Surgical management of congenital heart defects associated with heterotaxy syndrome

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Abstract

Objective: Heterotaxy syndrome (HS) is generally associated with complex congenital cardiac defects and has a high morbidity and mortality despite recent surgical progress. Only few reports deal with an overall surgical population. Methods: Between 1989 and 2008, 139 patients with HS entered a programme of surgical repair. Fifty-one patients were suitable for univentricular heart repair (UVR) and 88 for biventricular repair (BVR). Among those tracked for UVR, two were switched to BVR and 11 from BVR to UVR. Median age at first surgery was 4.4 months (range: 3 days to 43 years) of whom 34 were neonates. The mean number of surgical procedure per patient was 1.99. Primary BVR was performed in 37 patients. Re-operation was required in 22 patients, 15 after BVR and seven after UVR (p > 0.05). Results: The overall mortality was 20.8%. It was 7.2% after the first surgery, 6.6% after the second and 11.5% after the third. The overall mortality in patients with univentricular physiology was 25.5% and 18.2% in the biventricular group (p < 0.05). According to the surgical track, in the UVR group, mortality was 18% and 15.6% in the BVR group (p = NS). This rate was 40% in patients with long-lasting palliation (p < 0.05 vs both other groups). Median follow-up was 127 months (range: 1 month to 19 years). The overall survival rate at 15 years was 69.5% for UVR and 77% for BVR (p = NS). For the palliation group, it was 15% only at 15 years (p < 0.05 vs both other groups). Risk factors for overall mortality were neonatal surgery, long-standing palliation, total anomalous pulmonary vein return (TAPVR) and right ventricular outflow tract obstruction (RVOTO). At the last visit, all survivors were in the New York Heart Association (NYHA) class I to II and only two presented with supraventricular arrhythmias. Conclusions: HS remains a difficult situation with high morbidity and mortality. An aggressive approach to repair TAPVR when present should be considered. Early decision to track the patient in either uni- or biventricular repair programme should avoid long-lasting deleterious palliation.

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1. Introduction

Heterotaxy syndrome (HS) is a disorder that involves abnormal lateralisation of the abdominal viscera, thoracic organs and cardiac atria. In this disease, visceral placement falls in a spectrum between situs solitus and situs inversus, that is, situs ambiguous, and cardiac position can be variable. In addition to displacement, organs that typically manifest right—left asymmetry such as the lungs and atrial appendages, develop in a symmetrical or mirror-image way. Several genes, including ZIC3 and CRYPTIC, have been implicated in the development of HS; these genes are likely involved in the regulation of early left—right patterning in embryologic development [1]. Although this is a rare disorder, HS is frequently associated with complex congenital cardiac defects and has a high morbidity and mortality despite recent surgical progress [2,3]. In addition to the congenital heart disease, abdominal abnormalities are frequently observed. Splenic function may be normal, marginal (polysplenia) or absent (asplenia), leaving those affected individuals with splenic dysfunction vulnerable to bacterial infections. Intestinal malrotation is a common association, affecting up to 70% of children with HS and is not readily identified on routine examination [4]. Biliary atresia has been reported in up to 10% of those heterotaxy patients with left atrial isomerism (LAI) [1].

HS tends to fall into two readily recognised subtypes, namely right atrial isomerism (RAI) and LAI, although it is clear that some patients fall within the spectrum [5]. RAI is also frequently called asplenia-type or Ivemark syndrome, although the absence of the spleen is not a uniform feature. In RAI, the atrial appendages both typically have the morphologic features of a right atrial appendage (broad-based, triangular shape)

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and there is often absence or unroofing of the coronary sinus. There are usually two tri-lobed (right) lungs with bilateral eparterial bronchi and the liver is midline. In RAI, the systemic and pulmonary venous systems can be abnormal with bilateral superior vena cavae and total anomalous pulmonary venous connection (TAPVC) to an extracardiac site occurring frequently [6,7]. The inferior vena cava is often juxtaposed to the descending aorta and hepatic venous drainage may be contralateral to the inferior vena cava [3]. With regard to intracardiac anatomy, RAI is usually associated with complex congenital heart disease including common atrioventricular canal, conotruncal abnormalities such as transposition of the great arteries or double outlet right ventricle and pulmonary outflow obstruction in most cases. Systemic outflow obstruction is rare in RAI.

