International Journal of Cardiology 280 (2019) 61–66

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

The outcome of adults born with pulmonary atresia: High morbidity and mortality irrespective of repair

Claudia Montanaro [a,1], Assunta Merola [a,1], Aleksander Kempny [a,b], Belen Alvarez-Alvarez [a], Rafael Alonso-Gonzalez [a,b], Lorna Swan [a,b], Anselm Uebing [a,b], Wei Li [a,b], Sonya V. Babu-Narayan [a,b], Michael A. Gatzoulis [a,b], Konstantinos Dimopoulos [a,b,*]

[a] Adult Congenital Heart Centre and National Centre for Pulmonary Hypertension, Royal Brompton Hospital, London, UK
[b] NIHR Cardiovascular Biomedical Research Unit, Royal Brompton Hospital and National Heart and Lung Institute, Imperial College London, UK

ARTICLE INFO

Article history:
Received 8 April 2018
Received in revised form 15 October 2018
Accepted 5 November 2018
Available online 7 November 2018

Keywords:
Pulmonary atresia
Adult
Outcome
Congenital heart disease
Cyanosis

ABSTRACT

Objectives: To describe the characteristics and long-term outcome of a large adult cohort with pulmonary atresia.
Background: Patients with pulmonary atresia (PA) are a heterogeneous population in terms of anatomy, physiology and surgical history, and their management during adulthood remains challenging.
Methods: Data on all patients with PA followed in our center between January 2000 and March 2015 were recorded. Patients were classified into the following groups: PA with ventricular septal defect (PA-VSD, 1), PA with intact ventricular septum (PA-IVS, 2) and other miscellaneous PA (PA-other, 3).
Results: Two-hundred twenty-seven patients with PA were identified, 66.1% female, mean age 25.5 ± 8.7 years. Over a median follow-up of 8.8 years, 49 (21.6%) patients had died: heart failure ($n = 21$, 42.8%) and sudden cardiac death ($n = 8$, 16.3%) were the main causes. There was no significant difference in mortality between the 3 Groups ($p = 0.12$) or between repaired and unrepaired patients in Group 1 ($p = 0.16$). Systemic ventricular dysfunction and resting oxygen saturations were the strongest predictors of mortality. Additionally, 116 (51%) patients were hospitalized, driven mainly by the need for invasive procedures, heart failure and arrhythmias.
Conclusions: Adult survivors with pulmonary atresia have a high morbidity and mortality irrespective of underlying cardiac anatomy and previous reparative or palliative surgery. We present herewith predictors of outcome in adult life that may assist with their tertiary adult congenital care.

1. Introduction

Pulmonary atresia is defined as the absence of direct communication between the ventricular chamber/s and the pulmonary vascular bed. The traditional classification of PA divides patients into 2 groups, based on the presence or the absence of a VSD [1]. However, this defect can be present at birth in the context of a variety of cardiac morphologies and the pathophysiology cannot be fully described by this simple dichotomy. There is a third group of patients with PA, VSD and complex univentricular type of anatomy who are not suitable for biventricular repair. The resulting spectrum of anatomy is, therefore, broad and, despite major progress in surgical techniques and the ever expanding use of percutaneous interventions, morbidity and mortality for patients with PA remains high.

The management of PA in adult life is particularly challenging. One of the main difficulties lies precisely in the morphological heterogeneity of this population. Other variables, such as previous surgical management or individual medical history also influence patient outcome [2]. Previous studies mostly focused on a single type of anatomical defect or analyzed data only from pediatric patients [3–6]. In this study, we describe a large population of adults born with PA, inclusive of the full spectrum of cardiac defects and all past surgical history. Our aim was to define the spectrum of PA encountered in an adult congenital heart disease (ACHD) service and assess the morbidity and mortality associated with PA in adulthood.

Abbreviations: PA, pulmonary atresia; VSD, ventricular septal defect; RV, right ventricle; TCPC, total cavo-pulmonary connection; NYHA, New York Heart Association; MAPCAs, major aortopulmonary collateral arteries; PH, pulmonary hypertension; PPM, permanent pacemaker; AICD, Automated Implantable Cardioverter-Defibrillator; AF, atrial fibrillation; AV, atrio-ventricular; VA, ventriculo-arterial.

* Corresponding author at: Adult Congenital Heart Centre, Royal Brompton and Harefield NHS Foundation Trust, Sydney Street, SW3 6NP London, UK.
E-mail address: k.dimopoulos02@gmail.com (K. Dimopoulos).
[1] Authors contributed equally.

2. Methods

All adult patients (age ≥ 15 years) with a diagnosis of PA followed at our tertiary ACHD center in the period between January 2000 and March 2015 were identified from the hospital Electronic Patient Records. Medical records were retrospectively reviewed to obtain demographic information (gender, age at first assessment in the ACHD service), complete anatomic description of the original cardiac diagnosis (as extracted from original pediatric records or imaging assessments) and surgical/interventional history for each

https://doi.org/10.1016/j.ijcard.2018.11.011
0167-5273/

patient. According to this data, patients were grouped into the following diagnostic anatomic groups (Fig. 1):

