient selection

A prospectively constructed database of all congenital heart defects diagnosed in University Hospitals Leuven and that also included patients with PA-VSD-MAPCAs who were treated and followed up between 01/01/1980 and 02/02/2022 was used to identify patients eligible for inclusion. No exclusion criteria for PA-VSD-MAPCAs patients were applied. The study (MP023887) was approved by the Research Ethics Committee (conform to the ethical guidelines of the 1975 Declaration of Helsinki), complies with Belgian privacy legislation, and adheres to the statement of ethical publishing [13].

2.2. Review of the patient records

For all patients, demographic characteristics, medical history, and previous surgical procedures, NPAs size, and survival data were collected from the medical records through the hospital information system. If meanwhile the patient was deceased, age and cause of death was noted. Upon completion of data collection, the data were de-identified and coded. The University Hospitals Leuven remained owner of the database and no information was disclosed to third parties.

2.3. Survival

To determine and compare long-term prognosis, the patients were divided into three groups according to the treatment strategy. Group 1 were patients in whom a complete intracardiac repair was performed, in the patients of group 2 a shunt was placed without intracardiac repair, in the patients of group 3 the blood flow through the MAPCAs was only promoted by balloon dilatation and/or stent implantation or did not receive any surgical or interventional treatment at all.

Patients of group 1 were further divided according to whether they first had received a systemic-pulmonary shunt or whether the repair surgery was performed in one step. Patients were also stratified for statistical analysis whether they underwent an unifocalisation process or not. NPAs were coded as absent, hypoplastic, or well-developed. No absolute cut-off values were used. The assessment was done semi-quantitatively based on the diameter of the pulmonary arteries compared to the normal expected value. If catheterization revealed no native pulmonary arteries, this was recorded accordingly. If the pulmonary arteries were close to the normal expected diameter, they were coded as well-developed. All others were coded as hypoplastic.

2.4. Statistical analysis

Descriptive statistics were applied: mean (± standard deviation) and median (minimum and maximum range) for normally and non-normally distributed continuous variables, respectively. Proportions are presented as numbers and percentages. Survival estimates were calculated, Kaplan Meier curves plotted, and to compare groups Log Rank testing was performed. P-values below 0.05 were considered significant. All tests were two-tailed. IBM SPSS Statistics version 29 was used.

3. Results

3.1. Patient characteristics

A total of 169 PA-VSD-MAPCAs patients were selected and included from a database of 56,153 records (02/2022), 72 male and 97 female. The patient characteristics of the three groups are summarized in Table 1. A total of 36 patients underwent unifocalisation surgery. The median age at first complete intracardiac repair was 1.82 years (0.04–40.86 years). The mean age of patients alive at the time of data analysis (02/2024) was 25.45 ± 14.40 years. Table 2 refers to the proportional distribution of groups depending on the year of birth. The proportion complete repair increased over time.

Table 1
Patient characteristics.

	Group 1	Group 2	Group 3
Total (n)	104	40	25
Sex (n)			
Male patients	49	13	10
Age (years) mean ± SD	21.9 ± 13.4	20.0 ± 18.3	27.3 ± 3.0
NPAs (n)			
Absent	2	3	8
Hypoplastic	61	33	13
Well-developed (missing data)	9 (2)	1 (3)	2 (2)
Unifocalisation (n)	26	10	/
New York Heart Association*			
Alive (class) median (min-max range)	I (I-III)	I (I-III)	II (I-IV)
Death (class) median (min-max range)	II (I-IV)	III (I-IV)	II (I-II)
Saturation at latest follow-up			
Alive (%) mean ± SD	97 ± 3	85 ± 10	86 ± 9
Death (%) mean ± SD	85 ± 14	76 ± 10	70 ± 6

n: number; NPAs: native pulmonary arteries; SD: standard deviation; * for adult patients at latest follow-up.

Table 2
Proportional distribution of groups depending on the year of birth.

