Management and Outcomes of Right Atrial Isomerism: A 26-Year Experience

AIJAZ HASHMI, MD, FRCP(C), RIYADH ABU-SULAIMAN, MD,

BRIAN W. McCRINDLE, MD, FACC, JEFFREY F. SMALLHORN, MBBS, FACC,

WILLIAM G. WILLIAMS, MD, FRCS(C), ROBERT M. FREEDOM, MD, FACC

Toronto, Ontario, Canada

Objectives. We sought to determine, in a large series of patients with right atrial isomerism, factors associated with mortality.

Background. Right atrial isomerism is associated with complex congenital heart disease and high morbidity and mortality.

Method. All data from patients diagnosed with right atrial isomerism between January 1970 and March 1996 were reviewed.

Results. A total of 91 consecutive patients (54 male) were identified. Most patients (89%) presented within the first month of life, 62% at birth. Cardiac abnormalities included common atrioventricular (AV) valve (81%), ventricular hypoplasia or single ventricle (73%), abnormal ventriculoarterial connections (96%), pulmonary outflow tract obstruction (84%), anomalous pulmonary venous drainage (87%) and pulmonary vein obstruction (30%). The overall mortality rate was 69%. No interventions were planned or performed in 24%, 95% of whom died. The mortality rate for patients requiring their first cardiovascular operation in the neonatal period was 75% versus 51% for those with later first operations (p < 0.05). The surgical mortality rate for patients undergoing pulmonary vein repair was 95%. Overall survival estimates were 71% at 1 month, 49% at 1 year and 35% at 5 years. Independent risk factors for decreased time to death included the absence of pulmonary outflow obstruction (relative risk [RR] 2.23, p < 0.03), presence of major AV valve anomaly (RR 5.23, p < 0.03) and obstructed pulmonary veins (RR 5.43, p < 0.0001).

Conclusions. Right atrial isomerism continues to have an associated high mortality despite surgical innovations. Management of pulmonary vein obstruction remains a serious problem and is associated with high mortality.

(J Am Coll Cardiol 1998;31:1120–6)
©1998 by the American College of Cardiology

Hearts demonstrating right atrial isomerism are usually associated with complex congenital cardiac malformations (1–13). Many of these patients also have abnormalities of the spleen—usually, but not invariably, asplenia (2,6,14–16).

Patients with asplenia and complex congenital heart disease were once considered inoperable; but over the most recent two decades, there have been increasing reports (17–20) of surgical successes in patients with right atrial isomerism undergoing either a one-ventricle (Fontan) or biventricular repair. Such reports document outcomes for those relatively few patients undergoing operation but do not provide information about an institutional experience or outcomes from all such patients referred over a defined interval. We report patient outcomes for an institutional experience with right atrial isomerism seen over an era of evolving management strategies.

To determine factors associated with poor prognosis, we undertook a retrospective review of all patients diagnosed with right atrial isomerism at our pediatric center between January 1970 and March 1996.

Methods

Definitions and patient identification. How best to diagnose hearts associated with asplenia and right atrial isomerism remains controversial. Such patients have visceroatrial heterotaxia and atrial appendages that each tend to resemble morphologically right atrial appendages; most also have juxtaposition of the abdominal aorta and inferior vena cava. Many, but not all, have congenital abnormalities of the spleen, usually asplenia.

Radiologic diagnosis of right atrial isomerism may be suspected on plain X-ray films of the chest and abdomen by identifying the position of the liver, stomach and bronchial pattern (21). Echocardiographic or angiographic demonstration of a juxtaposed relation between the aorta and inferior vena cava and the morphology of the atrial appendages was used to support the diagnosis (22,23). When surgical interventions or autopsies made direct visual examination of the atrial morphology possible, the diagnosis was further verified.

The diagnosis of a common atrium was made if the interatrial septum was absent or if a very large secundum and primum defect with only a vestigial septum were present (3).

Hearts having only one identifiable pumping chamber with virtually an absent interventricular septum were classified as either single-ventricle or univentricular hearts of right ventricular morphology, left ventricular morphology or indeterminate type.

Single-outlet aorta refers to the ventriculoarterial connection in these patients with a single ventricle (single-outlet right, left or indeterminate ventricle) who have pulmonary atresia.

For the purpose of the present study, patients who had all four pulmonary veins draining individually to the left-sided atrium were considered to have "normal" drainage. The remainder were classified as having anomalous pulmonary venous connections. However, it was recognized that in certain cases of dextrocardia, the left-sided atrium may not be the "correct" one into which the pulmonary veins must drain. The diagnosis of pulmonary venous obstruction was based on clinical, radiographic, echocardiographic and angiocardiographic investigations (24–26). In addition, prostaglandin challenge (13) unmasked obstruction of total anomalous pulmonary venous connections in some patients.

