Pulmonary atresia with intact ventricular septum: Predictors of early and medium-term outcome in a population-based study

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Objectives: Pulmonary atresia with intact ventricular septum is a form of congenital heart disease usually associated with right-heart hypoplasia, with considerable morphologic heterogeneity and often poor outlook. Ascertainment of risk factors for poor outcome is an important step if an improvement in outcome is to be achieved.

Methods: The UK and Ireland Collaborative study of Pulmonary Atresia with Intact Ventricular Septum is an ongoing population-based study of all patients born with this disease from 1991 through 1995. All available clinical, morphologic, and investigative variables were directly reviewed, and risk factor analysis was performed for poor outcome.

Results: One hundred eighty-three patients presented with pulmonary atresia with intact ventricular septum. Fifteen underwent no procedure, and all died. Of the remainder, 67 underwent a right ventricular outflow tract procedure (catheter or surgical), 18 underwent an outflow tract procedure with shunt, and 81 underwent a systemic-to-pulmonary shunt alone. One- and 5-year survival was 70.8% and 63.8%, respectively. Results from Cox proportional hazards model analysis showed that low birth weight ($P = .024$), unipartite right ventricular morphology ($P = .001$), and the presence of a dilated right ventricle ($P < .001$) were independent risk factors for death. The presence of coronary artery fistulae, right ventricular dependence, or the tricuspid valvar z score did not prove to be risk factors for death. After up to 9 years of follow-up, 29% have achieved a biventricular repair, 3% a so-called one-and-a-half ventricular repair, and 10.5% a univentricular repair, with 16.5% still having a mixed circulation (41% died).

Conclusions: This population-based study has shown which features at presentation place an infant in a high-risk group. This is important information for counseling in fetal life and for surgical strategy after birth.

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Pulmonary atresia with intact septum (PAIVS) is a rare form of congenital heart disease¹⁻³ with considerable morphologic heterogeneity.⁴⁻⁷ Even large cardiac centers will see only a handful of cases each year. As a consequence, survival has until recently been poor.⁸⁻¹³ Such tremendous morphologic diversity prevents proscription of a single optimal operative strategy. Management strategies therefore need tailoring to individual morphologic subtypes at presentation.¹³⁻¹⁶ Management depends on the unique constellation of morphologic features present and can have long-lasting implications. The long-term aim in this condition is to separate the circulations. The main thrust of assessment in the newborn period is to enable this by predicting suitability for long-term biventricular, univentricular, or one-and-a-half ventricular repair. Many reports have addressed the optimal initial management strategy by using various morphologic features at presentation as a

TABLE 1. Range of morphology for entire patient group (n = 183)

Morphologic feature	Type	No.
Type of pulmonary atresia	Membranous	130/174 (74.7%)
	Muscular	44/174 (25.3%)
“Partite status” of the RV	Tripartite	84/143 (58.7%)
	Bipartite	48/143 (33.6%)
	Unipartite	11/143 (7.7%)
Coronary artery abnormalities	RV to coronary fistulae	60/132 (45.5%)
	Coronary artery stenoses, interruption, and ectasia	10/132 (7.6%)
Ebstein’s malformation		18/183 (9.8%)
Significant RV dilatation		8/183 (4.4%)
Size of tricuspid valve	Median z score*	−5.2 (range, −18.3 to 9.4)
Size of RV inlet	Median z score*	−5.1 (range, −16.0 to 3.5)

RV, Right ventricle/ventricular. *Z scores are calculated from echocardiographically derived normal values²³ and not from postmortem-derived normal values, as in other studies. Fifteen abnormalities of the left ventricle were documented, including 4 with extreme septal hypertrophy with bulging into the left ventricular outflow tract.

guide to initial management.^{10,12,14,15,17-22} One of the largest studies proposed a management algorithm dependent on the tricuspid valve (TV) z score on presentation.¹⁰ The aim of the current study is to clarify which presenting clinical and morphologic features play a role in determining early and medium-term outcome and, in particular, which are risk factors for poor outcome. This will be achieved within a population-based study.