Year of birth	Group 1	Group 2	Group 3
< 1980	30%	27%	43%
1980–1999	60%	25%	15%
> 1999	72%	20%	8%

3.2. Survival

Of the 169 patients included, 57 died during follow-up (34%). Thirty-six of the 57 patients (63%) died because of cardiovascular reasons, 7 patients died of non-cardiac causes, and the cause of death of 14 patients was not noted in the medical records. The median age at death was 8.4 years (0.0 year - 55.9 years). The overall mean survival time for patients with PA-VSD-MAPCAs was 38.5 years (95% confidence interval (95%-CI): 33.1–43.9). Survival for the entire cohort is plotted in Fig. 1.

3.3. Survival analysis according to the anatomy and the treatment strategy

Survival of the three different groups is visualised in Fig. 2. The mean survival time was the longest in group 1 with 43.8 years (95%-CI: 38.1–49.6). Mean survival times in groups 2 and 3 were 26.3 and 32.8 years, respectively (95%-CI: 19.0–33.5 and 95%-CI: 21.3–44.2, respectively). Survival times differed significantly between the 3 groups (Log Rank, $p < 0.001$). Significancy was driven by group 1.

To investigate whether staged repair had a different outcome on survival versus direct repair, a sub-analysis in group 1 was performed. A total of 89 patients (86%) received first a shunt, while the remaining 15 patients (14%) underwent direct repair. Corresponding survival curves are plotted in Fig. 3. The mean survival of patients with a previous shunt was 44.0 years (95%-CI: 37.9–50.1), the mean event free survival of the patients without a previous shunt was 31.0 years (95%-CI: 24.1–37.8). The difference was not statistically significant (Log Rank, $p = 0.542$).

3.4. Survival and the development of the native pulmonary arteries

The patients with well-developed NPAs (a total of 42 patients) had a mean survival time of 45.8 years (95%-CI: 39.5–52.1), in the patients with hypoplastic NPAs (a total of 107 patients) this was 36.6 years (95%-CI: 29.8–43.4), and in the patients without NPAs (a total of 13 patients) this was only 27.9 years (95%-CI: 18.6–37.3). The development of the NPAs significantly influenced the mean survival time (Log Rank, $p =$ 0.047). Significance was driven by the patients with well-developed NPAs. Fig. 4 shows event-free survival in relation to the different levels of NPAs development.

3.5. Survival of unifocalisation versus no surgical intervention

Finally, it was investigated whether the unifocalisation in patients with hypoplastic NPAs or no NPAs influenced survival versus a non-surgical treatment. Therefore, we compared the survival of patients from group 2 with no or hypoplastic pulmonary arteries who underwent unifocalisation ($n = 8$) with the survival of group 3. The mean survival of patients who underwent unifocalisation was 15.2 years (95%-CI: 6.5–23.9), while the mean survival time of patients who did not undergo unifocalisation was 32.8 years (95%-CI: 21.3–44.2). The difference was not statistically significant (Log Rank, $p = 0.167$), but the survival curves tended to diverge in favour of the non-surgical approach.

4. Discussion

This retrospective study investigated first the survival of patients with PA-VSD-MAPCAs according to the underlying anatomy and treatment strategy. Secondly, it was questioned whether the life expectancy of patients with no or severely hypoplastic NPAs would be better after surgical treatment than after a non-surgical, conservative approach.

As reported in other studies [4,14], the analysis of this series of patients with PA-VSD-MAPCAs confirmed that overall outcome is compromised. Patients born with this complex cyanotic heart defect have a high mortality rate and a lower life expectancy.