A prominent feature of right atrial isomerism, *asplenia* is suggested by the presence of erythrocytic inclusion bodies on a peripheral blood smear. Nevertheless, these Howell-Jolly bodies may be transiently present in normal newborns as well as in patients with megaloblastic hemolytic anemias, thalassemia and leukemia (3). In this series the status of the spleen was determined and confirmed by a combination of tests, including blood smear for presence of Howell-Jolly bodies, abdominal ultrasound, radionuclide spleen scan and autopsy findings. Right atrial isomerism is often used synonymously with the term asplenia. However, asplenia is not a constant feature of right atrial isomerism, as demonstrated by the presence of a spleen in five of our patients and by similar published reports (2,5,14–16).

The databases of the Divisions of Cardiology and Cardiovascular Surgery and Department of Pathology of The Hospital for Sick Children in Toronto were reviewed for patients with right atrial isomerism between January 1970 and March 1996; all eligible patients were included in the present report.

The variables analyzed to identify risk factors for mortality included birth weight and length of gestation; patient age, cyanosis and prostaglandin dependence at presentation; presence of cardiac lesions, including anomalous heart position, common atrium, major atrioventricular (AV) valve anomaly, pulmonary outflow obstruction, anomalous pulmonary venous connections, obstruction of pulmonary venous connections and aortic outflow obstruction; presence of extracardiac lesions; age at first surgical intervention; and types of interventions performed.

Data analysis. Results are presented as number (percent) of patients or mean value $\pm$ SD, as appropriate. Kaplan-Meier estimates were used to plot survival curves. Wilcoxon and log rank tests were used to test the effect of intervention on time to death. The independent effects of demographic and anatomic variables on survival were analyzed with Cox proportionate hazards modeling using forward stepwise variable selection. Variables related to mortality in univariate analysis with $p < 0.10$ were tested in stepwise selection, with model selection entry criteria set at $p < 0.05$. A separate multivariate analysis was performed to determine the independent effect of interventions. SAS version 6.04 software was used to perform all statistical analyses.

Results

Patients. A total of 91 consecutive patients (54 male) were identified with a diagnosis of right atrial isomerism between January 1970 and March 1996. The mean birth weight was 3.0 ± 0.6 kg (n = 79, the number of patients for which the particular datum was available) and the mean length of gestation was 39 ± 3 weeks (n = 81).

The majority of the patients presented at birth (56 [62%] of 90), with 80 (89%) of 90 presenting within the first month of life. Age at presentation ranged from newborn to 7.7 months. Cyanosis was evident during the first 24 h of life in 58 (67%) of 87 patients. As well, 40 (51%) of 79 patients required prostaglandin infusion at presentation to maintain oxygen saturation.

Cardiac lesions. The cardiac position was levocardia in 56 (63%) of 89 patients and dextrocardia in 33 (37%) of 89. A common atrium was identified in 76 (84%) of 91 patients. A common AV valve was present in 74 (81%) of 91 patients, with absent left connection in 7 (8%) of 91. Ventricular hypoplasia or single ventricle was present in 66 (73%) of 90 patients. Hypoplastic right ventricle was noted in 28 (31%) of 90 patients, hypoplastic left ventricle in 27 (30%) of 90 and a single ventricle in 11 (12%) of 90.

The ventriculoarterial connection was abnormal in 87 (96%) of 91 patients, with double-outlet right ventricle in 29 (32%) of 91, ventriculoarterial discordance in 44 (48%) of 91, single-outlet aorta in 11 (12%) of 91 and double-outlet left ventricle in 3 (3%) of 91. Ventriculoarterial concordance was present in 4 (4%) of 91 patients.

Pulmonary outflow tract obstruction was identified in 76 (84%) of 91 patients and included pulmonary atresia in 23 (25%) of 91.

The majority of the patients (80 [88%] of 91) had no systemic outflow obstruction. However, aortic valve stenosis was present in 1 patient, aortic atresia in 1, subaortic stenosis in 5 (5%) of 91 and coarctation of the aorta in 4 (4%) of 91. A right aortic arch was present in 43 (49%) of 87 patients.

