CONGENITAL HEART DISEASE

Outcome of infants with right atrial isomerism: is prognosis better with normal pulmonary venous drainage?

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Objective: To compare the outcome of infants and children who have right atrial isomerism and normal pulmonary venous drainage with those who have anomalous drainage, and to determine factors associated with poor outcome.

Design and patients: Retrospective review of management and outcome of 116 infants and children determined to have right atrial isomerism between January 1980 and December 2000.

Setting: Tertiary paediatric cardiac centre.

Results: The 116 patients presented at a median of one day (range 1 day to 3.7 years) with cyanosis in the majority (96%). No interventions were planned in 31 (27%) patients, all of whom died. The early surgical mortality for pulmonary venous repair was 25% (2 of 8), Fontan procedure 26% (5 of 19), cavopulmonary shunting 7.7% (1 of 13), and systemic pulmonary arterial shunt insertion 1.9% (1 of 53). Late mortality was related to infection (n = 10), sudden death of unknown aetiology (n = 7, 5 with history of arrhythmia), and documented arrhythmia (n = 1). Patients with obstructed anomalous pulmonary venous drainage had the worst survival (p < 0.001). The mean (SEM) survival estimates for those with normal pulmonary venous drainage at 1, 5, 10, and 15 years was 81 (5.3%), 67 (6.6%), 60 (7.8%), and 43 (12%), respectively, similar to those for patients with non-obstructed anomalous drainage (p = 0.06). Independent risk factors for mortality included pulmonary venous obstruction (relative risk 3.8, p = 0.001) and a single ventricle (relative risk 2.9, p = 0.016). An analysis of only patients with normal pulmonary venous drainage identified no risk factors for mortality.

Conclusions: The long term outcome of infants and children with right atrial isomerism in association with a normal pulmonary venous drainage remains unfavourable. Sepsis and sudden death that may potentially be related to cardiac arrhythmia are major causes of late mortality.

The complex congenital cardiac malformations associated with right atrial isomerism are well documented. Among these, total anomalous pulmonary venous drainage with or without obstruction has been shown to be a significant risk factor for mortality. In a large necropsy series of asplenia syndrome, the median survival of babies with total anomalous pulmonary venous drainage was three months. This natural outcome, however, has not improved with surgical interventions. In the few clinical studies published, the surgical mortality for patients with right atrial isomerism undergoing pulmonary venous repair ranged from 70–100%. The prognosis of this subgroup of patients hence remains poor despite surgical management and the latter must be regarded at best as palliative.

In contrast to the uniformly poor prognosis of patients with right isomerism and total anomalous pulmonary venous drainage, the outcome of those with normal, non-obstructed pulmonary venous drainage has not been defined. Previous reports documented the outcome in a relatively small number of patients who underwent palliative surgery, the majority or all of whom had total anomalous pulmonary venous drainage. Even in the largest clinical series published so far of 91 patients, the small proportion with normal pulmonary venous drainage (13%) renders outcome analysis of this subgroup difficult.

Given the paucity of clinical data, we reviewed the management and outcome of 116 infants and children with right atrial isomerism. 48% of whom had normal pulmonary venous drainage. We compared the outcome of those with normal pulmonary venous drainage with those with anomalous drainage and determined factors that are associated with a poor outcome.

PATIENTS AND METHOD
The clinical records of 116 consecutive infants and children (71 boys) in whom right atrial isomerism was diagnosed between January 1980 and December 2000 at the Grantham Hospital, Hong Kong, were reviewed.

Diagnosis
The diagnostic criteria of right atrial isomerism remain controversial. The bronchial pattern and position of the liver on chest and abdominal radiography, respectively, may suggest the diagnosis. Further support was obtained from echocardiographic and angiographic evidence of the juxtaposition of the abdominal aorta and inferior vena cava, and the morphology of the atrial appendages. Direct inspection of atrial morphology during operation or necropsy further verified the diagnosis. The intracardiac anatomy was delineated by two dimensional echocardiography. For this study, a normal pulmonary venous connection refers to connection of all pulmonary veins to the left sided atrium, although it is recognised that the right sided atrium is the pulmonary venous atrium in some cases of dextrocardia. The diagnosis of pulmonary venous obstruction was based on clinical presentation, chest roentgenographic appearance, two dimensional

Abbreviations: CI, confidence interval; RR, relative risk
echocardiographic imaging, and Doppler assessment of pulmonary venous flow velocities.