- Group 1, PA with VSD (PA-VSD): this Group comprises of all patients with PA and VSD, with two atrio-ventricular (AV) valves and concordant AV connections, with intracardiac anatomy of tetralogy of Fallot (TOF), including patients with double outlet RV (i.e. DORV). Pulmonary arterial supply varies in this Group, ranging from well-developed confluent native pulmonary arteries supplied by a patent arterial duct (PDA), to absent or greatly diminished central pulmonary arteries, in the presence of MAPCAs, supplying segments of the lungs. According to the surgical history, Group 1 was divided into two further subgroups: Group 1a (previous biventricular repair) including patients who on entry to our study had undergone complete repair (defined as restoration of biventricular circulation, closure of VSD and connection of the RV with the pulmonary arterial bed with a conduit) and Group 1b (no biventricular repair) including patients in whom complete repair had not been attempted or was not feasible; these patients either never had any intervention or had undergone one or more palliative procedures (i.e. arterial shunts) by the time of their inclusion in the study.
- Group 2, PA with intact ventricular septum (PA-IVS): this Group includes patients without VSD or with a restrictive VSD. These patients have confluent, sizable central pulmonary arteries. Obstacle to biventricular repair may be the size of the RV, which can be hypoplastic.
- Group 3, miscellaneous "complex" PA (PA-other): this Group comprises of patients with PA and complex anatomy, including atrial isomerism, anomalies

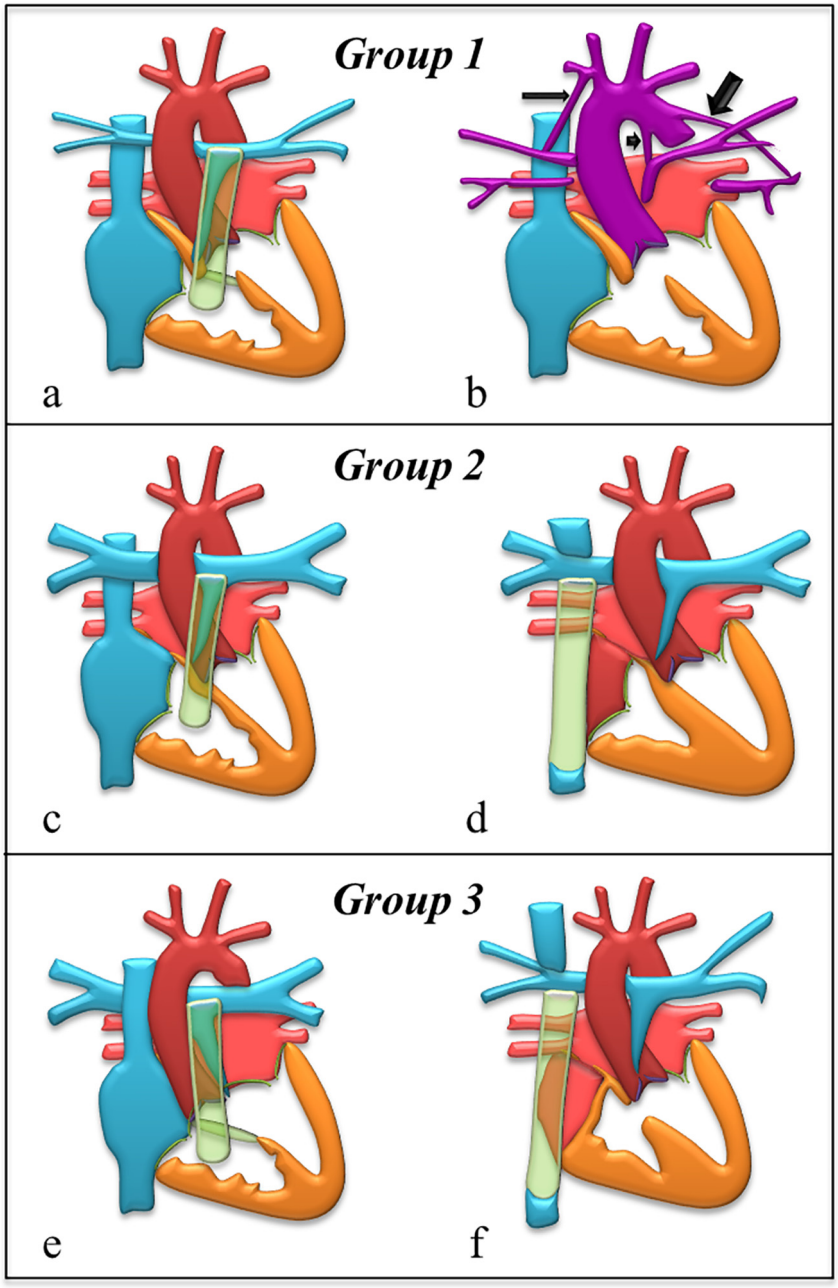

Fig. 1. Diagnostic Groups of pulmonary atresia. Group 1: PA with a VSD, divided into patients with previous biventricular repair (Group 1a, Figure a), and those without previous repair (Group 1b, Figure b). Repair involves VSD closure and implantation of a RV-to-pulmonary artery conduit (Figure a, in transparent green) with ligation of collateral vessels. In unrepaired cases (Figure b), non-confluent pulmonary arteries may be supplied by an arterial shunt (thin long arrow), a patent ductus arteriosus (thick short arrow) or MAPCAs (thick long arrow). Group 2: PA with intact ventricular septum, without or with significant hypoplasia of the RV (Figures c and d, respectively). When hypoplasia to the RV is present, biventricular repair may not be possible and a Fontan circulation is established: in Figure d, TCPC, with a Glenn shunt i.e. superior vena cava-to-right pulmonary artery connection, plus an extracardiac conduit from the inferior vena cava to the RPA. Group 3: Miscellaneous "complex" PA. An example of transposition of great arteries, with a VSD and pulmonary atresia is shown in Figure e, with a Rastelli-type repair involving VSD closure with a long patch channeling the aorta to the left ventricle and a RV-to-pulmonary artery conduit (green). In figure f, PA with tricuspid atresia, atrial and VSDs and a hypoplastic RV is shown. Many patients in this Group undergo a Fontan-type operation. A TCPC repair is shown.