Total anomalous pulmonary venous drainage was present in 77 (87%) of 89 patients, was supracardiac in 42 (47%) of 89, cardiac in 19 (21%) of 89 and infradiaphragmatic in 11 (12%) of 89. Mixed-type anomalous pulmonary venous drainage was present in 5 (6%) of 89 patients. Pulmonary venous obstruc-
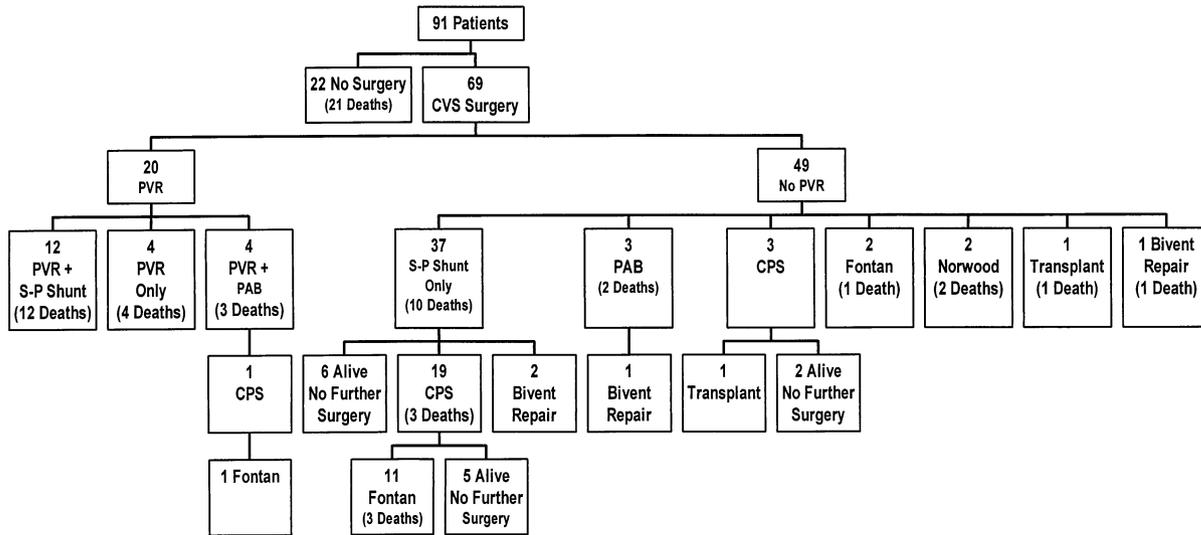
Figure 1. Flowchart showing surgical interventions and deaths. CPS = cavopulmonary shunt; Bivent = biventricular; CVS = cardiovascular surgery; PAB = pulmonary artery band; PVR = pulmonary vein repair; S-P = systemic to pulmonary artery; transplant = heart transplantation.

tion, as demonstrated by a combination of clinical, radiographic, echocardiographic and angiocardiographic investigations, was present in 25 (30%) of 84 patients.

Superior vena cava anomalies were present in 55 (64%) of 86 patients; 23 (27%) of 86 had a single left-superior vena cava; 22 (26%) of 86 had bilateral superior vena cavae without a bridging innominate vein; and 10 (12%) of 86 had bilateral superior vena cavae with a bridging innominate vein.

The inferior vena cava drained into the right-sided atrium in 41 (52%) of 79 patients, into the left-sided atrium in 34 (43%) of 79 and into the midline of the atrium in 4 (5%) of 79.

The hepatic veins drained normally into the inferior vena cava in 41 (62%) of 66 patients. Total anomalous hepatic venous drainage was present in 19 (29%) of 66 patients in the presence of a normal intrahepatic inferior vena cava. Partial anomalous hepatic venous drainage was present in 6 (9%) of 66 patients. Of the 19 patients with total anomalous hepatic venous drainage, 12 have died, and autopsies have confirmed that these were indeed cases of right atrial isomerism.

The most common combination of cardiac anomalies (n = 46, or 51%) comprised anomalous pulmonary venous drainage, pulmonary outflow obstruction, common atrium, major AV valve anomaly, single ventricle or ventricular hypoplasia, abnormal ventriculoarterial connection and no aortic outflow obstruction.

Extracardiac lesions. A midline liver position on clinical examination and X-ray film was present in 66 (77%) of 86 patients. The liver was right-sided in 13 (15%) of 86 patients and left-sided in 7 (8%) of 86.

Most patients had asplenia, with the exception of four who

each had a single rudimentary spleen and one with multiple splenuli.

Gastrointestinal anomalies were present in 29 (34%) of 86 patients, with the most common defect (16 [19%] of 86) being malrotation of the bowel such that the position of the cecum (and appendix) was variable but not in the usual right lower quadrant. Other anomalies included tracheoesophageal fistula with esophageal atresia in one patient, hiatus hernia in one, duodenal web in one, annular pancreas in two and anal atresia in three.

Genitourinary anomalies (hydronephrosis, horseshoe kidney, bilateral polycystic kidneys, absence of one kidney or cryptoorchidism) were present in 7 (9%) of 82 patients.

Mortality without surgical intervention. After assessment, no cardiovascular surgical interventions were planned or performed in 22 (24%) of 91 patients, 21 (95%) of whom died at a median age of 4 days. Of these patients, 12 (with no notable differences in complexity of cardiac lesions) were considered inoperable by their attending cardiologist during the early part of the study period. Of the other 10 patients, 5 had severe noncardiac conditions (including disseminated cytomegalovirus in 1); 2 died during initial operation for noncardiovascular anomalies; 1 was diagnosed at autopsy after sudden infant death syndrome; and 1 patient's parents refused intervention. One patient who presented recently is doing well and is awaiting intervention.