The most important characteristic for long-term survival is whether the patients can undergo a complete intracardiac repair. This operation is in use since 1960 by closing the VSD and placing a (valved) conduit between the RV and the pulmonary circulation. This constantly evolving technology is still improving the results of this therapeutic approach [10,12]. Also, in our series in the last decades complete repair is more and more pursued (Table 2). The mean event-free survival of patients who underwent palliation surgery, MAPCA dilation/stenting, or conservative therapy was clearly shorter than that of patients who underwent complete repair. New in this study is that if patients undergo complete intracardiac repair (group 1), the decline in survival is slow and relatively stable over time (survival curves in Fig. 2) and that the overall outcome is far better than in patients with an incomplete repair. The latter suggests that, if possible, a complete repair needs to be pursued.
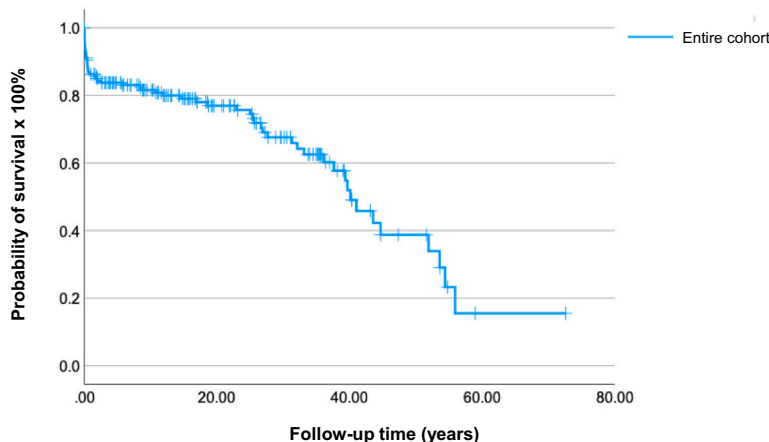

Number at risk	169	107	69	44	19	10	02	01	00
Number of events	0	30	35	42	49	53	57	57	57

Fig. 1. Event-free survival for the entire PA-VSD-MAPCAs cohort.

Fig. 2. Forty-year event-free survival according to the anatomy and the treatment strategy.
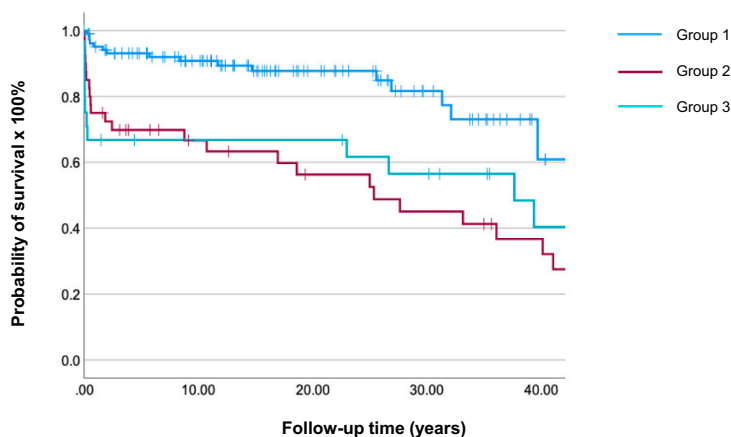
Group 1	Number at risk	104	71	38	19	04
	Number of events	0	30	35	42	49
Group 2	Number at risk	40	30	15	11	07
	Number of events	0	10	16	22	22
Group 3	Number at risk	25	14	12	10	05
	Number of events	0	08	09	10	12
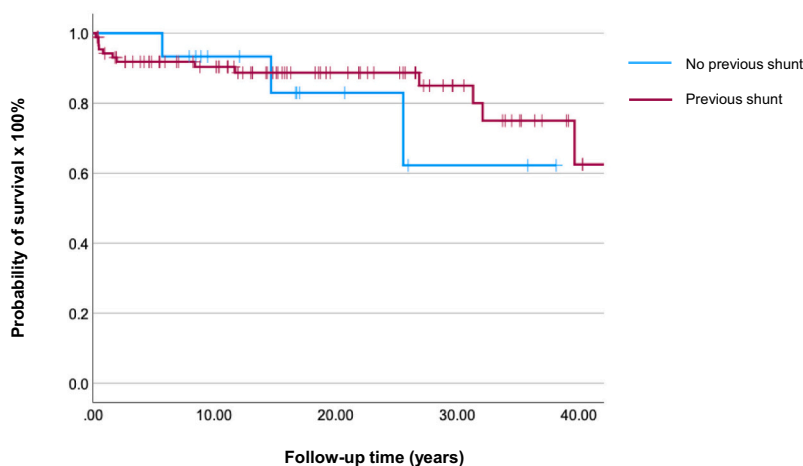
| No previous shunt	Number at risk	15	10	05	02	0
	Number of events	0	01	02	03	03
Previous shunt	Number at risk	88	61	34	17	04
	Number of events	0	08	09	10	13