Data collection
The following data were retrieved from the clinical records and entered as covariates in a Cox regression model to determine risk factors for mortality: (1) demographic data including age and year at presentation and sex; (2) morphological variables including location of cardiac apex, number of atrioventricular valves, atrioventricular valvar regurgitation, number of ventricles, morphology of the main ventricular chamber, aortic outflow obstruction, pulmonary outflow obstruction, pulmonary arterial anatomy, type of pulmonary venous drainage, and presence of pulmonary venous obstruction; (3) haemodynamic data including oxygen saturation at presentation, and use of intravenous prostaglandin infusion; (4) electrocardiographic variables including P wave axis, P wave morphology, heart block, and history of arrhythmia. Other data that were retrieved were the type of surgical intervention offered and the outcome; for patients who died, the age at death and cause of death; and for survivors, their further management and follow up duration.

Statistical analysis
Results are expressed as mean (SEM), unless otherwise specified. The survival of patients was analysed by Kaplan-Meier actuarial survival analysis and patient groups were compared by log rank test. The independent effects of demographic, morphological, haemodynamic, and electrocardiographic variables on survival were analysed by Cox regression model. A probability value of p < 0.05 was considered significant. All statistical analyses were performed using SPSS version 7.5 (SPSS Inc, Chicago, Illinois).

RESULTS
Patients
All except three patients were term infants and all but eight were ethnic Chinese. The median age at presentation was 1 day (range 1 day to 3.7 years). Seventy six per cent of patients presented within their first week of life. The presenting symptom was cyanosis in 111 (96%) patients and heart failure in five (4%). Intravenous prostaglandin infusion was given in 52 (45%) patients. Fifty two (45%) patients presented during or before 1990. Surgery was not planned in 31 patients, all of whom died. The median follow up duration of the remaining 85 patients who either had or are awaiting surgery was 5.8 years (range 0.7–25 years). Three patients were lost to follow up.

Cardiac morphology
Levocardiia was present in 81 (70%), dextrocardia in 29 (25%), and mesocardia in 6 (5%) patients. A common atrium was present in 68 (59%). A common atrioventricular valve was found in 107 (92%). A univentricular heart with or without a rudimentary chamber was present in 96 (83%) patients. Ventriculoarterial connections were single outlet with pulmonary atresia in 48 (41%), double outlet right ventricle in 29 (25%), double outlet indeterminate ventricle in 19 (16%), double outlet left ventricle in 9 (8%), ventriculoarterial concordance in 6 (5%), and ventriculoarterial discordance in 5 (4%).

Pulmonary outflow was obstructed in 96 (83%) patients, 42 of whom had pulmonary atresia. Systemic outflow obstruction was present in only four (3%) patients, two each of coarctation of aorta and subaortic stenosis.

Anomalous pulmonary venous connection was present in 60 (52%) patients. It was supracardiac in 28, cardiac in 18, infradiaphragmatic in 11, and partial in 2 patients; one patient had complete atresia of pulmonary veins. Pulmonary venous obstruction was present in 15 of these 60 (25%) patients.

Intervention not planned or awaited
Surgical interventions were not planned in 31 of 116 (27%) patients. Of these, 26 had cardiac lesions considered too complex for surgery and five had parents who refused surgery; they all died soon after birth. Surgical interventions to be performed at an older age were planned in 11 patients who had pulmonary stenosis with a balanced haemodynamic status at initial presentation. Of these, three were lost to follow up; one died of viral pneumonia while awaiting intervention; two were subsequently managed conservatively, one because of pulmonary hypertension and one unfavourable pulmonary arterial anatomy; and five were awaiting interventions.
Interventions performed

**Obstructed anomalous pulmonary venous drainage**

Surgical interventions were performed in only 4 (27%) of 15 patients with obstructed anomalous pulmonary venous drainage (fig 1). The overall mortality was 75% (3 out of 4).