Methods

The UK and Ireland Collaborative study of PAIVS is an ongoing, multicenter, population-based study of all children born with PAIVS in the United Kingdom and Ireland (population just over 60 million) over a 5-year time period from 1991 through 1995. The methodology has been detailed in a previous report.⁷ In summary, completeness of data collection was accomplished by a single investigator visiting all 18 UK and Ireland pediatric cardiac centers on several occasions from 1993 through 2003. Ethical approval appropriate for this era was obtained. Local databases, admission and operative records, fetal diagnoses, and regional pathology records were directly inspected. All relevant cardiac investigations (presentation chest radiogram, serial echocardiograms, and angiocardiograms) were directly reviewed by 2 investigators. Z scores were calculated for the TV and right ventricular (RV) inlet length from available echocardiographically derived nomograms.²³ RV dilatation was defined as present when there was a markedly dilated, thin-walled RV invariably associated with a dysplastic TV and severe tricuspid regurgitation. Although a qualitative judgment, this subgroup is easily delineated in practice. Most recent follow-up and clinical status were evaluated from questionnaires sent to all the relevant individual cardiologists. Patients were included if they had PAIVS without associated complex abnormalities (patients with PAIVS with Ebstein’s malformation were included, as were patients with tiny ventricular septal defects). Patients were excluded if they were born outside the United Kingdom and Ireland. Patients with critical pulmonary stenosis were excluded. At most recent follow-up, each patient was assigned to a particular type of circulation. Biventricular repair was

used when there was complete separation of the systemic and pulmonary circulations, one-and-a-half ventricular repair was assigned when each ventricle ejected into the appropriate great vessel in the presence of a bidirectional superior cavopulmonary anastomosis with all intracardiac and additional extracardiac shunts closed, and univentricular repair was assigned when the Fontan operation or modification had been performed (with or without patent fenestration). Mixed circulation denoted all other circulations.

This was an observational study, and no attempt was made to influence management by investigators. The primary outcome measure was death. Risk factors were sought from the list in Appendix E1 online. Continuous risk factors were expressed as medians with ranges. The Cox proportional hazards model was used to investigate risk factors for death. A forward-step procedure was used to select prognostic factors. Risk factors with *P* values of less than .1 in the univariate analyses were included in the multivariate models. In the multivariate models *P* values of less than .05 were considered significant.

Results

During the 5-year recruitment period, there were 183 infants born with PAIVS. These patients were referred to 18 cardiac centers, 17 in the United Kingdom and 1 in Ireland.

Pathology

The range of morphology in this population has been described in a previous publication⁷ and is summarized in Table 1.

Unoperated Patients

Fifteen of the 183 patients did not undergo any intervention to increase pulmonary blood flow, with 1 patient only having a balloon atrial septostomy. Three of the 15 patients were never admitted to a cardiac hospital. In half of the patients, there was no intervention because the individual clinician believed the anatomy, clinical presentation, or

associated noncardiac anomalies to be too severe for intervention to be worthwhile, and in the other half, the child died precipitously before intervention could be initiated. All these patients have subsequently died. Survival to 1 and 3 years was 6.7% (range, –6.0 to 19.3) and 0%, respectively. One patient with severe pulmonary hypoplasia and multiple aortopulmonary collaterals lived to 2½ years and died without undergoing an operation.

Balloon Atrial Septostomy

Balloon atrial septostomy was performed in 45 (25%) patients: 30 before the first surgical or catheter procedure, 14 after the first surgical or catheter procedure, and 1 as the only intervention. The majority (36/45) of these patients underwent construction of systemic-to-pulmonary shunts. Three underwent a transannular patch procedure, 3 underwent a valvotomy with shunt, 2 underwent catheter intervention, and 1 underwent no further procedure.

Of 81 patients undergoing a systemic-to-pulmonary shunt alone as the primary surgical procedure, 26 (32%) had a septostomy beforehand (2 of whom also underwent an atrial septectomy at the time of the shunt). After the initial shunt procedure, 10 patients underwent a septostomy between 0 and 161 days later, and 4 patients required atrial septectomy between 2 and 339 days later (2 of whom had a septostomy before the shunt and 1 who had a septostomy after). Freedom from septostomy-septectomy 4 and 8 months after a systemic-to-pulmonary shunt *alone* was 82.1% (95% confidence interval [CI], 71.4%-92.8%) and 75.8% (95% CI, 62.8%-88.7%), respectively, for patients who had not undergone a septostomy beforehand (censoring for subsequent outflow tract procedure, cavopulmonary anastomosis with septectomy, or death).