of the AV connection (AV valve atresia or common AV valve), VA discordance (transposition of the great arteries, TGA), or double outlet VA connection with a hypoplastic ventricle and a VSD.

Mortality data were retrieved from national databases. Predictors of outcome were assessed for the entire population and for the 3 Groups: cardiac diagnosis including situs, presence of right aortic arch, presence of MAPCAs, previous surgical procedures (type and number, i.e. palliation, repair, etc.), number of sternotomies and/or thoracotomies, presence of segmental PH (confirmed at cardiac catheterization), baseline cardiac rhythm, QRS duration, resting oxygen saturation (O_2), baseline functional class according to the New York Heart Association (NYHA), cardiothoracic ratio (CTR), systemic ventricular systolic function, hemoglobin (Hb) and creatinine levels and heart failure therapy.

Outcome endpoints included: all-cause mortality, death from arrhythmia/sudden cardiac death (SCD), the composite endpoint of death or cardiac-hospitalization for intervention (surgical or percutaneous), sustained arrhythmia or decompensated heart failure. Admissions for diagnostic assessment and non-cardiac causes were excluded from the analysis.

2.1. Statistical analysis

Data were summarized as mean ± SD for continuous variables and number (%) for categorical variables. Comparison of continuous variables between Groups was performed using non-parametric Wilcoxon rank sum test or Kruskal-Wallis test and categorical variables were compared using Fisher's exact test. The relation between clinical parameters and outcome measures was assessed using univariable and multivariable Cox proportional hazard regression analysis, using the date of the oldest full assessment within the ACHD unit as start date. For all analyses, a two-tailed p-value < 0.05 was used as the criterion for statistical significance. Statistical analyses were performed using R version 3.0.1 (The R Foundation for Statistical Computing).

3. Results

3.1. Patient characteristics

A total of 227 adult patients fulfilled entry criteria and were included in the study. Baseline characteristics of the entire cohort and of the 3 individual Groups are summarized in Table 1. Mean age at first assessment was 25.5 ± 8.7 years: patients in Group 2 were significantly younger while those in Group 1 were older ($p < 0.001$). Female gender was prevalent (66.1%). One fifth of patients had a right aortic arch (22%), mostly in Group 1 (26.3%); 6.2% of patients had a situs abnormality, all in Group 3. Approximately half of our adult PA patients (53.7%) had undergone complete anatomical repair, mainly in Groups 1 and 2 ($p < 0.001$), while 39.6% had received definitive palliation, mainly in Group 3 ($p < 0.001$, Fontan-type operation 54.3%).

The vast majority (88.1%) were in NYHA class ≤ II. Group 3 patients had a lower NYHA class, more impaired systemic ventricle function and were more likely to be on heart failure medication at baseline. The vast majority of patients were in sinus rhythm at first presentation (94.3%) and the QRS interval was longer in Group 1 ($p < 0.001$); 7 patients (3.1%) had paced rhythm and 2 an Automatic Implantable Cardioverter Defibrillator (AICD). In the overall population, a significant proportion of patients had a diagnosis of PH at baseline assessment (8.4%), and this doubled by the end of follow-up (16%). Segmental PH was the most common form (11% at the end of follow-up), often related to the presence of large aortopulmonary collaterals. Pulmonary arterial hypertension therapies were used by 7.4% of patients over the entire study period.

Significant differences were observed between Groups 1a and 1b (Table 2); out of 59 patients with no biventricular repair (Group 1b), 14 were in natural history. Group 1b also had lower resting oxygen saturations ($p < 0.001$) and higher hemoglobin ($p < 0.001$). No difference in the prevalence of ventricular dysfunction was observed.

3.2. All-cause mortality

Over a median follow-up of 8.8 years [IQR 4.3–13.2], death from any cause occurred in 49 (21.6%) patients: 32 patients belonged to Group 1 (65.3%, equally split between Groups 1a and 1b), 2 to Group 2 (4.1%) and 15 to Group 3 (30.6%). The most common overall cause of death was heart failure (42.8%), followed by arrhythmia/SCD (16.3%), hemoptysis (12.2%), brain hemorrhage (6.1%), ischemic heart disease (2%), renal failure (2%), other non-cardiac causes (12.2%); in 6.1% of cases the precise cause of death was unknown. There was no significant difference in mortality between the 3 Groups ($p = 0.12$, Fig. 2a) and, there was no significant difference in survival between Group 1a and 1b within the PA-VSD Group ($p = 0.16$, Fig. 2b).