LAI or polysplenia syndrome exhibits bilateral left-sidedness. Multiple, small spleens are usually present with poor function [8]. Both atrial appendages tend to have a long, tubular appearance with a narrow neck (left atrial appendage). The sinus node may be absent or hypoplastic. The lungs are both bi-lobed with hyparterial bronchi. The systemic and pulmonary venous connections are also abnormal. Interruption of the inferior vena cava with ayzygos continuation to the superior vena cava is a hallmark finding of LAI and occurs in approximately 60—90% of cases [2,6]. More than 50% of patients with LAI also have bilateral superior vena cavae [6]. Bilateral connection of the pulmonary veins to the right- and left-sided atria (so-called ipsilateral pulmonary veins) occurs in some cases, typically in association with a common atrium [2,6]. TAPVC directly to the right atrium can also occur, particularly when there is predominant situs inversus. The intracardiac abnormalities of LAI can be less severe than those seen in RAI. In one report, approximately 13% of those with LAI had normal intracardiac anatomy [2]. However, common atrioventricular canal, common atrium, single ventricle and pulmonary outflow obstruction are still prevalent [2]. In some cases, left-sided obstructive lesions and even hypoplastic left-heart syndrome can be seen. Another unique feature of LAI is the presence of congenital complete heart block in association with congenital heart disease [2,9].

Historically, visceral heterotaxy has been associated with significant morbidity and mortality [2,3,10,11]. Right atrial isomerism has been described by some as one of the worst forms of contemporary heart disease [12] with overall 5-year survival ranging from 30% to 74% [13,14]. The results are better in left atrial isomerism with 5-year survival rates ranging between 65% and 84%, which remains considerably lower than survival for most other forms of congenital heart disease [10,14]. The combination of structural abnormalities of systemic and pulmonary venous connections, increased incidence of single ventricle physiology, the presence of obstruction to the pulmonary and aortic outflows, the increased incidence of significant arrhythmias and sepsis associated with splenic dysfunction have all been implicated in the poor surgical outcomes in these patients [2,3,10,11,13—15].

Generally, reports are published after splitting patient groups into cohorts that underwent either biventricular or univentricular repair, but very few deal with an overall population starting from the first surgical procedure until the end of the surgical programme.

We report herein our overall experience in patients with HS over the past 20 years and try to identify risk factors for mortality and/or morbidity.

2. Patients and methods

All consecutive patients who were admitted to our Institution for surgical intervention between 1989 and 2008 with so-called HS were included in this retrospective study.

Diagnosis was confirmed after review of echocardiographic reports and anatomic description from either the operative or post-mortem reports. Chest X-rays, angiography and, more recently, computed tomography (CT) scan allowed defining bronchial and abdominal situs.

2.1. Definitions

First pathologic descriptions of patients with HS emphasized the concepts of asplenia or polysplenia. These denominations were then abandoned because they are fairly accurate and many exceptions to this definition were demonstrated. Debate then occurred whether the anatomy of atrial appendages could serve as a landmark for classification or not, namely LAI or RAI, each corresponding to a spectrum of malformations. Here again, several exceptions to this rule were found and, therefore, inclusion criteria were based on the discordance between abdominal, cardiac and bronchopulmonary situs. However, because in many charts a nomenclature using atrial isomerism was employed, mention of LAIs or RAIs has been maintained throughout this work when it was impossible to verify the true atrial situs.

2.2. Data collection and analysis

The following data were noted: (1) basic demographic data, (2) cardiac morphology data, (3) surgical history including the date of surgery and (4) follow-up information obtained from the last recorded clinic visit including NYHA class, presence of arrhythmias and need for pacemaker insertion. If the last visit was too far from this retrospective study, the patients were then re-appointed for evaluation either in our Institution or to the referring cardiologist. Early mortality was recorded as a death event within 30 days following any of the surgical procedures. Late mortality was recorded as a death event only after hospital discharge.

Results for quantitative variables are reported as mean with standard deviation or median with ranges. Frequencies are given for qualitative variables and dependencies are tested with chi-square or Fisher’s exact test. Patient survival was estimated by actuarial survival method and log-rank test was used to compare groups. Univariate analysis was used to describe the effect of various variables on mortality. In a multivariate model, risk factors were estimated using a logistic regression model. Comparison of survival rates was performed by the log-rank test. A $p$ value below 0.05 was
considered significant. All analyses were performed using Statview.

This work was approved by the Institutional ethical committee.

3. Results

A total of 139 patients met the criteria for inclusion in this study. There were 78 males and 61 females. Median age at first surgery was 4.4 months (range: 3 days to 43 years).

Anatomic description is presented in Tables 1 and 2.

3.1. Surgical Interventions

In the beginning of this experience as it started in the late 1980s, TAPVR repair was not carried out as routine initial procedure unless there was a patent obstruction. As well, AV valve repair was frequently left unrepaired until valve incompetence reached a significant grade. Since 1995, a more aggressive approach to these morbid associations was decided upon. TAPVR were repaired according to the standard technique, the suture-less technique being reserved for recurrent pulmonary vein stenosis. AV valves were repaired by means of commissuroplasties.