Pulmonary venous repair was performed in two patients: one died immediately after surgery of low cardiac output syndrome, the other with concomitant pulmonary arterial banding survived and is awaiting further intervention.

A systemic pulmonary arterial shunt was placed in two patients with unmasking of associated obstructed supracardiac pulmonary venous connections. Both patients died after subsequent pulmonary venous repair. One had a supracardiac type of anomalous drainage with left pulmonary venous stenosis and died of sepsis two months after pulmonary venous repair. The other patient developed cardiac arrest immediately after pulmonary venous repair. Although she was successfully resuscitated, she developed renal failure that required peritoneal dialysis for more than two months and eventually died of sepsis and peritonitis.

**Non-obstructed anomalous pulmonary venous drainage**

Surgical interventions were performed in 27 (60%) of 45 patients with non-obstructed anomalous pulmonary venous drainage (fig 2).

Pulmonary venous repair was performed in two patients. One who had concomitant placement of a systemic pulmonary arterial shunt developed low cardiac output syndrome postoperatively and died on day 3 after surgery. The other required a shunt operation three weeks later and died of viral bronchiolitis three months afterwards. Pulmonary arterial banding was performed in two patients, one of whom died of sepsis 2.5 years after surgery. The arterial duct was ligated in one patient, who is surviving and awaiting further surgery. Fontan operation was performed in three: one died of low cardiac output syndrome one day after surgery. Cavopulmonary shunt was performed in three patients: one underwent revision of the stenosed shunt but collapsed suddenly five weeks after the revision as a result of milk aspiration.

A systemic pulmonary arterial shunt was placed for initial palliation in 16 patients. The shunt became stenosed in one patient, who then had stenting of the arterial duct and is awaiting cavopulmonary shunt insertion. Two patients had subsequent pulmonary venous repair: one, who had concomitant atrioventricular valve repair for severe regurgitation, survived while the other died suddenly 1.5 months after surgery. The latter required amiodarone and propafenone to control her supraventricular tachycardia that occurred early postoperatively. Two died after Fontan procedure: one failed to wean off cardiopulmonary support while one died of an unknown cause three years after the procedure. One patient had an uneventful cavopulmonary shunt operation. Three died while awaiting further interventions: two were sudden deaths of unknown cause two and six months after shunting, respectively; one died of brain abscess that occurred six years after shunting. The remaining seven patients are alive with no further interventions yet.

**Normal pulmonary venous drainage**

Surgical interventions were performed in 43 (77%) of 56 patients with normal pulmonary venous drainage (fig 3).

Pulmonary arterial banding was performed in one patient who subsequently died of ventilatory failure caused by associated tracheal stenosis. Fontan operation was performed in
four: one failed to wean off cardiopulmonary bypass. Three patients had cavopulmonary shunt insertion: one collapsed suddenly without obvious cause two days after the operation and could not be resuscitated; one required atrioventricular valve replacement five years later.

A systemic pulmonary arterial shunt was placed for initial palliation in 35 patients. There were nine deaths: one patient returned to the intensive care unit with low cardiac output syndrome and died; one died of severe heart failure three years after shunting; three died suddenly of unknown causes, one of whom had atrioventricular valve replacement after initial shunting; and four died of infection. Of the 26 survivors, 10 subsequently had a Fontan procedure with three deaths: two died early postoperatively of multiorgan failure; one, who had concomitant atrioventricular valve replacement, died five years after surgery of prosthetic valve dysfunction. Six had cavopulmonary shunt insertion: one collapsed six months after the operation due to an episode of supraventricular tachycardia and could not be resuscitated. A pacemaker was implanted in one patient who had associated congenital complete heart block; he died of pneumonia one week after the implantation. The remaining nine patients are alive with no further interventions yet.