Surgical history for the total cohort was associated with survival: patients with definitive palliative procedures had the worst survival compared to patients with biventricular repair following earlier palliation (HR 5.77, 95%CI: 1.38–24.16, $p = 0.02$) and to those with primary repair without previous palliation (HR 2.05, 95%CI:1.10–3.82, $p = 0.02$). Patients who had undergone Fontan (atriopulmonary or TCPC) or Glenn operation (31% in Group 2, 54.3% in Group 3) had a high mortality (21% died during follow-up), but this was not statistically different to the remainder (Logrank $p = 0.98$).

Systemic ventricular dysfunction was associated to mortality: patients with mild (HR 2.67, 95CI: 1.37–5.19, $p = 0.004$) or moderate-severe impairment (HR 2.94, 95%CI: 1.04–8.33, $p = 0.04$) had a higher mortality risk compared to the remainder. Patients in NYHA class II (HR 1.96, 95%CI: 1.02–3.76, $p = 0.04$) and III (HR 4.28, 95%CI: 2.02–9.07, $p < 0.001$) had a higher mortality compared to asymptomatic patients. Patients with PH had a higher mortality compared to those without (HR 2.50, 95%CI: 1.12–5.59, $p = 0.03$). There was also higher mortality in patients with lower resting oxygen saturations (HR 1.70 per 10% decrease in saturation, 95%CI: 1.25–2.3, $p < 0.001$, Fig. 2c) and higher hemoglobin levels (HR 1.11, 95%CI: 1.01–1.21, $p = 0.03$).

Multivariate Cox analysis, including the presence of PH, oxygen saturation and hemoglobin levels, resulted in only oxygen saturation being predictive of death. Functional class was the only predictor of mortality in a model including previous repair and previous palliation. Finally, in a model including NYHA, ventricular function and oxygen saturation, only the latter two remained in the model and were the strongest predictors of mortality (HR 1.72 per 10% decrease in saturation, 95%CI: 1.28–2.33, $p < 0.001$; HR 2.84 for impaired systemic systolic ventricular function, 95%CI: 1.56–5.17, $p < 0.001$).

3.3. Sudden cardiac death/resuscitated cardiac arrest

Resuscitated cardiac arrest (RCA) or SCD occurred in 9 patients (8 deaths, 1 RCA, 3.96% of the total population) with an incidence of 0.4/100 person-year: 5 from Group 1a, 2 from Group 1b and 2 from Group 3. Kaplan–Meier analysis did not demonstrate a significant difference in arrhythmic/SCD amongst the 3 Groups (Log-rank $p = 0.61$). In univariate Cox analysis, QRS duration and systemic ventricular systolic dysfunction did not predict SCD/RCA. Of the 152 patients with PA-VSD, 8 (5.2%) had an ICD implanted at the time of last follow-up: 3 for secondary prevention and 5 for primary prevention following risk stratification with or without electrophysiological studies in the remaining. None had received appropriate device therapy by the study end (median follow-up 8.8 years).

3.4. Hospitalization for cardiac causes

During the median of 8.8 years of follow-up, 116 (51%) patients required hospitalization for cardiac causes, for a total number of 262 admissions. The most common causes for the first hospitalization were percutaneous or surgical cardiac intervention (51.7%), arrhythmias (13.8%), heart failure (8.6%) and initiation of PAH therapy (7.8%). Less common causes for admission were endocarditis (6.9%), bleeding (5.2%), arrhythmia ablation (3.4%), ICD implantation (0.9%), thrombosis (0.9%) and venesection (0.9%). Group 1 had the highest number of hospitalizations (75.9%), reaching an incidence of 13/100 person-year, followed by Group 3 (19%) with an incidence of 11/100 person-years, while Group 2 (5.2%) had the lowest rate of admission (incidence 5/100 person-years, Log-rank $p = 0.05$). There was no difference in the hospitalization-free survival rates between Groups 1a and 1b

Table 1
Patient characteristics.