Among the whole series, 51 patients were initially tracked for univentricular heart palliation through staged Fontan procedure and 88 for biventricular repair. Of the so-called single ventricle, 19 had Fontan operation, while 19 after the second stage programme with a bidirectional Glenn and six received a Kawashima type of cavopulmonary connection. Among this cohort, two had a biventricular repair and 10 are still with initial palliation waiting for a further step of the programme. Among those with two well-balanced ventricles, 62 had biventricular repair, 11 were switched to univentricular repair, six underwent a Fontan procedure and five patients had a bidirectional Glenn and were waiting for the final step. Fifteen patients are waiting with palliation until the next procedure. Two patients initially tracked for univentricular repair were converted to biventricular repair. One presented with complete AV canal, small left ventricle and abnormal systemic venous return and the other had complete AV canal associated to DORV, RVOTO and intracardiac anomalous pulmonary venous return. After initial palliation, the left ventricle demonstrated significant growth and allowed biventricular repair.

The median number of surgical procedure per patient was two. Table 3 depicts the different surgical procedures performed in the entire cohort of patients and Fig. 1 depicts the surgical track for all the patients.

![Fig. 1. Surgical track according to ventricular anatomy.](image-url)
Of the whole group of patients, 34 required a neonatal procedure. Indications for early surgery were mandated by symptomatology due to ducto dependency and compromising associated lesions. Fig. 2 describes the global decision tree for neonatal surgery.

Within the group of patients having a univentricular programme, one had total cavopulmonary connection as the single and primary procedure; 12 had staged cavopulmonary connection with a bidirectional Glenn as initial procedure; and 23 had an initial palliation followed by bidirectional Glenn and total cavopulmonary connection (TCPC) completion.

Biventricular repair was performed as the initial procedure in 37 patients, 22 had a previous palliation and five had multiple previous palliations.

### 3.2. Re-operations

Redo surgery after the final step of the surgical programmes, either univentricular or biventricular, was necessary in 22 patients. Indications for surgery in the group of biventricular repair were right ventricle to pulmonary artery (RV to PA) conduit replacement with PA plasty in four, AV valve repair in four, surgery for left ventricular outflow tract obstruction in four, residual VSD in one, pace maker insertion in one and heart transplantation in one patient. In the group of patients receiving univentricular repair, after the final Fontan procedure, seven patients required re-interventions for conversion to extra cardiac conduit in two, hepatic veins reincorporation in two after Kawashima procedure with pulmonary arteriovenous fistulae, pace maker insertion in one and pulmonary veins stenosis in one. The mean delay between the end of the surgical programme and re-operation was 53 ± 17 months. The delay was 27 months in biventricular repair and 67 months in univentricular repair \((p < 0.05)\).

### 3.3. Mortality

There were 23 early (16.5%; 70% confidence limits (CL): 13–20%) and six late deaths for an overall mortality of 20.8% (70% CL: 17–25%, 29 patients). Eleven patients died after the very first surgery (7.2%, 70% CL: 4.8–10.2%). Six out of 90 died after the second surgical procedure (6.6%, 70% CL: 3.7–10.6%) and 6 out of 52 (11.5%; 70% CL: 6.5–18%) died after the third surgical procedure. The early deaths were essentially due to low cardiac output in 14 patients despite postoperative assist device support in five, sepsis in three and pulmonary hypertension for the others. Late deaths were due to meningitis in one, haemorrhage due to inadequate anticoagulation in one patient with Eisenmenger’s syndrome, thrombosed Blalock–Taussig (BT) shunt during the interim period in three and due to unknown causes in the other patients.

Within the different track groups, mortality rates were as follow: in the univentricular group, there were 10 early and three late deaths for an overall mortality in this group of 25.5% (70% CL: 18.5–33.5%) and in the biventricular group, there were 13 early and three late deaths for an overall mortality of 18.2% (70% CL: 13.5–23.5%) \((p = 0.04)\).

Because, in this series, some patients initially tracked to any of the surgical programme were switched to the other track, mortality was also analysed according to the type surgical procedure. Fifty patients with either anatomically single ventricle or with non-septatable biventricular hearts had a univentricular repair, 64 had biventricular repair and 25 were still under palliation without any clear distinction between further uni- or biventricular repair. In the univentricular repair group, there were nine early and no late deaths for an overall mortality of 18% (70% CL: 12–25%). In the biventricular repair group, there were nine early deaths and one late death for an overall mortality rate of 15.6% (70% CL: 10–22%) and in the palliative group, there were five early and five late deaths for an overall mortality rate of 40% (70% CL: 28–52%) \((p = 0.02)\) vs both other groups.