**Mortality**

The causes of death are summarised in table 1. The early surgical mortality (death within one month of operation) for pulmonary venous repair was 25% (2 of 8), Fontan procedure 26% (5 of 19), cavopulmonary shunting 7.7% (1 of 13), and systemic pulmonary arterial shunt insertion 1.9% (1 of 53). Late mortality was related to infection in 10 patients and arrhythmia in one. Sudden death of unknown aetiology occurred in seven patients, five of whom had a history of cardiac arrhythmia. Two had re-entrant supraventricular tachycardia, two had ventricular extrasystoles, and one had atrial tachycardia and flutter. The overall prevalence of symptomatic arrhythmia in those who had or planned to have surgery was 18% (15 of 85).

When all patients were included in the Cox regression model, significant independent risk factors for mortality were pulmonary venous obstruction (relative risk (RR) 3.8, 95% confidence interval (CI) 1.7 to 8.3; p = 0.001) and a single main ventricular chamber (RR 2.9, 95% CI 1.2 to 6.9; p = 0.016). Patients with normal pulmonary venous connections (RR 0.33, 95% CI 0.17 to 0.64; p < 0.001) and those with higher oxygen saturation at presentation (RR 0.96, 95% CI 0.94 to 0.98; p = 0.01) were associated with lower mortality. In contrast, when only those with normal pulmonary venous drainage were included in the model, no risk factors were identifiable.

**Survival**

The overall mean (SEM) survival at one month and 1, 5, 10, and 15 years was 80 (3.7)% 65 (4.6)% 51 (5.0)% 43 (5.5)% and 34 (7.4)% respectively (fig 4A). Survival for patients with obstructed pulmonary venous drainage was worse than for those with either normal or non-obstructed anomalous pulmonary venous drainage (p < 0.001) (fig 4B). There was no significant difference in survival between the latter two subgroups (p = 0.06). Assessment of the independent effect of pulmonary outflow obstruction on survival found that patients with pulmonary stenosis had a better survival than
those with either atresia or absence of obstruction \( (p = 0.02) \) (fig 4C). There was no significant difference in survival between those presenting before and those after 1990 \( (p = 0.07) \) (fig 4D).

### DISCUSSION

To our knowledge, this is the largest clinical series from a single institution to date. There is a suggestion that right atrial isomerism is more prevalent in oriental children. Furthermore, from this and another study, it seems that the prevalence of normal pulmonary venous connection is higher in orientals than in whites. Nonetheless, regardless of whether pulmonary venous connections are normal, the outcome of infants and children with this cardiac lesion remain discouraging despite surgical interventions. Pulmonary venous obstruction and a single main ventricular chamber are significant risk factors for mortality. When only patients with normal pulmonary venous connection are analysed, no risk factors for mortality can be identified. The absence of other predicting risk factors suggests that right isomerism by itself is a risk factor in the disappointing long term outcome.

### Obstructed anomalous pulmonary venous connection

The unfavourable outcome of patients with right isomerism and obstructed anomalous pulmonary venous connections is well documented. The use of prostaglandin to augment pulmonary blood in the presence of severe pulmonary outflow obstruction or an atretic outflow helps to unmask obstructed pulmonary venous drainage, although infrequently the latter may be apparent only after insertion of a systemic pulmonary arterial shunt, as in two of our patients. Because primary pulmonary venous repair was performed in only 4 of 15 (27%) patients with obstructed anomalous pulmonary venous drainage, the outcome in this subgroup approximates the natural outcome. The Kaplan-Meier survival curve of the our patients, however, closely approximates that in a series described by Hashmi and colleagues, in which 14 of 25 (56%) patients with obstructed drainage underwent pulmonary venous repair. This is probably explainable by their high surgical mortality of pulmonary venous repair (95%), which does little to alter the eventual outcome of this subgroup. Even after creation of an adequate anastomosis between the pulmonary venous confluence and the atrium, the smaller pulmonary veins in association with heterotaxy syndrome might predispose these patients to recurrent obstruction and explain their poor survival despite surgery.

