Survival into adulthood of patients with atrial isomerism undergoing cardiac surgery

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Objectives: To identify determinants of adverse outcomes in patients with atrial isomerism.

Methods: Determinants of survival were analyzed for the group as a whole as well as separately for left and right atrial isomerism.

Results: There were 78 cases with right and 104 with left atrial isomerism. Nineteen patients were not offered surgery; 49 (47%) of those with left atrial isomerism and 60 (77%) with right atrial isomerism were directed to single ventricle palliation. A total of 67 patients died. Survival to 25 years was 62% (95% confidence interval [CI], 53%-69%). Independent predictors of mortality were obstructed total anomalous pulmonary venous drainage ($P < .001$; hazard ratio [HR], 5.2; 95% CI, 2.7-9.7) and asplenia ($P = .008$; HR, 2; 95% CI, 1.2-3.3). There was no evidence that patients born in the recent era had improved survival ($P = .47$; HR, 1.1; 95% CI, 0.8-1.5). Survival was better for patients with left than right atrial isomerism: 18 years survival 74% (95% CI, 63%-82%) versus 50% (95% CI, 38%-60%). Independent predictors of mortality for patients with left atrial isomerism were dextrocardia ($P = .009$; HR, 3.0; 95% CI, 1.3-6.7) and pulmonary stenosis ($P = .042$; HR, 0.3; 95% CI, 0.1-0.9) and patients with right atrial isomerism, biventricular repair ($P < .001$; HR, 6.0; 95% CI, 2.8-13), and obstructed total anomalous pulmonary venous drainage ($P < .001$; HR, 4.2; 95% CI, 2.0-8.6).

Conclusions: A significant proportion of patients with isomerism still die before reaching adulthood. Only a fraction of those with obstructed pulmonary veins survive. Having biventricular repair does not confer a survival advantage to those born with right atrial isomerism. (J Thorac Cardiovasc Surg 2015;149:1509-14)

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Predictions of survival for patients born with atrial isomerism (ie, heterotaxia) are dismal, and seem worse for those born with right atrial isomerism (ie, heterotaxia/asplenia) than for those with left atrial isomerism (ie, heterotaxia/polysplenia). The association of several cardiac defects, the complexity of their surgery related to their anomalous systemic and pulmonary venous connections, their disposition to experience dysrhythmias, and the susceptibility of those born with asplenia to experience sepsis all seem to contribute to a large mortality in infancy.[1,2] There are scarce data enabling us to predict survival beyond adolescence. In recent years, several teams have claimed to have observed an improvement in outcomes in these patients; however, none of these reports present perspectives of survival beyond age 5 years.[3-6]

We reviewed our experience in the Royal Children's Hospital to determine survival expectations to adulthood of patients born with atrial isomerism and predictors affecting this survival.

PATIENTS AND METHODS

The design of the study was approved by the Royal Children's Hospital Research Ethics Committee and the need for consent was waived because of the retrospective nature of the study. All patients quoted to have atrial isomerism were identified in the hospital database. Between 1965 and 2012 a total of 223 patients were identified. Forty-one overseas patients were excluded because of the difficulty to gather their follow-up, leaving 182 as the cohort of this study. Diagnosis of atrial isomerism was made using a combination of echocardiography and catheterization with or without direct operative confirmation of atrial morphology. Seventy-eight patients had right atrial isomerism (43%) and 104 were diagnosed with left atrial isomerism (57%). The

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Abbreviations and Acronyms
NYHA = New York Heart Association
TAPVD = total anomalous pulmonary venous drainage

characteristics of the patients are described in Table 1. Fifty of the 78 patients born with right atrial isomerism had anomalous pulmonary venous connection and 18 of those 50 presented with obstructed total anomalous pulmonary venous obstruction.

Statistical Analysis

Survival from birth was examined using the Kaplan-Meier estimator of the survival curve. Risk factors for mortality were examined using Cox proportional hazards regression. Factors measured on a continuous scale (including calendar time) were converted to a z score scale for analysis to make estimated hazards ratios more comparable between continuous and binary factors. Due to the relatively small number of deaths (27 for left atrial isomerism and 40 for right atrial isomerism), the number of factors included in the multivariable models were restricted to approximately 1 factor per 10 deaths, with preference given to factors with the largest effect sizes (eg, hazard ratio [HR] > 2.0 or HR < 0.5) and strongest evidence against the null hypothesis (lowest P values). All analyses were performed using Stata 12 (StataCorp, College Station, Tex).