Two patients died as a consequence of a restrictive atrial septum, one of them 2 days after a shunt, having had an inadequate septostomy beforehand. Another who had not undergone a septostomy or septectomy presented 159 days after a shunt with a restrictive intra-atrial septum bulging to the left and died as a consequence. Both died immediately after an emergency atrial septectomy.

Primary Procedure

The primary procedure, excluding balloon atrial septostomy, comprised a systemic-to-pulmonary shunt in 81 patients, percutaneous transcatheter valvotomy in 40 patients, and surgical outflow tract reconstruction alone in 27 patients and with a concomitant shunt in another 18 patients. One patient had a stent placed in the arterial duct, and another underwent oversewing of the TV, plication of the right atrium, and construction of a systemic-to-pulmonary shunt (Starnes procedure²⁴). These are shown in Table 2. None was listed for transplantation.

TABLE 2. Primary procedures performed

Procedure	No shunt	Shunt
Valvotomy	11*	13
Transannular patch	16†	5
Systemic-to-pulmonary shunt	—	81‡
Radiofrequency–laser–wire perforation of imperforate pulmonary valve	40§	—
Other		2
No procedure		15
Total		183

*With atrial septectomy in 1 patient. †With atrial septectomy in 2 patients, one with banding of the arterial duct. ‡With atrial septectomy in 2 patients. §With balloon tricuspid valvuloplasty in 1 patient. ||Stenting of arterial duct in 1 patient and pulmonary valvotomy, systemic-to-pulmonary shunt, oversewing of the tricuspid valve, and plication of the right atrium in another (coexistent severe Ebstein's malformation).

Survival

After follow-up of up to 9 years, 75 (41%) of 183 patients have died. Excluding 15 patients who did not undergo an operative procedure, there were 60 (36%) deaths among 168 patients. Probability of survival from birth to 1 and 5 years for all 183 patients was 65.6% (95% CI, 58.7%-72.5%) and 58.6% (95% CI, 51.4%-65.8%), respectively. Survival from the first procedure to 1 and 5 years for all 168 patients undergoing an operative procedure was 70.8% (95% CI, 63.3%-77.1%) and 63.8% (95% CI, 55.9%-70.6%), respectively (Figure 1). The hazard function shows that risk of death is highest during the first 6 months, decreases steadily during the next 12 months, and levels off afterward (Figure 1). There were no deaths after 55 months. Death was perioperative in 44 of 60 patients and sudden (mostly at home) in 14 patients, of whom 3 died from shunt thrombosis, 2 from known coronary abnormality, and 7 from unknown cause. In addition, 1 died from endocarditis and 1 from a car accident.

Survival data grouped for initial procedure are shown in Figure 2. Patients undergoing a shunt as the primary procedure had a worse outlook ($P = .036$, log-rank test).

Predictors of Survival

Univariate analysis of risk factors for subsequent death is shown in Table 3 for all 168 patients undergoing an operative procedure. To understand further whether the risk factors for death differ among initial treatment groups, we did a subgroup analysis for each primary procedure category. We appreciate that type of operation is a surrogate for underlying morphology and might be regarded as an outcome rather than a variable, but it does have some clinical relevance. For patients undergoing construction of a systemic-to-pulmonary shunt only, risk factors conferring a higher risk of subsequent death ($P < .05$) were lower birth weight, ventilation on admission,

Figure 1. Left, Survival curve for patients undergoing operative procedures (n = 168). Inset shows the hazard function. Right, Survival curve for all patients undergoing operative procedures grouped by so-called partite status of the right ventricle (n = 168). CI, Confidence interval.

presence of RV dilatation, so-called unipartite RV morphology, presence of Ebstein’s malformation, smaller RV inlet length, and not having a septostomy. For patients undergoing RV outflow tract reconstruction with a shunt, the only risk factor was lower birth weight ($P < .05$). For

those undergoing an RV outflow tract reconstruction without a shunt, irrespective of whether the RV outflow procedure was performed by means of surgical intervention or by means of the transcatheter technique, no risk factors were identified.