### Non-obstructed normal and anomalous pulmonary connections

The presence of a normal pulmonary venous connection, although associated with a lower mortality, does not imply a good long term outcome. The mean (SEM) survival at 1, 5, 10, and 15 years of age was 81 (5.3)%, 67 (6.6)%, 60 (7.8)%, and 43 (12)%, respectively (fig 4B), similar to that of patients with non-obstructed anomalous pulmonary venous drainage. Late mortality in these two subgroups of patients was related mainly to sepsis and sudden death of unknown aetiology. Although antibiotic prophylaxis is a routine practice in our institution for all patients diagnosed with right atrial isomerism, including the seven patients who each had a single rudimentary spleen, sepsis remains an important cause of

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**Table 1** Causes of death after interventions

<table>
<thead>
<tr>
<th>Surgery</th>
<th>Causes</th>
<th>Pulmonary venous drainage</th>
<th>Overall mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Obstructed anomalous</td>
<td>Non-obstructed</td>
</tr>
<tr>
<td>S-P shunt</td>
<td>Early death</td>
<td>1</td>
<td>23</td>
</tr>
<tr>
<td>[n=53]</td>
<td>Late death</td>
<td>Infection: Pneumonia</td>
<td>Brain abscess</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Severe heart failure</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sudden death (3/5 had history of cardiac arrhythmia)</td>
<td>2</td>
</tr>
<tr>
<td>PV repair</td>
<td>Early death</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>[n=8]</td>
<td>Late death</td>
<td>Infection: Bronchitis</td>
<td>Peritonitis</td>
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<tr>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sudden death (while on antiarrhythmic medications)</td>
<td></td>
</tr>
<tr>
<td>CP shunt</td>
<td>Early death</td>
<td>1</td>
<td>23</td>
</tr>
<tr>
<td>[n=13]</td>
<td>Late deaths</td>
<td>Aspiration of milk</td>
<td>Supraventricular tachycardia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Fontan</td>
<td>Early deaths</td>
<td>Failure to wean off cardiopulmonary bypass</td>
<td></td>
</tr>
<tr>
<td>[n=19]</td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Multivisceral failure</td>
<td>Dysfunction of prosthatic atrioventricular valve</td>
</tr>
<tr>
<td>PA banding</td>
<td>Early death</td>
<td>1</td>
<td>67</td>
</tr>
<tr>
<td>[n=3]</td>
<td>Late death</td>
<td>Sepsis</td>
<td></td>
</tr>
<tr>
<td>Pacemaker</td>
<td></td>
<td>Pneumonia</td>
<td></td>
</tr>
<tr>
<td>insertion</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>[n=1]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CP, cavopulmonary; PA, pulmonary arterial; PV, pulmonary venous; S-P, systemic pulmonary
mortality in this subgroup. As reported previously,1 break-
through episodes of infection do occur despite antibiotic
prophylaxis. Associated immunodeficiency, involving both the
humoral17 and cellular18 arms, probably contributes signifi-
cantly to the vulnerability to infection.

Sudden death accounted for 7 of 21 (33%) late deaths (table
1) in these two patient groups. It occurred after systemic pul-
monary arterial shunt insertion, pulmonary venous repair,
cavopulmonary shunt, and Fontan procedure. The paired
atrioventricular nodes described in right atrial isomerism pre-
dispose patients to development of supraventricular
tachycardia.19 The risk of cardiac arrhythmia is further
increased after the Fontan operation.20 Tachyarrhythmic
episodes may compromise borderline single ventricular
haemodynamics. Whether the sudden collapse of our patients
is related to tachyarrhythmia is speculative. Nevertheless, it is
noteworthy that five of these seven patients had a history of
arrhythmia. Predictors of the development of arrhythmia in
right atrial isomerism have not been defined, although one
study suggests that the presence of two ventricles is associ-
ated with the development of supraventricular tachycardia.19 It is
not surprising, therefore, that none of the electrocardio-
graphic variables emerges as a risk factor for mortality.