TABLE 1. Patient characteristics

Morphology	Left atrial isomerism (n = 104)	Right atrial isomerism (n = 78)
Dextrocardia	30 (28)	28 (36)
Bilateral superior vena cava	55 (52)	46 (59)
Interrupted inferior vena cava	93 (89.4)	0 (0)
Partial anomalous pulmonary venous connection	20 (19)	6 (8)
Total anomalous pulmonary venous connection	2 (2)	44 (56)
Partial atrioventricular septal defect	13 (13)	1 (1)
Complete atrioventricular septal defect	14 (14)	71 (91)
Double outlet right ventricle	35 (34)	55 (71)
Single ventricle	49 (47)	59 (76)
Pulmonary stenosis	32 (31)	34 (44)
Pulmonary atresia	13 (13)	35 (45)
Right sided aortic arch	24 (23)	34 (44)
Hypoplastic aortic arch	14 (13)	3 (4)
Coarctation of the aorta	13 (13)	0
Normal intracardiac morphology	9 (8.65)	0
Documented asplenia	12 (11.5)	60 (77)

Values are presented as n (%).

RESULTS

A total of 67 patients with atrial isomerism died during the course of their follow-up. The mean follow-up was 13.8 ± 9 years. Overall survival to 25 years of age was 62% (95% confidence interval [CI], 53%-69%). Independent predictors of overall mortality were obstructed total anomalous pulmonary venous drainage (TAPVD) (P < .001; HR, 5.2; 95% CI, 2.7-9.7) and asplenia (P = .008; HR, 2; 95% CI, 1.2-3.3) (Table 2). Only 4 of the 18 patients presenting with obstructed TAPVD achieved late survival. All of them had right atrial isomerism and went along the univentricular pathway. Patients born in the recent era did not have improved survival (HR, 1.1 per 9.5 years progression in calendar time; 95% CI, 0.8-1.5; P = .47).

Patients with left atrial isomerism had a much better survival outcome than patients with right atrial isomerism: 18 years survival 74% (95% CI, 63%-82%) versus 50% (95% CI, 38%-60%), presumably due to the higher prevalence of obstructed TAPVD (23% for right vs 0% left) and asplenia (73% for right vs 10% for left) amongst patients with right atrial isomerism (Figure 1).

Outcomes of Patients With Left Atrial Isomerism

Of the 104 patients with left atrial isomerism, 14 received conservative management without any surgical intervention. Thirteen patients in this group did not have any cardiac lesions necessitating operative intervention. One patient presenting with Eisenmenger syndrome in the context of a common atrium and high mean pulmonary arterial pressure of 60 mm Hg with no additional pathology received conservative management. On last follow-up, at age 14 years, she was alive with New York Heart Association (NYHA) functional class II. Forty of the 90 patients who were offered surgery underwent a biventricular repair and underwent 48 procedures, consisting of atrioventricular septal defect repair (n = 14), ventricular septal defect closure (n = 8), aortic arch or coarcation repair (n = 8), atrial septal defect closure (n = 7), repair of anomalous pulmonary venous drainage (n = 5), resection of subaortic membrane (n = 4), and tetralogy of Fallot repair (n = 2). After a mean of 10.4 ± 8 years, there were 6 deaths and the remaining 34 patients were in NYHA functional class I or II.

Fifty patients were directed to univentricular palliation. Forty-four underwent a first palliative procedure at a median age of 54 days consisting of Norwood procedure (n = 4), systemic-pulmonary shunt (n = 25), pulmonary artery banding procedure (n = 15), or Damus-Kaye-Stansel procedure (n = 7). Detailed outcomes of patients with left atrial isomerism undergoing univentricular palliation are detailed in Figure 2, *A*. At final follow-up, the 2 patients with bidirectional cavopulmonary shunt and the 26 patients after Fontan were in NYHA functional class I or II.

Forty-one of the 104 cases needed insertion of permanent pacemakers (39%): 10 for sick sinus syndrome and 31 for conduction abnormalities, including complete heart block/junctional bradycardia/Wenckebach syndrome.

Independent predictors of mortality for patients with left atrial isomerism were the presence of dextrocardia (P = .009; HR, 3.0; 95% CI, 1.3-6.7) and pulmonary stenosis (P = .042; HR, 0.3; 95% CI, 0.1-0.9) (Table 3).