Fig. 3. Forty-year event-free survival of complete repair, shunt versus no previous shunt.

Data in the literature suggest that in many cases direct repair is preferred [15,16]. However, an interesting finding in this series was that patients who underwent a staged repair had a similar outcome compared to those who were treated with a direct repair. At University Hospitals Leuven, it is customary to prefer direct repair if the size, the maturation status, and the flow area of the NPAs permit it. Given that most patients were treated with a staged approach, this likely reflects a more cautious, but feasible and effective strategy [17,18]. In a qualitative analysis of the dataset, long-term survival seems mainly related to circulatory failure.

Patients who underwent only shunt surgery (group 2) had a high early mortality, but after the peri-operative period the survival curve seemed to follow the curve of patients with complete intracardiac repair. This new finding shows that despite the high early mortality, these patients fare quite well in the long term. Dealing particularly with the peri-

and postoperative complications of this group could further improve the overall outcome. Reviewing the patients' records, peri- and post-operative mortality was mainly associated with overall hemodynamic failure, which might be related to the complexity of the underlying anatomy.

Patients who did not receive a surgical intervention but only balloon dilatation and/or stenting of the MAPCA's (one part of group 3, separate data not shown) had relatively stable survival in the first two decades of life, but then a rapid decline in survival occurred. This decline could be explained by the nature of the MAPCAs that tend to close further in the third and fourth decade of life and leads to irreversible severe central cyanosis. Moreover, neointimal in-stent fibroproliferation and stent fracture can be expected as complications in mid-term follow-up [19]. Patients with a conservative treatment (second part of group 3, separate data not shown) most probably because the impossibility for a
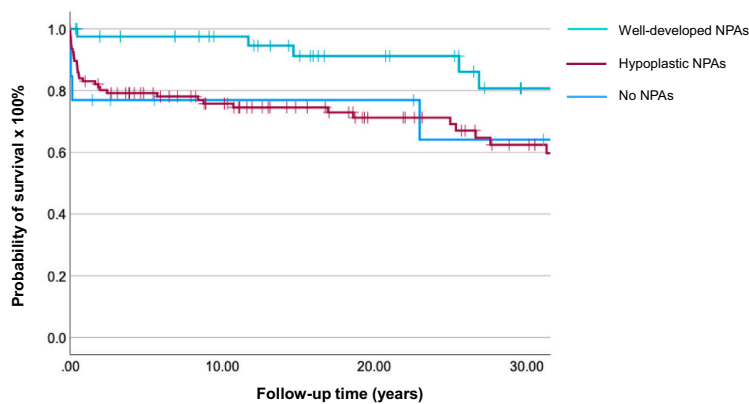
Well-developed NPAs	Number at risk	42	33	21	12
	Number of events	0	01	03	05
Hypoplastic NPAs	Number at risk	107	63	38	25
	Number of events	0	25	28	32
No NPAs	Number at risk	13	07	06	05
	Number of events	0	03	03	04

Fig. 4. Thirty-year event-free survival in relation to the different levels of native pulmonary arteries development.

percutaneous intervention to improve oxygenation had a very high perinatal mortality. Severe central cyanosis should be considered as the main driver of death.