The results from the multivariate Cox proportional hazard model analysis are displayed in Table 4 for all patients undergoing an operative procedure. Of all risk factors included in this study, 3 variables are identified as independent predictors of death: birth weight, RV dilatation, and so-called partite status of the RV. Each additional 1-kg increase in birth weight is associated with a 44% decrease in the risk of death (95% CI, 7%-66%; $P = .024$). RV dilatation is also strongly associated with the risk of death: patients with RV dilatation are at high risk of death ($P < .001$). In terms of the effect of so-called partite status for the ventricular cavity, unipartite morphology has the highest risk of death compared with the bipartite or tripartite variants ($P = .046$ and $.001$, respectively) (Figure 1).

To investigate whether there were different risk factors for different initial procedures, we performed interaction tests with multivariate analysis and found that there was no significant difference between procedures.

Figure 2. Survival curve for all patients undergoing operative procedures grouped by initial procedure (n = 166). The figure excludes 2 patients, one with stenting of the arterial duct and the other with oversewing of the tricuspid valve with a systemic-to-pulmonary shunt procedure. RVOT, Right ventricular outflow tract.

TABLE 3. Risk factors at presentation for subsequent death determined by means of univariate analysis for all patients undergoing an operative procedure (n = 168)

Variable	Data available	Hazard ratio	95% CI	P value
Birth weight (kg)	163	0.57	0.37-0.88	.011
Ventilated at admission	114	1.76	0.93-3.31	.082
RV dilatation	168	4.95	1.78-13.79	.002
Bipartite (vs unipartite)	135	0.44	0.18-1.03	.060
Tripartite (vs unipartite)	135	0.25	0.11-0.60	.002
Ebstein's malformation	168	1.80	0.89-3.66	.104
Surface area at first procedure (m ²)	164	0.000	0-3.59	.089
RV inlet z score	145	0.92	0.84-1.01	.066
First procedure (shunt vs other procedures)	168	1.78	1.06-3.00	.029

Variables are only shown if *P* value is .10 or less. Height at first procedure was also significant. *CI*, Confidence interval; *RV*, right ventricular.

Outcome in High-Risk Groups

Patients with unipartite anatomy of the RV cavity at presentation who underwent a procedure had a particularly poor outcome, with 7 of 9 dying (some at subsequent procedures; Figure 1). These were procedure related in 2 patients (during insertion of a central shunt in 1 patient and after a Fontan procedure in another), sudden arrest in 2 patients, blocked shunt in 1 patient, after an RV outflow tract procedure in another patient having had a large shunt and coil occlusion of major RV-to-coronary connections, and necrotizing enterocolitis in 1 patient (after the placement of a large shunt). Similarly, 4 of 5 patients presenting with a significantly dilated RV and undergoing a procedure died (all early after the first procedure). Four of 6 patients with birth weights of less than 2 kg and undergoing a procedure died (1 as a consequence of a postoperative seizure, 1 as a consequence of an oversized shunt, 1 after an eventual catheter procedure at 4 months, and 1 suddenly at home 4 months after a successful initial procedure). Of these 6 patients, only 2 underwent an initial procedure within 7 days of birth (1 death), with the other 4 waiting up to 111 days (3 deaths). Three others with birth weights of less than 2 kg died without undergoing procedures (Cornelia de Lange, severe Ebstein's malformation, and severe and lethal apnea caused by prostaglandin).

The presence of an RV-dependent coronary circulation was not found to be an operative risk factor for poor outcome, although the number of patients in this group was small. Ten patients were found to have this morphology: 2 of 7 died after surgical intervention, and 3 did not undergo a procedure and died.

Achievement of Separated Circulations

At latest follow-up of up to 9 years, 53 (29%) of 183 patients have achieved a biventricular repair, 6 (3%) have achieved a one-and-a-half ventricular repair, 19 (10.5%) have achieved a univentricular repair, and 30 (16.5%) are still in a mixed circulation. Seventy-five (41%) have died.

For those achieving a biventricular circulation, 44 of 53 underwent an initial RV outflow procedure (catheter or surgical), 5 underwent an outflow tract procedure with shunt, and 4 underwent an initial shunt alone. For those achieving a one-and-a-half ventricular repair (n = 6), 2 underwent an RV outflow procedure alone, 2 underwent an RV outflow procedure and shunt, and 2 underwent a shunt alone. For those achieving a univentricular repair, 18 of 19 had an initial shunt, and 1 had an RV outflow procedure.