Surgical interventions and mortality (Fig. 1). Cardiovascular surgical interventions were performed in the majority of patients (69 of 91).

Repair of anomalous pulmonary venous drainage was required at initial intervention in 20 patients, 14 with evidence of pulmonary venous obstruction at the time of repair; there were 19 postoperative deaths (95%). Four patients had pulmonary vein repair only (all died); 4 had concomitant pulmonary artery banding (3 died); and 12 had concomitant placement of a systemic to pulmonary-artery shunt (all died). Causes of death in the immediate postoperative period included pulmonary

vein obstruction with pulmonary edema in 12 and 1 patient each with obstructed shunt, excessive pulmonary blood flow with pulmonary vein obstruction, ventricular fibrillation, electromechanical dissociation, cerebral infarction, pericardial tamponade and severe bradycardia with cardiac arrest after endotracheal suctioning. The one survivor went on to undergo creation of a cavopulmonary anastomosis, followed by a successful Fontan procedure.

The initial intervention was placement of a systemic to pulmonary artery shunt alone in 37 patients, 7 of whom died immediately after operation (blocked shunt in 2, excessive pulmonary blood flow and low cardiac output in 3, cerebral infarction in 1, pulmonary embolus in 1). There were 3 additional late deaths because of blocked shunt (at 5 months after operation), pneumococcal meningitis (7 months) and pneumonia (12 months after). Of the 27 survivors, 6 are alive with no further operation to date, and 2 have had successful biventricular repair. The other 19 patients have had takedown of shunt and creation of a cavopulmonary anastomosis; 3 of these patients died of pulmonary artery thrombosis (1 immediately after the operation, 1 of pneumococcal sepsis while receiving antibiotic prophylaxis 1 year postoperatively, 1 overseas patient from unknown causes 1 year postoperatively). Of the 16 survivors after cavopulmonary anastomosis, 5 are alive with no further operation to date. The other 11 patients have undergone the Fontan procedure; 3 of these patients died of intraoperative right ventricular myocardial infarction, prolonged cardiopulmonary bypass with myocardial failure and cerebral infarction, respectively.

Pulmonary artery banding alone was the initial intervention in three patients, two of whom died postoperatively (one with no clear cause, one from bleeding complications). The remaining patient has since had successful biventricular repair.

Three patients had creation of a cavopulmonary anastomosis as their initial intervention. Two of these patients are alive with no further operation to date. The other patient developed progressive congestive heart failure and survived heart transplantation at 23 years of age.

Two patients underwent Fontan procedure with no previous interventions; one patient later died of protein-losing enteropathy that developed after a pulmonary artery thrombosis in the immediate postoperative period.

Two patients with subaortic obstruction and aortic arch hypoplasia died immediately after the Norwood procedure (1 of intraoperative complications, other postoperatively of low cardiac output).

Another patient, who had nonconfluent pulmonary arteries and bilateral patent ductus arteriosi, died of multiorgan failure after primary heart transplantation at the age of 3 months.

The one remaining patient underwent biventricular repair with no previous interventions. This patient died intraoperatively during repair of AV septal defect.

Postoperative management and mortality (Fig. 2). Management and outcomes were further analyzed to determine the likelihood of successful completion of intended management strategy after the initial surgical intervention. Of the 69
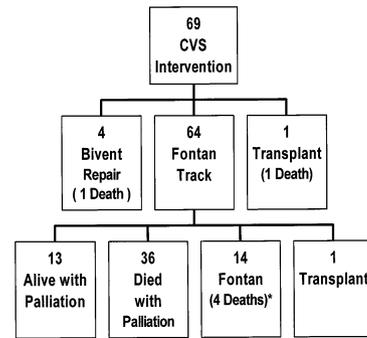

Figure 2. Intended management strategy after initial surgical intervention. *Three early postoperative deaths and one late death. Abbreviations as in Figure 1.

patients who had initial cardiovascular surgical interventions, 64 were deemed to be on a Fontan track, whereas 4 were directed toward biventricular repair. Primary heart transplantation was the initial strategy in the remaining patient (described above).

Of the 64 patients on the Fontan track, 62 had varying pre-Fontan palliations (described earlier), and 2 had a single-stage Fontan procedure (1 of whom died later). The total mortality rate with pre-Fontan palliation was 56% (36 patients died), with 13 patients alive without further intervention to date and 12 patients undergoing staged Fontan procedure (3 died). The remaining patient, described earlier, had heart transplantation after pre-Fontan palliation.