Characteristics	Overall population $N = 227$	Group 1 $N = 152$	Group 2 $N = 29$	Group 3 $N = 46$	p-Value
Age (y)	25.5 ± 8.7	27.1 ± 9.0	19.9 ± 3.7	23.9 ± 8.7	<0.001
Born before 1980	105 (46.3%)	83 (54.6%)	3 (10.3%)	19 (41.3%)	<0.001
Female gender	150 (66.1%)	105 (69.1%)	18 (62.1%)	27 (58.7%)	0.4
Right aortic arch	50 (22%)	40 (26.3%)	1 (3.4%)	9 (19.6%)	0.02
Situs					
Solitus	213 (93.8%)	152 (100%)	29 (100%)	32 (69.6%)	<0.001
Inversus	6 (2.6%)	0	0	6 (13%)	
Right isomerism	3 (1.3%)	0	0	3 (6.5%)	
Left isomerism	5 (2.2%)	0	0	5 (10.9%)	
Complete repair	122 (53.7%)	93 (61.2%)	20 (69%)	9 (19.6%)	<0.001
Definitive palliation*	90 (39.6%)	45 (29.6%)	9 (31%)	36 (78.3%)	<0.001
Fontan/TCPC/Glenn	38 (16.7%)	4 (2.6%)	9 (31%)	25 (54.3%)	<0.001
Natural history	15 (6.6%)	14 (9.2%)	0	1 (2.2%)	<0.001
Previous central shunt†	41 (18.1%)	28 (18.4%)	3 (10.3%)	10 (21.7%)	0.45
Number of shunts ≥ 2	80 (35.2%)	47 (30.9%)	7 (24.1%)	26 (56.5%)	0.003
Number of palliations ≥ 2	95 (41.9%)	49 (32.2%)	11 (37.9%)	35 (76.1%)	<0.001
Number of thoracotomies ≥ 2	89 (39.2%)	57 (37.5%)	6 (20.7%)	26 (56.6%)	0.006
Number of sternotomies ≥ 2	68 (30%)	40 (26.3%)	11 (37.9%)	17 (37%)	0.2
Hemodynamic procedures‡	63 (27.8%)	36 (23.7%)	14 (48.3%)	13 (28.3%)	0.02
NYHA class					
I	120 (52.9%)	81 (53.3%)	21 (72.4%)	18 (39.1%)	0.03
II	80 (35.2%)	56 (36.8%)	6 (20.7%)	18 (39.1%)	
III	27 (11.9%)	15 (9.9%)	2 (6.9%)	10 (21.7%)	
Heart failure medications	38 (16.7%)	15 (9.9%)	2 (6.9%)	21 (45.7%)	<0.001
Rhythm					
Sinus	214 (94.3%)	148 (97.4%)	28 (96.6%)	38 (82.6%)	0.02
AF	3 (1.3%)	1 (0.7%)	0	2 (4.3%)	
Atrial Flutter	1 (0.4%)	1 (0.7%)	0	0	
Paced	7 (3.1)	1 (0.7%)	1 (3.4%)	5 (10.9%)	
Complete heart block	2 (0.9%)	1 (0.7%)	0	1 (2.2%)	
Cardio-thoracic ratio	0.55 ± 0.07 (*n.* 183)	0.57 ± 0.07 (*n.* 120)	0.5 ± 0.07 (*n.* 26)	0.53 ± 0.08 (*n.* 37)	<0.001
Systemic ventricle SF					
Good	189 (83.3%)	131 (86.2%)	27 (93.1%)	31 (67.4%)	0.005
Mildly impaired	28 (12.4%)	17 (11.2%)	2 (6.9%)	9 (19.6%)	
Moderately or severely impaired	10 (4.4%)	4 (2.6%)	0	6 (13%)	
PH at inclusion	19 (8.4%)	14 (9.2%)	1 (3.4%)	4 (8.7%)	0.6
Segmental PH	14 (6.2%)	11 (7.2%)	0	3 (6.5%)	0.3
PAH Therapy	2 (0.9%)	1 (0.7%)	1 (3.4%)	0	0.3
AICD	2 (0.9%)	1 (0.7%)	0	1 (2.2%)	0.5
PPM	9 (4%)	2 (1.3%)	1 (3.4%)	6 (13%)	0.002
QRS duration (msec)	130 ± 32 (*n.* 174)	137 ± 31(*n* 124)	101 ± 26 (*n.* 18)	119 ± 32 (*n.* 32)	<0.001
Hemoglobin (g/dl)	16 ± 3 (*n.* 213)	16.1 ± 3.2 (*n.* 145)	16 ± 2.5 (*n.* 25)	15.9 ± 3.1 (*n.* 43)	0.9
Creatinine (umol/L)	73.3 ± 18.4 (*n.* 206)	74.7 ± 19 (*n.* 141)	72.4 ± 17.2 (*n.* 25)	69.1 ± 14.4 (*n.* 40)	0.3
O_2 Saturation (%)	91.7 ± 8.5	91.4 ± 9	95.2 ± 5.8	90.5 ± 7.8	0.01

AICD: Automated Implantable Cardioverter-Defibrillator. AF: atrial fibrillation. NYHA: New York Heart association. MAPCAs: major aortopulmonary collateral arteries. PAH: pulmonary arterial hypertension. PH pulmonary hypertension. PPM: permanent pacemaker. SF: systolic function. TCPC: total cavo-pulmonary connection. VSD: ventricular septal defect.

* Palliation includes: central shunt (Potts, Waterston), Blalock-Taussig (BT) modified or classical shunt, Glenn shunt, classic and modified Fontan circulation, TCPC, RV to pulmonary arteries conduit without closure of the VSD, unifocalization, atrial septectomy.

† Any time before the inclusion, irrespectively of the final surgery.

‡ At any point before the inclusion.

(Log-rank $p = 0.23$). However, hospitalization for heart failure was more common in Group 1b ($n = 14$, 70%, Log-rank $p = 0.003$) and hospitalization for reintervention was more frequent in Group 1a ($n = 46$, 86.8%, Log-rank $p < 0.001$).

4. Discussion

Adult patients with PA are a heterogeneous population in terms of underlying anatomy, physiology and previous interventions. We have shown herewith that PA is associated with significant morbidity and mortality amongst adult survivors, not only in unrepaired or palliated patients, but also in those with previous biventricular repair [2,3]. Systemic ventricular dysfunction and resting oxygen saturations were predictive of all-cause mortality. In the current era of early repair and specialist ACHD care, the management of adult patients with PA remains challenging, and requires high levels of expertise and further efforts to identify patients at highest risk of adverse events.