Discussion

PAIVS is a disease with great morphologic variability particularly affecting the TV–RV–pulmonary valve complex but also including the coronary arteries.⁴⁻⁷ Such tremendous diversity prevents proscription of a standard preferred surgical or catheter intervention. This has led to the concept of management strategies tailored to individual morphologic subtypes.¹³⁻¹⁶ Numerous strategies have been proposed, often based on novel classifications of the RV or coronary arteries.^{8,10,12,14,15,18-22,25-28} De Leval and Bull and coworkers^{17,25} based their strategy on the so-called partite classification of the RV, Hanley and colleagues¹⁰ on the size of the TV, Pawade and associates¹⁵ on the size of the infundibulum, and Giglia and coworkers¹⁹ on the presence of coronary artery stenoses.

TABLE 4. Risk factors at presentation for subsequent death determined by means of multivariate analysis for patients undergoing a shunt alone or outflow tract procedure (catheter or surgical) with or without a shunt (n = 132)

Variable	Hazard ratio	95% CI	P value
Birth weight (kg)	0.56	0.34-0.93	.024
RV dilatation	11.41	3.63-35.87	<.001
Bipartite (vs unipartite)	0.41	0.17-0.99	.046
Tripartite (vs unipartite)	0.22	0.09-0.55	.001

CI, Confidence interval; *RV*, right ventricular.

Because of its rarity, many studies of PAIVS contain relatively few patients but are contemporary; others achieve larger numbers by spanning many years, making them essentially historical. In addition, single-institution studies might have ascertainment bias because of specific referral patterns. Multi-institutional studies might be more powerful in delineating the relative merits of treatment strategies,⁹ and they might allow identification of risk factors for specific outcome measures.^{10,11,13} This is generally not possible in smaller single-institution studies. The strengths of the UK and Ireland Collaborative Study comprise inclusion of all children identified with the disease at birth, the large number of patients enrolled, its population-based nature (thus avoiding selection bias), and the high quality of the data collected facilitated by a single investigator visiting all study sites and directly reviewing investigations, ensuring completeness, as well as quality, of data collection.

Balloon Atrial Septostomy

Conventional management of infants undergoing a systemic-to-pulmonary shunt is that a septostomy should be performed or at least considered before the shunt. In this study clinicians elected in some cases not to perform this procedure, presumably on the grounds that there was an adequate passage across the atrial septum. One quarter of patients not undergoing a septostomy before a shunt nonetheless required a septostomy or septectomy alone by 8 months. More concerning was that 2 deaths were directly attributable to a restrictive atrial septum, one occurring 2 days after a shunt and the other occurring 5 months after a shunt.

Risk Factors at Presentation for Subsequent Death

Several clinical and morphologic features at presentation proved to be independent predictors of subsequent death: so-called unipartite anatomy (and, to some degree, bipartite anatomy), low birth weight, and significant RV dilatation. Systemic-to-pulmonary shunting as the primary procedure was also associated with subsequent risk of death in univariate, but not multivariate, analyses, but this is likely to be because it was primarily performed in patients with greater degrees of RV hypoplasia. It is unclear why unipartite RV morphology per se should be a risk factor for death, especially because neither RV-dependent coronary circulation nor fistulae between the RV and coronary arteries were identified as risk factors for death, and all were progressing toward a univentricular repair after an initial shunt procedure. Because this was an observational study, there was no requirement for clinicians to perform a cardiac catheterization before or after an initial shunt procedure (actually, a cardiac catheter was performed in 54% before the first procedure and in 85% at any time). Therefore it might be that important fistulae and stenoses were overlooked in those who died. Alternatively, the functionally unipartite

ventricle itself might represent the most extreme morphologic subtype in this disease, with consequences as yet unknown.

Low birth weight is perhaps a more understandable risk factor for death, irrespective of whether the patient underwent an operation. Weight at the time of the procedure has been identified by all of the larger studies as an independent risk factor,^{8-10,13} and low birth weight has been identified as a risk factor by the other major population-based study.¹¹ Only one third with a birth weight of less than 2 kg survived. In some centers there was a strategy of immediate operation. In others, an attempt was made for them to grow, both with poor outcome. This is a controversial topic in all forms of congenital cardiac disease. Recent reports suggest that early surgical intervention in infants born with low weight is technically possible with good results and indeed is preferable.²⁹

Significant RV dilatation was also found to be a poor prognostic indicator. Our previous study of the range of morphology in this condition revealed that RV dilatation was associated with abnormalities of the TV, such as dysplasia and Ebstein's malformation, and hypoplastic pulmonary arteries.⁷ Coles and colleagues⁸ found that the presence of Ebstein's malformation was an independent risk factor for poor outcome. Many such patients die in utero,³⁰ and when they survive to birth, their management is unclear. Some groups have advocated patching off the TV and performing a systemic-to-pulmonary shunt.²⁴ This was performed in 1 patient without success but perhaps should have been undertaken in more patients. Other investigators have removed this group from their analysis,¹⁰ but we elected to include them because PAIVS is already a very heterogeneous phenotype.