Only four patients had cardiac anatomy suitable for biventricular repair. One patient with an AV septal defect, including foramen primum atrial septal defect, small ventricular septal defect and left valve cleft underwent patch closure of the atrial septal defect and suture closure of the ventricular septal defect and the cleft in the left AV valve. The patient sustained an intraoperative cardiac arrest and could not be weaned from cardiopulmonary bypass. One patient had a large foramen secundum atrial septal defect, ventriculoarterial discordance with intact ventricular septum and unobstructed total anomalous pulmonary venous drainage to a confluence behind the left atrium, draining through the vertical vein to the right superior vena cava. This patient underwent pulmonary artery banding at 1 year, followed by an arterial switch operation and anomalous pulmonary vein repair 4 months later. This patient is currently alive at 3.3 years of age. Two other patients underwent a Rastelli repair for double-outlet right ventricle with pulmonary outflow tract obstruction; both are currently alive at 9.8 and 23 years of age, respectively.

Risk factors for mortality. Kaplan-Meier survival analysis showed an overall survival rate of 71% (95% confidence interval [CI] 62% to 81%) at 1 month, 49% (95% CI 38% to 59%) at 1 year and 35% (95% CI 25% to 45%) at 5 years (Fig. 3). Survival for patients presenting from 1990 onward was significantly worse (Wilcoxon test, $p = 0.09$; log rank test, $p = 0.03$) than for those presenting earlier, with a survival rate of 68% at 1 month and 32% at 1 year in the more recent cohort.
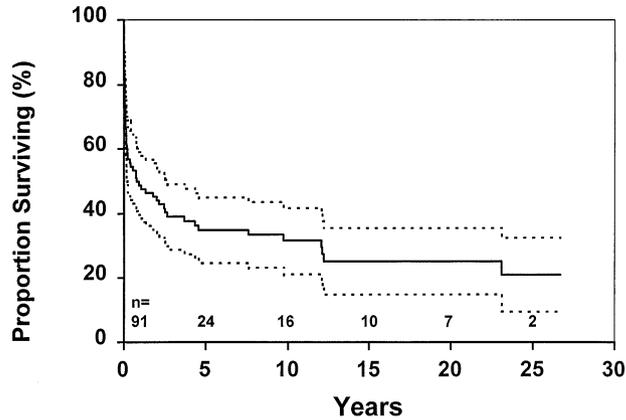
Figure 3. Kaplan-Meier survival estimates of overall survival of 91 patients with right atrial isomerism. The overall mortality rate was 69%. **Dashed lines** = 95% CI.

Significant independent risk factors for time to death from Cox proportionate hazards modeling are shown in Table 1 (see Methods for variables analyzed to identify risk factors for mortality).

Patients were classified into three groups according to their requirement for and timing of cardiovascular surgical intervention (Table 2): those for whom none was planned or performed; those who required it during their neonatal period (≤4 weeks of age); and those who required their first surgical intervention after the neonatal period. Kaplan-Meier survival curves for these groups are shown in Figure 4.

The independent effect of intervention on time to death was likewise explored with Cox proportionate hazards modeling. Only the presence of pulmonary vein obstruction remained an additional independent risk factor; differences in survival between intervention groups remained statistically significant when controlled in the regression model for pulmonary vein obstruction. Relative to the group requiring cardiovascular intervention after the neonatal period, the relative risk for the nonintervention group was 5.57 (p < 0.0001); and for the group requiring their first surgical intervention during the neonatal period, 2.15 (p = 0.02).

Discussion

To our knowledge, this is the largest single clinical series reported in English to date cataloging the various cardiac and extracardiac lesions, along with management and outcomes. This analysis reviewed the clinical presentation and course of 91 consecutive patients presenting to this institution over the past 26 years.

Cardiac anatomy and outcomes. Patients with right atrial isomerism constitute a heterogeneous group with severe and complex congenital heart disease and extracardiac anomalies. Several clinical and necropsy series (1–3,6–12,27) have listed the range of cardiac anomalies in this disorder, the frequencies of which were similar to those noted here.

Influence of pulmonary vein anomalies. Patients with total anomalous pulmonary venous drainage (present in 87% of our patients, with 30% having obstructed pulmonary veins) had uniformly poor outcomes, as reported elsewhere (28–30); the surgical mortality rate in patients with pulmonary vein repair was 95%. Jenkins et al. (31) have demonstrated that patients with heterotaxy syndrome have a mean indexed pulmonary vein sum significantly smaller than that of patients without heterotaxy. They have also reported that pulmonary vein size is a strong predictor of survival in patients with total anomalous pulmonary venous connections. Although individual pulmonary vein diameters were not routinely measured in our patients, these factors may be an additional contributing factor for the high mortality in this group of patients.