The clinical classification of PA remains somewhat elusive with different versions having been proposed [7,8]. The presence or absence of a VSD defines both natural history and surgical approach. Within the Group of patients with a VSD (Group 1), the majority is represented by those who can be classified as TOF-PA with overriding of the aorta and anterocephalad deviation of the outlet septum, i.e. within the spectrum of tetralogy of Fallot. There are also patients with DORV in this Group who are grouped with TOF patients.

Unrepaired individuals in Group 1 (1b) were likely to have more complex extracardiac anatomy in terms of their pulmonary vascular bed. Such patients typically have MAPCAs supplying their small central pulmonary arteries, which may or may not be confluent. Many of these patients may not be amenable to repair, the main limiting factor being the absence of sizable, confluent central pulmonary arteries to anastomose to the RV and close the VSD. A subset of this Group may have been considered or indeed been subjected to a unifocalization protocol, which involves a staged approach of reconstruction of the left and right pulmonary arteries and arterial shunting, eventually bringing them in continuity and anastomosing them to the RV with a conduit-type of repair. The complexity of this route, the level of expertise and resources required and, for

Table 2
Baseline characteristic of the two subgroups of PA-VSD (Group 1a versus Group 1b).

	Complete repair (*n* 93) Group 1a	Unrepaired (*n* 59) Group 1b	*p*
Age (y)	25.4 ± 8.6	29.8 ± 9.0	0.002
Born before 1980	40 (43%)	43 (72.9%)	<0.001
MAPCAs	36 (38.7%)	52 (88.1%)	<0.001
Right aortic arch	22 (23.6%)	18 (30.5%)	0.2
Fontan/TCPC/Glenn	0	4 (6.8%)	0.02
Cardiothoracic ratio	0.56 ± 0.06 (n. 79)	0.58 ± 0.07 (n. 41)	0.08
NYHA class			
I	66 (71%)	15 (25.4%)	<0.001
II	25 (26.9%)	31 (52.5%)	
III	2 (2.2%)	13 (22%)	
Hemoglobin (g/dl)	14.3 ± 1.7 (n.86)	18.7 ± 3 (n. 59)	<0.001
O_2 saturation, resting (%)	97.4 ± 4.4	82.1 ± 6.0	<0.001
PH	4 (4.3%)	10 (16.9%)	0.02
Systemic ventricular SF			
Normal	79 (84.9%)	52 (88.1%)	0.1
Mildly impaired	13 (14%)	4 (6.8%)	
Moderately-severely impaired	1 (1.1%)	3 (5.1%)	

NYHA: New York Heart Association. MAPCAs: major aortopulmonary collateral arteries. PH pulmonary hypertension. PPM: permanent pacemaker. SF: systolic function. TCPC: total cavo-pulmonary connection.

some patients, a well-balanced circulation with MAPCAs accounts for a select subgroup that make it to adulthood without repair (unoperated or with palliative arterial shunts). It is, indeed, only relatively recently that the survival of children with intact ventricular septum PA and complex-PA has improved, and this is reflected in the age composition of our patient population [9–11].

Despite substantial differences between the 4 Groups (1a, 1b, 2 and 3), little difference in morbidity and mortality was observed in adult life. This may appear surprising, as unoperated and palliated patients are expected to have a significantly higher event rate compared to patients who were suitable and received biventricular repair, in view of the complex pulmonary and intracardiac anatomy of the former Group, coupled with chronic cyanosis in some [12–14]. This paradox is explained by the design of this study, focusing on adults with PA and their outcome once they have reached adult life and are under the care of ACHD services; a natural selection process, "allowing" for patients with best anatomy or most balanced pulmonary circulations to survive into adulthood without repair may explain the lack of difference in outcome between repaired and unrepaired adult patients. Our survival analysis accounted for this study design and the data presented here are important for adult cardiologists, as they portray and analyze the PA population as it is encountered in adult life, with a natural history and complications that differ from those observed in the pediatric population.

Our data suggest that late onset heart failure drives mortality in patients with repaired PA (Group 1a); this is likely to relate to both left and right ventricular dysfunction secondary to early cyanosis and RV hypertension, previous multiple interventions, RV-PA conduit stenosis and/or regurgitation. Patients in Group 1a also had significant morbidity related to the need for reintervention, mostly for RV-PA conduit failure and residual peripheral pulmonary artery stenosis. Arrhythmias in this Group were also common relating to previous surgical scars and right ventricular dysfunction, both systolic and diastolic, and secondary RA dilatation and stretch. Although the documented arrhythmia burden is at 13.8% in this study, we expect paroxysmal events to be more common. We are confident that in the future, modern devices,