It was perhaps surprising that morphologic features identified as risk factors for death by other groups were not confirmed in this study. Hanley and associates¹⁰ reported that the TV *z* score could be used as a guide to initial procedure, but neither TV diameter or *z* score nor RV inlet length or *z* score predicted death in the current series. This might support those who have criticized basing an operative strategy on a single anatomic index and, in particular, might indicate that the TV might not always reflect the size of the RV. Ashburn and colleagues,¹³ in the Congenital Heart Surgeons Study, the largest study to date, concluded that although TV is a primary determinant of type of repair, other variables need to be considered.

Alternatively, it might be that clinicians in the United Kingdom and Ireland have already been tailoring their approach to the initial procedure on the basis on the size of the TV. The reasons why RV dependence was not identified as a risk factor, unlike in some other studies,¹⁰ have already been alluded to (RV angiography is not always performed before surgical intervention), but al-

ternatively, clinicians might be already tailoring their approach to this feature by not decompressing the RV in these situations.^{14,16}

Medium-Term Outcome

The UK and Ireland Collaborative Study of PAIVS is ongoing, and at the most recent follow-up, only two thirds of patients have reached a definitive separated circulation. Therefore it is too early to identify risk factors at presentation for achievement of these circulations. This is an important difference compared with the Congenital Heart Surgeons Study, in which all had achieved a definitive repair by 15 years.¹³ This might reflect a different philosophy in the timing of transition from a superior to a total cavopulmonary anastomosis in the United Kingdom and Ireland. By contrast, there is a remarkable similarity in the proportion of patients who have died or achieved a biventricular or one-and-a-half ventricular repair. It is of additional interest that in a study with up to 9 years' follow-up, there have been no deaths in patients older than 6 years.

Study Limitations

This was an observational study, with no attempt to influence management. This results in institutional variations, including differing strategies, nonconformity of surgical or transcatheter techniques, variation in procedural expertise, and standards of postoperative care. These differences can confound the interpretation of results in a multi-institutional study such as this. As discussed previously,⁷ the incidence of PAIVS in our study was 4.5 cases per 100,000 live births, lower than other estimates. This was due to the development in the United Kingdom of fetal diagnosis and subsequent termination of pregnancy. Our previous work did not observe a difference, however, in the range of morphology at birth between those detected and not detected prenatally.⁷

Conclusion

In conclusion, this population-based study has shown that the presence of low birth weight, unipartite RV morphology, and significant RV dilatation are all independent risk factors at presentation that place an infant at high risk of death. This information is important to guide surgical strategy after birth and for counseling in fetal life.

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Appendix E1

Potential risk factors examined for death in patients undergoing an operative procedure ($n = 168$). For each variable, the figure in parentheses denotes the number of patients for whom complete data were available.

Patient risk factors: Date of birth (168), birth weight (163), sex (168), and race (58); height (164), weight (164), and body surface area (164) at initial procedure.

Morphologic variables: Presence of RV-coronary fistulae (125), presence of coronary artery stenoses, ectasia or interruptions (121), Ebstein's malformation (168), type of atresia (membranous-muscular; 151), number of portions of RV not overgrown by muscular hypertrophy (so-called tripartite, bipartite, or unipartite ventricle; 135), RV dilatation (168), TV z score (145), RV inlet z score (145), angle that duct subtends on descending aorta (102).

Investigative variables: Cardiothoracic ratio on admission chest radiogram (110), right atrial (38) and ventricular (52) pressures before the initial procedure.

Clinical variables: Patient intubated on admission (114), balloon atrial septostomy performed before or after primary procedure (168).

Procedural variables: Initial surgical or catheter intervention (168).

Acknowledgements E1

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