The large pooled autopsy series of asplenia cases reported by Phoon and Neill (30), which approximates a natural history study, found that the prognosis for total anomalous pulmonary venous return is poor, with a median age of 3 months at death. When both total anomalous pulmonary venous return and pulmonary atresia were present, the median age at death decreased to 1 month. Thus, it would seem that in this subset of patients, surgical intervention does little to improve the natural history.

Although all the patients in our series that had pulmonary

Table 2. Outcomes by Age at First Required Intervention

Intervention	Pulmonary Venous Obstruction	Mortality Rate (p = 0.002)*
None (n = 22)	5 (38%)†	95%
≤4 wk old (n = 32)	15 (47%)	75%
>4 wk old (n = 39)	5 (13%)	51%

*Chi-square test. †This information was available for only 13 of the 20 patients in this group.

Table 1. Independent Risk Factors for Mortality (Cox proportionate hazards modeling)*

Variable	Beta-Coeff	SE	p Value	RR (95% CI)
Absence of pulmonary outflow obstruction	−0.801	0.369	0.03	2.23 (1.08–4.59)
Presence of major AV valve anomaly	1.654	0.728	0.03	5.23 (1.25–21.8)
Presence of obstructed pulmonary veins	1.691	0.336	0.0001	5.43 (2.81–10.5)

*Final model based on n = 84 observations with nonmissing values. AV = atrioventricular; CI = confidence interval; Coeff = coefficient; RR = relative risk.
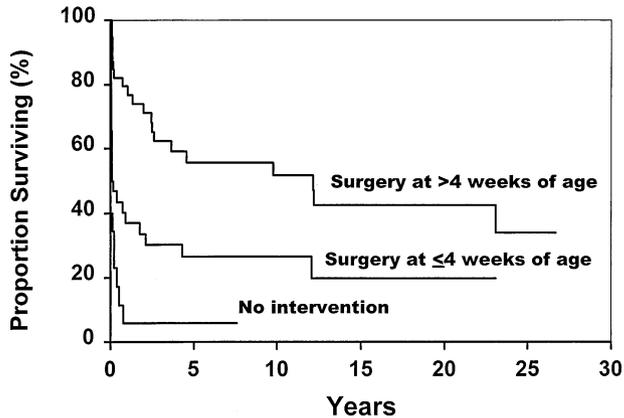
Figure 4. Kaplan-Meier survival estimates for patients with right atrial isomerism for whom no intervention was performed (95% mortality rate), patients requiring their first surgical intervention during the neonatal period (75% mortality rate) and patients requiring their first surgical intervention after 4 weeks of age (51% mortality rate). The differences in risk for the three groups of patients was significant at p = 0.0001 (Wilcoxon and log rank tests).

vein repair with concomitant systemic to pulmonary shunts for pulmonary outflow obstruction died, the independent risk factor for decreased time to death was pulmonary vein obstruction. The additive risk of concomitant pulmonary outflow obstruction could not be accurately assessed. However, absence of pulmonary outflow obstruction was an independent risk factor for decreased time to death. One might speculate that patients with a potential for excessive pulmonary blood flow in conjunction with pulmonary vein obstruction may be at higher risk for poor outcomes.

Influence of AV valve anatomy. A major AV valve anomaly, present in 89% of our patients, was found to be an independent risk factor for increased mortality. Common AV valve regurgitation has been reported to be more common in patients with than in those without heterotaxy, with an accompanying greater need for AV valve surgery (32). Because diagnostic modalities have changed during a study of this length, accurate assessment of AV valve regurgitation outcomes was not possible in the present cohort.

Surgical outcomes of Fontan procedure. The majority of the patients (93%) were candidates for single-ventricle palliation. However, only 22% of these patients had completion of their Fontan connection, with a surgical mortality rate of 21%. Fifty-six percent of these patients with single-ventricle palliation died with palliation before a Fontan operation. The remaining 20% of the patients on the single-ventricle track are alive with palliation (i.e., pre-Fontan palliation). We speculate that perhaps half of these patients may be suitable candidates for a Fontan procedure. Thus, about one third of patients with single-ventricle palliation may undergo the Fontan operation, with a surgical mortality rate of 21%.

Recently, the Mayo Clinic reported their results for the Fontan procedure (32). Patients with asplenia had a mortality rate of 15% compared with an overall mortality of 9%.

Notably, the median age at time of operation in their Fontan procedure cohort was 7 years, which may introduce a potentially significant selection bias. However, it is encouraging that mortality was dramatically lower than in their earlier (1973 to 1986) cohort (32), with a mortality rate for the asplenia group of 61%.

Culbertson et al. (17) reported on surgical outcomes for 12 patients with asplenia who underwent the Fontan procedure. The mortality rate in this group was 33%. They identified the presence of important AV valve regurgitation, hypoplastic pulmonary arteries and mean pulmonary artery pressures >15 mm Hg after 6 months of age as factors that significantly increased risks associated with the Fontan procedure.