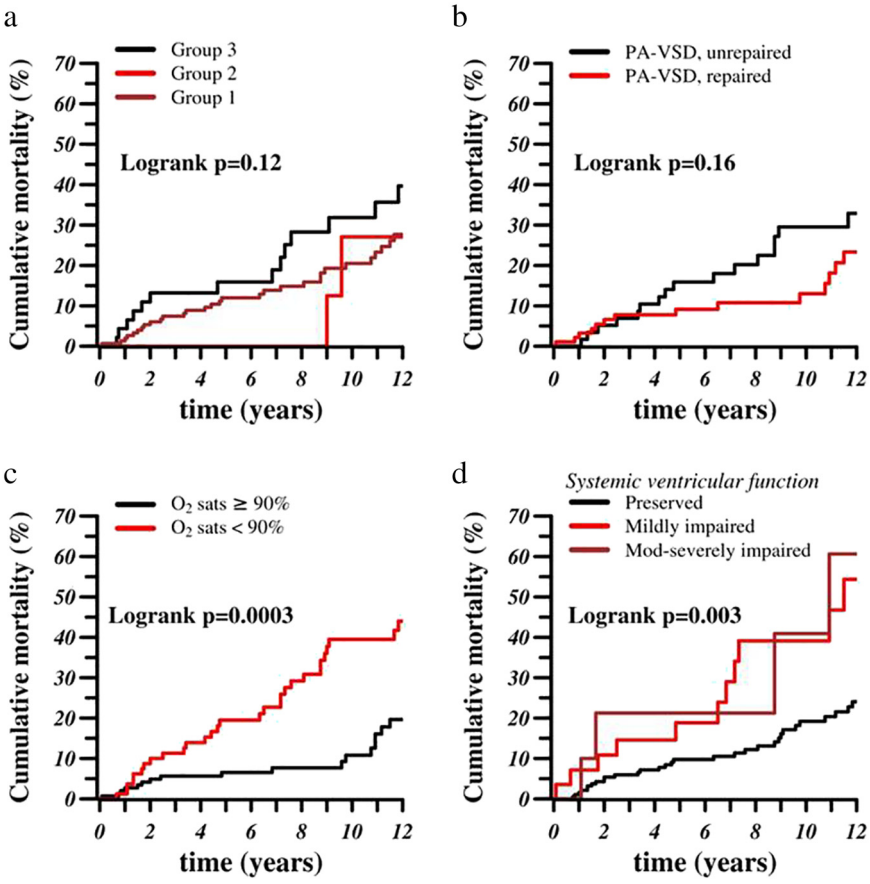

Fig. 2. Mortality. Cumulative mortality comparison between the 3 PA Groups (a), repaired (Group 1a) and unrepaired patients (Group 1b) in PA-VSD Group (b), patients with and without resting cyanosis (c) and according to the systemic ventricular function (d).

such as loop recorders or wearable monitors, will give us more accurate information on the exact incidence of arrhythmias in patients with congenital heart disease, allowing better risk stratification and earlier management.

Morbidity was substantial over the follow-up period in the overall population. One half (51%) of the patients were admitted at least once for investigations/intervention or as a cardiac emergency. The majority of admissions were related to the need for a reintervention, heart failure and/or arrhythmia. Patients with more advanced disease who have developed chronic heart failure are clearly prone to arrhythmic events. Moreover, PA patients were prone to repeat admissions. Little is known regarding the optimal management of heart failure in PA, with a minority treated with traditional heart failure medication in our cohort. Further studies are required to determine the optimal management of heart failure in patients with PA.

Sudden cardiac death/resuscitated cardiac arrests were less common in our adult population of adult PA patients when compared to previous studies, and the majority of cases were seen in Group 1 [6]. Many patients can indeed be classified as having TOF, with a well-established associated risk of malignant arrhythmias [15–18]. Previous papers have not focused on patients with PA and it is not clear whether established risk factors for TOF can be applied to the PA population. We found no correlation between SCD and QRS duration or previous palliative shunts. Systolic dysfunction of the systemic ventricle (not common in our population) was mostly encountered in Groups 1a and 3 and was predictive of SCD [19]. Further work is clearly required to develop and validate a risk stratification score for PA patients.

PH was common in this cohort, commonly described as "segmental" characterized by both hypertensive and hypoperfused regions of the lung, depending on the distribution of collateral circulation and peripheral pulmonary stenoses. Indications for the use of advanced (PAH) therapies in this population remain unclear. Small intention-to-treat case series have reported an, overall, favorable outcome on functional class and exercise tolerance [20,21].

5. Limitations

This is a retrospective study from a single tertiary center on a fairly heterogeneous population. Patients of various ages and anatomies, who represent different eras of management, were included and, therefore, may not be directly comparable. However, the purpose of this study was to describe all PA patients seen and followed in a contemporary adult cardiology centers, irrespective of age or anatomy, and identify predictors of outcome for such an adult cohort, guiding modern ACHD management. The limited sample size and number of events did not allow us to account for time-varying covariates, and a limited the number of variables could be included in multivariate models. Immortal time bias may account, at least in part for the lack of difference in the outcome between unrepaired and repaired patients in Group 1, as adult survivors with PA in their 20s or 30s and beyond almost certainly represent the best end of the spectrum. However, our study was not aimed at assessing the natural history of PA from birth, but rather the survival prospects of contemporary adult PA patients followed in a tertiary ACHD center or other adult Cardiology service, and our survival analysis followed this study design.

6. Conclusion

Pulmonary atresia is associated with significant morbidity and mortality amongst adult survivors, affecting unrepaired, palliated and patients who underwent biventricular repair. Adult patients with pulmonary atresia are a heterogeneous patient population in terms of underlying anatomy, physiology and previous intervention/s and warrant life-long expert tertiary care.

Disclosures

AK, KD, SL and MAG from the Royal Brompton Hospital have received unrestricted educational or research grants from Bayer, Pfizer, Actelion and GSK. Furthermore, they have received support from the Pulmonary Hypertension Association (UK) and the British Heart Foundation. KD and MAG have acted as Consultants to Pfizer, Actelion and GSK. CM has received educational grants from the Italian Society of Cardiology and MSD Italia-Merck Sharp & Dohme Corporation. SBN was supported by the British Heart Foundation (FS/11/38/28864).