### 3.4. Risk factors for mortality

Using logistic regression, the presence of TAPVR and RVOTO was significant risk factors for overall mortality for the entire series. Among patients tracked for univentricular repair, only the presence of a TAPVR was a significant risk factor for mortality. Although the year (before and after 1995) of surgery was not a risk factor for early death, a more aggressive approach to early repair TAPVR – initiated in 1995 – allowed the patients with univentricular heart to reach the final TCPC step \((5\text{ out of }29 \text{ before }1995\text{ vs }14\text{ out of }21\text{ after }1995, p = NS)\). On the other side, in patients scheduled for biventricular repair, RVOTO was a significant risk factor for mortality. Neonatal surgeries as well as long-standing palliation were also significant risk factors for mortality.

### 3.5. Follow-up and survival

Median follow-up was 127 months (range: 1 month to 19 years). Ten percent of survivors, mainly overseas patients, were lost to follow-up.

The overall survival rates were 84%, 81.8%, 76% and 70.6% at 15 months, 5, 10 and 15 years, respectively. When considering ventricular anatomy, survival rates were 86.3%, 81.4%, 78.3% and 69% at 15 months, 5, 10 and 15 years, respectively, for the univentricular group. They were 82.3%, 82.3%, 74.2% and 74.2% at 15 months, 5, 10 and 15 years,
respectively for the biventricular group ($p > 0.05$). According to the type of surgical approach, survival rates were 93.5%, 93.5%, 90.3% and 85.1% at 15 months, 5, 10 and 15 years, respectively for univentricular repair. They were 88.5%, 88.5%, 77%, and 77% at 15 months, 5, 10 and 15 years, respectively, for biventricular repair ($p > 0.05$) and for the palliation group, they were 45%, 31.2%, 31.2% and 15% at 15 months, 5, 10 and 15 years, respectively ($p = 0.03$ vs both other groups) (Figs. 3–5).

At the last visit, most of the patients were in NYHA class I to II; those having a univentricular repair were under medication. Episodes of supraventricular arrhythmias were demonstrated in two patients who were under anti-arrhythmic medications. Patients with biventricular repair were also in NYHA class I with almost no occurrence of supraventricular arrhythmias.

4. Discussion

Although the terms of atrial isomerism were not employed throughout this work, it remains difficult to analyse our results in view of the literature, which extensively uses this nomenclature. Isomerism was, therefore, arbitrarily considered as a synonym of HS. Very few series [2,3,16] deal with the entire cohort of patients with such a syndrome but rather split their results into biventricular repair [11,16–19], univentricular repair [20–22] or even results of intermediary surgical procedures such as TAPVR repair in such patients [23,24]. The overall outcome of children with HS has generally shown a poor prognosis. Of 20 patients diagnosed with right isomerism, reported by Sadiq and colleagues [23], overall survival was 45%, and only nine patients were potential candidates for a Fontan-type operation. Hashmi and colleagues [3] reported a mortality rate of 69% for children with RAI, and Gilljam and colleagues [2] from the same institution described a mortality of 44% in children born with LAI. These cohort studies include patients with normal functioning hearts, hearts amenable for a biventricular repair, as well as hearts with a single functioning ventricle. Recently, Agnastopopoulos and colleagues [16] reported a series of 45 patients starting from birth with excellent results. These authors were able to neutralise several risk factors such as neonatal surgery and TAPVR. Of the many associated malformations found in HS with single ventricle, atrioventricular valve regurgitation and anomalous pulmonary venous connection are considered the most important contributors to increased mortality. As Gaynor and colleagues [24] have recently analysed, many of the children with single ventricle physiology and total anomalous venous connection die before they reach the stage of a Fontan completion. Mortality was 53% before or at the initial palliative operation, and mortality risk for the subsequent cavopulmonary anastomosis was 38%. For patients who reach the stage of Fontan completion, however, the outlook is better; but historically, it has still been worse than for other patients with single ventricle. Michelion and colleagues [25] reported that a 5-year survival was greater than 70% for patients having a Fontan-type operation after 1986. The authors attributed the improved outcome to the development of more effective Fontan modifications such as the lateral tunnel and intra-atrial conduit. For a number of patients with anomalous location of the pulmonary vein orifices, extra-cardiac tube grafts have added a further option for direction of IVC or hepatic venous drainage to the pulmonary arteries, or both.