Surgical outcomes of heart transplantation. Only two patients in our study underwent heart transplantation, with one survivor. The Loma Linda group (33) has recently reported their experience with heart transplantation in patients with heterotaxy (20 with asplenia, 10 with polysplenia). They reported a 5-year survival rate of 65%. Rates of rejection and infection after transplantation were not different from those of age-matched transplant recipients without heterotaxy. Additionally, they noted that asplenia was not an independent risk factor for death.

Influence of age at initial intervention. Of our patients who needed surgical intervention during the neonatal period, three to four times as many had obstructed pulmonary veins as those with later first operations. However, after controlling for the presence of pulmonary vein obstruction, neonatal surgical intervention remains a statistically significant risk factor for poor outcome. This finding may suggest that patients who require surgical intervention in the neonatal period have other important adverse anatomic or physiologic risk factors.

Influence of sepsis. Three patients were identified as having infection as the primary cause of death (already detailed). However, because data on episodes of sepsis in the patients were not always sufficient (especially in earlier records) or available (many patients were likely to have been treated elsewhere and not referred back to our cardiac center during infectious illnesses), sepsis could not be accurately analyzed as an independent risk factor for mortality.

Trends in outcomes. The retrospective nature of the present study allowed a review of cases from a long interval spanning 26 years. Despite the many advances in surgical techniques and postoperative management of children with congenital heart disease over this period, patients with right atrial isomerism continue to have a very poor prognosis. In fact, our data revealed that survival among patients presenting from 1990 onward was significantly worse. Earlier diagnosis and more aggressive management of high risk patients in the recent years, as well as changes in the referral pattern of severe congenital heart disease, may have influenced this increase in the mortality rate. A selection bias may have occurred, such that more children who survived the immediate postnatal period (with the administration of prostaglandin infusions and improved neonatal care and transport) and reached a diagnosis were in the latter cohort. Indeed, the number of cases present-

ing per year, the proportion of patients having surgical intervention and the proportion of patients undergoing pulmonary vein repair have all increased from 1990 onward. However, these differences did not reach statistical significance.

Summary. Our institution's 26-year experience with management of patients with right atrial isomerism highlights the complexity of associated cardiac lesions reported in other, smaller series. Independent risk factors for earlier mortality include absence of pulmonary outflow obstruction, presence of major AV valve anomaly and pulmonary vein obstruction. Patients who require surgical intervention for obstructed pulmonary veins or a combination of pulmonary vein repair and augmentation of pulmonary blood flow by a systemic to pulmonary shunt have an exceedingly high mortality.

Given the high mortality in this group of patients despite recent innovations in congenital heart surgery, it seems prudent to reassess conventional management strategies. Because more centers are acquiring experience and expertise in neonatal and infant heart transplantation, this option will have to be systematically evaluated as an alternative course of management in selected patients; in other patients with multiple risk factors for poor outcome, conservative management may be an appropriate option.