References

[1] E.J. Baker, R.H. Anderson, Tetralogy of Fallot with pulmonary atresia, in: R.H. Anderson, E.J. Baker, D. Penny, A. Redington, M.L. Rigby, G. Wernovsky (Eds.), Paediatric Cardiology, 3rd ed.Churchill Livingstone, 2010.
[2] A.J. Marelli, J.K. Perloff, J.S. Child, H. Laks, Pulmonary atresia with ventricular septal defect in adults, Circulation 89 (1994) 243–251.
[3] A.S. John, C.A. Warnes, Clinical outcomes of adult survivors of pulmonary atresia with intact ventricular septum, Int. J. Cardiol. 161 (2012) 13–17.
[4] K. Bull, J. Somerville, E. Ty, D. Spiegelhalter, Presentation and attrition in complex pulmonary atresia, J. Am. Coll. Cardiol. 25 (1995) 491–499.
[5] J. Hörer, J. Friebe, C. Schreiber, et al., Correction of tetralogy of Fallot and of pulmonary atresia with ventricular septal defect in adults, Ann. Thorac. Surg. 80 (2005) 2285–2291.
[6] H. Leonard, G. Derrick, J. O'Sullivan, C. Wren, Natural and unnatural history of pulmonary atresia, Heart 84 (2000) 499–503.
[7] C.I. Tchervenkov, N. Roy, Congenital heart surgery nomenclature and database project: pulmonary atresia—ventricular septal defect, Ann. Thorac. Surg. 69 (2000) S97–105.
[8] M. Barbero-Marcial, Classification of pulmonary atresia with ventricular septal defect, Ann. Thorac. Surg. 72 (2001) 316–317.
[9] D.A. Ashburn, E.H. Blackstone, W.J. Wells, et al., Determinants of mortality and type of repair in neonates with pulmonary atresia and intact ventricular septum, J. Thorac. Cardiovasc. Surg. 127 (2004) 1000–1007.
[10] N.E. Lightfoot, J.G. Coles, H.K. Dasmahapatra, W.G. Williams, K. Chin, G.A. Trusler, R.M. Freedom, Analysis of survival in patients with pulmonary atresia and intact ventricular septum treated surgically, Int. J. Cardiol. 24 (1989) 159–164.
[11] T. Hoashi, K. Kagisaki, M. Kitano, et al., Late clinical features of patients with pulmonary atresia or critical pulmonary stenosis with intact ventricular septum after biventricular repair, Ann. Thorac. Surg. 94 (2012) 833–841.
[12] H. Sakazaki, K. Niwa, S. Echigo, T. Akagi, M. Nakazawa, Predictive factors for long-term prognosis in adults with cyanotic congenital heart disease—Japanese multi-center study, Int. J. Cardiol. 120 (2007) 72–78.
[13] A.F. Corno, G. Milano, M. Samaja, P. Tozzi, L.K. von Segesser, Chronic hypoxia: a model for cyanotic congenital heart defects, J. Thorac. Cardiovasc. Surg. 124 (2002) 105–112.
[14] N.A. Silverman, J. Kohler, S. Levitsky, D.G. Pavel, R.B. Fang, H. Feinberg, Chronic hypoxemia depresses global ventricular function and predisposes to the depletion of high-energy phosphates during cardioplegic arrest: implications for surgical repair of cyanotic congenital heart defects, Ann. Thorac. Surg. 37 (1984) 304–308.
[15] M.A. Gatzoulis, S. Balaji, S.A. Webber, et al., Risk factors for arrhythmia and sudden cardiac death late after repair of tetralogy of Fallot: a multicentre study, Lancet 356 (2000) 975–981.
[16] M.A. Gatzoulis, J.A. Till, J. Somerville, A.N. Redington, Mechanoelectrical interaction in tetralogy of Fallot. QRS prolongation relates to right ventricular size and predicts malignant ventricular arrhythmias and sudden death, Circulation 92 (1995) 231–237.
[17] P. Khairy, A. Dore, N. Poirier, et al., Risk stratification in surgically repaired tetralogy of Fallot, Expert. Rev. Cardiovasc. Ther. 7 (2009) 755–762.
[18] J.T. Bricker, Sudden death and tetralogy of Fallot. Risks, markers, and causes, Circulation 92 (1995) 158–159.
[19] A. Ghai, C. Silversides, L. Harris, G.D. Webb, S.C. Siu, J. Therrien, Left ventricular dysfunction is a risk factor for sudden cardiac death in adults late after repair of tetralogy of Fallot, J. Am. Coll. Cardiol. 40 (2002) 1675–1680.
[20] K. Dimopoulos, S.J. Wort, M.A. Gatzoulis, Pulmonary hypertension related to congenital heart disease: a call for action, Eur. Heart J. 35 (2014) 691–700.
[21] K. Dimopoulos, G.P. Diller, A.R. Opotowsky, M. D'Alto, H. Gu, G. Giannakoulas, W. Budts, C.S. Broberg, G. Veldtman, L. Swan, M. Beghetti, M.A. Gatzoulis, Definition and Management of Segmental Pulmonary Hypertension, J. Am. Heart Assoc. 7 (14) (2018) https://doi.org/10.1161/JAHA.118.008587 pii: e008587.