**Other risk factors**

**Single ventricle**

The ejection fraction of a single ventricle has been shown to be
less than that of a normal systemic ventricle and decrease fur-
ther after the Fontan procedure.21 Ventricular diastolic
function may likewise be affected in the pre- and post-Fontan
state.21,22 An increase in crosslinking of collagen, shown to
occur in experimentally induced volume overload left ven-
tricular hypertrophy,23 may reduce ventricular compliance.
Furthermore, atriointerual valve regurgitation occurs with
increasing prevalence on follow up of patients with a volume
loaded single ventricle.21 The presence of major atriointerior
valve anomaly is a risk factor for mortality in patients with
right atrial isomerism.6 The structure of a common atriointer-
valve, present in the majority (92%) of our patients, in
the setting of double inlet ventricle and atrial isomerism has
been shown to differ from that in the setting of biventricular
atriointerior connection and appears less suited to
function as an inlet valve for the systemic circulation.21 In fact,
17% (16 of 96) of our patients with a single main ventricle had
moderate to severe atriointerior valve regurgitation,
compared with 5% (1 of 20) of those with biventricular hearts.
The atriointerior valve was replaced in three and repaired
in one of our patients. Thus, progressive ventricular failure
with increasing atriointerior valve regurgitation may com-
promise the long term outcome. The combination of a single
ventricle and total anomalous pulmonary venous drainage
worsens the prognosis further.26

**Systemic oxygen saturation**

Both pulmonary atresia9 and absence of pulmonary outflow
obstruction6 have been shown to be significant risk factors for
mortality. We further showed that patients with pulmonary

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**Figure 4** Kaplan-Meier survival estimates for (A) the entire cohort, (B) patients with different types of pulmonary venous drainage [p < 0.001],
(C) those with different degrees of pulmonary outflow obstruction (p = 0.02), and (D) those who presented before and after 1990 (p = 0.07).
stenosis had a significantly better survival than those with either atresia or absence of obstruction (fig 4C). It seems logical, therefore, to speculate that a V shaped curve might best fit the relation between mortality and degree of pulmonary outflow obstruction. RR approaching unity (95% CI 0.94 to 0.98) may reflect such a biphasic relation between oxygenation, an index of pulmonary flow, and mortality. Even with the ability to manipulate pulmonary blood flow, either by augmenting it with a shunt or by controlling it with a band and ductal ligation, surgery seems to have done little to alter the natural risk associated with either an atriectomy or unrestrictive pulmonary outflow. This perhaps reflects the complex interaction between pulmonary arterial flow, pulmonary venous pressure, and compliance and size of the pulmonary veins.6

Surgery
All of our patients were considered candidates for univentricular repair. Despite the seemingly varied surgical approach over the long study period, the operations were basically staged towards eventual Fontan type procedures. The important initial steps of controlling pulmonary arterial flow and elimination of pulmonary venous obstruction have been alluded to earlier. Reduction of significant atrioventricular regurgitation by either valvoplasty or replacement was achieved either before or at the time of the Fontan procedure. Our 26% surgical mortality rate of Fontan procedure is comparable with the 21% and 33% reported, respectively, by Hashmi and colleagues27 and Culbertson and associates28 but higher than the 15% reported from the Mayo Clinic.28 The surgical mortality in patients with right atrial isomerism is nonetheless higher than the reported overall mortality of 9%.24 A common atrioventricular valve, atrioventricular valve regurgitation, and surgery, either repair or replacement, are significant risk factors for early mortality after the Fontan operation.27 28 rather than the syndrome of heterotaxy.29

Summary
The long term outcome of infants and children with right atrial isomerism in association with a normal pulmonary venous drainage remains unfavourable, despite avoiding the reported high risk associated with pulmonary venous repair. Their outcome approximates those with anomalous but non-obstructed pulmonary venous connections. Sepsis and sudden death that may potentially be related to cardiac arrhythmia are major causes of late mortality. Rigorous prevention of infection by antibiotic prophylaxis and vaccinations should be emphasised and aggressive treatments should be instituted early during the course of infection. Further studies are warranted to identify possible predictors of arrhythmia.

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