References

1. Van Mierop LHS, Gessner IH, Schiebler GL. Asplenia and polysplenia syndromes. Birth Defects 1972;8:36–44.
2. Anderson RH. Is isomerism of the atrial appendages a real thing? Cardiol Young 1995;5:207–8.
3. Rose V, Izukawa T, Moes CAF. Syndromes of asplenia and polysplenia: a review of cardiac and non-cardiac malformations in 60 cases with special reference to diagnosis and prognosis. Br Heart J 1975;37:840–52.
4. Van Praagh R, Van Praagh S. Atrial isomerism in the heterotaxy syndromes with asplenia, or polysplenia, or normally formed spleen: an erroneous concept. Am J Cardiol 1990;66:1504–6.
5. Anderson C, Devine WA, Anderson RH, Debich DE, Zuberbuhler JR. Abnormalities of the spleen in relation to congenital malformations of the heart: a survey of necropsy findings in children. Br Heart J 1990;63:122–8.
6. Liberthson RR, Hastreiter AR, Sinha SN, Bharati S, Novak GM, Lev M. Levocardia with visceral heterotaxy—isolated levocardia: pathologic anatomy and its clinical implications. Am Heart J 1973;85:40–54.
7. Ivemark BI. Implications of agenesis of the spleen on the pathogenesis of cono-truncus anomalies in childhood: an analysis of the heart malformations in the splenic agenesis syndrome, with fourteen new cases. Acta Paediatr Scand 1958;44:9–100.
8. Winer-Muram HT, Tonkin ILD. The spectrum of heterotaxic syndromes. Radiol Clin North Am 1989;27:1147–70.
9. Berman W, Yabek SM, Burstein J, Dillon T. Asplenia syndrome with atypical cardiac anomalies. Pediatr Cardiol 1982;3:35–8.
10. Phoon CK, Neill CA. Asplenia syndrome: insight into embryology through an analysis of cardiac and extracardiac anomalies. Am J Cardiol 1994;73: 581–7.
11. Yoo SJ, Nykanen DG, Freedom RM, Benson LN, Moes CAF, Burrows PE. Retrobronchial vertical vein in totally anomalous pulmonary venous connection to the innominate vein and its specific occurrence in right isomerism. Am J Cardiol 1993;71:1198–1203.
12. Freedom RM. Aortic valve and arch anomalies in the congenital asplenia syndrome: case report, literature review, and re-examination of the embryology of the congenital asplenia syndrome. Hopkins Med J 1974;135:124–34.
13. Freedom RM, Olley PM, Coceani F, Rowe RD. The prostaglandin challenge: test to unmask obstructed total anomalous pulmonary venous connections in asplenia syndrome. Br Heart J 1978;40:91–4.
14. Layman TE, Levine MA, Amplatz K, Edwards JE. "Asplenic syndrome" association with rudimentary spleen. Am J Cardiol 1967;20:136–40.
15. Muir CS. Splenic agenesis and multilobulate spleen. Arch Dis Child 1959; 34:431–5.
16. Sharma S, Devine W, Anderson RH, Zuberbuhler JR. The determination of atrial arrangement by examination of appendage morphology in 1842 heart specimens. Br Heart J 1988;60:227–31.
17. Culbertson CB, George BL, Day RW, Laks H, Williams RG. Factors influencing survival of patients with heterotaxy syndrome undergoing the Fontan procedure. J Am Coll Cardiol 1992;20:678–84.
18. Humes RA, Feldt RH, Porter CJ, Julsrud PR, Puga FJ, Danielson GK. The modified Fontan operation for asplenia and polysplenia syndromes. J Thorac Cardiovasc Surg 1988;96:212–8.
19. Okita Y, Miki S, Tamura T, et al. Bidirectional cavopulmonary anastomosis using vertical vein for right isomerism, pulmonary atresia and TAPVR. Ann Thorac Surg 1991;52:544–6.
20. Okita Y, Miki S, Kusuhara K, et al. Annuloplastic reconstruction for common atrioventricular valvular regurgitation in right isomerism. Ann Thorac Surg 1989;47:302–4.
21. Freedom RM, Fellows KE. Radiographic visceral patterns in the asplenia syndrome. Radiology 1973;106:387–91.
22. Elliot LP, Cramer GG, Amplatz K. The anomalous relationship of the inferior vena cava and abdominal aorta as a specific angiocardiographic sign in asplenia. Radiology 1966;87:859–63.
23. Huhta JC, Smallhorn JF, Macartney FJ. Two-dimensional echocardiographic diagnosis of situs. Br Heart J 1982;48:97–108.
24. Smallhorn JF, Burrows P, Wilson G, Coles J, Gilday DL, Freedom RM. Two-dimensional and pulsed Doppler echocardiography in the postoperative evaluation of total anomalous pulmonary venous connection. Circulation 1987;76:298–305.
25. Smallhorn JF, Pauperio H, Benson L, Freedom RM, Rowe RD. Pulsed Doppler assessment of pulmonary vein obstruction. Am Heart J 1985;110: 483–5.
26. Smallhorn JF, Freedom RM, Olley PM. Pulsed Doppler echocardiographic assessment of extraparenchymal pulmonary vein flow. J Am Coll Cardiol 1987;9:573–9.
27. Freedom RM. The asplenia syndrome: a review of significant extracardiac structural abnormalities in 29 necropsied patients. J Pediatr 1972;81:1130–3.
28. Sadiq M, Stumper O, De Giovanni JV, et al. Management and outcome of infants and children with right atrial isomerism. Heart 1996;75:314–9.
29. Di Donato R, di Carlo D, Squitieri C, et al. Palliation of cardiac malformations associated with right isomerism (asplenia syndrome) in infancy. Ann Thorac Surg 1987;44:35–9.
30. Phoon CK, Neill CA. Asplenia syndrome—risk factors for early unfavorable outcome. Am J Cardiol 1994;73:1235–7.
31. Jenkins KJ, Sanders SP, Orav EJ, Coleman EA, Mayer JE, Colan SD. Individual pulmonary vein size and survival in infants with totally anomalous pulmonary venous connection. J Am Coll Cardiol 1993;22:201–6.
32. Cetta F, Feldt RH, O'Leary PW, et al. Improved early morbidity and mortality after Fontan operation: the Mayo Clinic experience, 1987 to 1992. J Am Coll Cardiol 1996;28:480–6.
33. Larsen R, Eguchi J, Vander Dussen L, et al. Heart transplantation in children with visceral heterotaxy and complex congenital heart disease [abstract]. J Am Coll Cardiol 1997;29 Suppl A:105.