Another characteristic for outcome is the degree of the development of the NPAs. Poorly developed NPAs are a known risk factor for compromised outcome [18]. In this study, patients with normal, well-developed NPAs had a significant better life expectancy. Rehabilitation of NPAs before definitive repair, however, is necessary and feasible in most of the PA-VSD-MAPCA patients [1,20].

Interesting to note is that shunt surgery seemed not to significantly improve the survival when complete repair was not possible. This might be related to the need for reinterventions [21]. As such the justification for palliative surgery to improve pulmonary blood flow remains to be established [22]. In fact, patients who had no surgery at all (group 3) had a similar trend of survival when compared to the patients of group 2. Also, performing a unifocalisation (in patients with poorly developed NPAs) without definitive repair, did not have a positive effect on survival in our series. These results contradict previous publications which claimed that unifocalisation was associated with a better prognosis [4,18,23]. However, comparison between groups must be done carefully, as they represent different patient characteristics. Moreover, it has to be emphasized that potential complications of the (re)operation must always be considered, as the intervention itself can also be a cause of mortality [12,21]. Nevertheless, unifocalisation is important in case of a definite repair to optimize outcome [24].

A final observation is the wide range of mean survival in group 3. This is partly caused by a patient who survived at least to the age of 72.6 years. In this specific case, the pulmonary blood supply was entirely provided by untouched MAPCAs. The patient was still alive at the time of data analysis. However, this patient suffered from pulmonary hypertension, dyspnoea, and moderate cyanosis. It is unclear to what extent this large spread in the third group affected the trend that was found in the analysis.

The study had some limitations. As this congenital heart defect is very rare, the power of this analysis is low. Only 169 patients with PA-VSD-MAPCAs were registered in the University Hospitals Leuven database. This number seems to be relatively low but is in the size order expected [25]. Patients were post hoc divided into three groups according to the anatomy and the treatment strategy. As such, randomisation was not done, and the groups were not evenly distributed. To be able to compare the characteristics of the patients in the different groups, patient selection and distribution were described in detail. In

addition, the three groups were very heterogeneously composed, specifically the third group, with too few patients and too many events per group, so that statistical power was insufficient to apply associative statistics. The study had to deal with some missing data and loss to follow-up in all three groups. Indeed, some of the patients were transferred to another hospital for further follow-up. However, this number was low and only the hard endpoint (death) was reviewed (which is systematically updated in the database). Finally, biases could have occurred: selection bias: when a shunt is placed, the intention is always to achieve a complete repair, which means that these patients already have a better prognosis in se; information bias: there may be an error in the accuracy of the measurements used for data analysis, although accuracy was monitored as much as possible.

5. Conclusions

This analysis confirmed that patients with PA-VSD-MAPCAs who underwent complete cardiac repair had the best overall outcome. A surgical intervention in patients in whom complete repair was not possible did not significantly prolong survival on the long-term. A trend in our series was noticed that a conservative, non-surgical approach in patients with poorly developed native pulmonary arteries or in whom blood flow through the MAPCAs was promoted by balloon dilatation or stenting had similar survival than those who had a systemic-pulmonary shunt constructed. As such, if complete repair is not possible, the use of one or several interventions remains debatable. Large, multi-centre trials are needed to see if the benefits of surgery outweigh the risks in the most diseased patients.

CRediT authorship contribution statement

Sophie Berghmans: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Bénédicte Eyskens:** Writing – review & editing, Methodology, Data curation, Conceptualization. **Filip Rega:** Writing – review & editing, Methodology, Investigation. **Philip Moons:** Writing – review & editing, Writing – original draft, Validation, Methodology. **Els Troost:** Writing – review & editing, Methodology. **Pieter De Meester:** Writing – review & editing, Writing – original draft, Methodology. **Alexander Van De Bruaene:** Writing – review & editing, Writing – original draft, Methodology. **Werner Budts:** Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration,

Methodology, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

These authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation; no grant support; no conflict of interest.

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