In contrast, some of HS patients are amenable to biventricular repair. When considering a surgical strategy for heterotaxy patients, we, as others [17–19], have pursued biventricular repair in the presence of two ventricles of adequate volume and function, and septatable AV valves and venoatrial connections. Despite the presence of favourable
anatomic components, some patients with complex combined lesions may not be amenable to a biventricular repair. This situation was encountered in 11 patients, which probably explains the discordance between early deaths in this group with a similar or even better long-term survival rate. Mortality rates seem as well to be confounding because the patients were analysed according to different views — either anatomic description or surgical pathway description. Indeed, mortality analysis gives different rates according to the type of approach (anatomic or surgical). The major point in this type of analysis is that early non-decision-making seems to be very deleterious in terms of outcome (long-standing palliation group). It is important to recognise that patient selection is an important determinant of success. Given the extent of the anatomic variability of these patients, there are no clear criteria to determine suitability for biventricular repair for these patients, and each has to be considered on an individual basis. Excellent long-term outcomes have been achieved in this subgroup of patients with, however, a high rate of re-interventions and arrhythmias [16,17]. When biventricular seems to carry too high a risk, the Fontan-type procedure can be proposed provided there is adequate indication. Koh and colleagues [18] have recently demonstrated that these patients displayed similar anaerobic testing as those patients after biventricular repair. Our series is remarkable by several points. It encompasses a 20-year experience of a single institution. Early in this experience, aggressive approach to TAPVR and/or AV valve regurgitation was not performed. In addition, it was believed that the later the Fontan procedure is performed the better for the patients. This ‘old-fashioned’ approach has progressively changed through time and our data tend to demonstrate that improvements can be achieved through a more aggressive follow-up, or that at least those with so-called univentricular heart anatomy are amenable to the final total cavopulmonary connection with good results.

Another point of interest was the poor outcome of patients with long-standing palliation. Probably because during this era, there were hesitations with regard to the surgical option, these patients were felt to remain clinically stable and no other options were offered. Analysis of our data shows also that this conservative approach, instead of pursuing a correction programme, carries a very high mortality rate. Twenty-five patients were left with only palliations without any other surgical proposition toward either bi- or univentricular repair. Within this group, 15-year survival only reaches 30%, which suggests that all efforts should be made to propose an adequate surgical solution even if a stable clinical status is sought.

5. Conclusion

This series represents the overall outcome of patients with HS from a single institution. Surgical care has moved from an attentive attitude to a more aggressive approach. However, the data do not show any time-related difference. Some important points should be considered. TAPVR and AV valve regurgitation should be addressed more frequently. Neonatal surgery in this subset carries a high operative risk of mortality. Biventricular repair when feasible should be favoured; however, single ventricle physiologic repair gives good long-term outcome. Re-operations are not infrequent particularly after biventricular repair. Incidence of post-operative supraventricular arrhythmias was not found as described in the literature. Early decision to track the patient in either uni- or biventricular repair programme should avoid long-lasting deleterious palliation.

References

Appendix A. Conference discussion

**Dr G. Stellin** *(Padova, Italy)*: In the introduction section, the authors review in detail the cardiac and noncardiac malformations which are linked with the two different groups, right isomerisms and left isomerisms.

They also analyse their results in comparing biventricular and univentricular repair. I wonder whether, to improve their study, they should also compare the right isomerism and left isomerism groups.

For instance, TAPVD in a right isomerism is very much different from TAPVD in a left isomerism. Therefore it would be nice to know if there is a different risk in correcting TAPVD when associated with right isomerisms or left isomerisms.

The authors also conclude that biventricular repair should be favoured when possible. However, long-term survival after Fontan circulation is good and equivalent to other malformations with a physiological single ventricle. It should be stated in the manuscript when the authors would favour a biventricular versus a univentricular repair in complex lesions with two ventricles, and also therefore planning a univentricular versus a biventricular repair.

It would also be of interest to know the short and long-term results of very complex lesions (which are usually linked to right isomerism) when a functional single ventricle is associated to right atrial isomerism and obstructed TAPVD.

**Dr Serraf**: Actually, we decided to abandon the term of ‘heterotaxy’ because the concept of ‘isomerism’ does not cover the entire spectrum of ‘heterotaxy syndrome’ and vice versa. That is, you may have patients with heterotaxy syndrome but without any atrial isomerism, while on the other hand you may have hearts with atrial isomerism in patients without heterotaxy syndrome.

Trying to answer your question and make a correlation between outcome and right or left isomerism, it was quite difficult to define if we were dealing with right or left isomerism in this retrospective analysis because the files were coded as heterotaxy syndrome and although we reviewed chest X-ray, the echo, or the post-mortem examination when available, it was impossible to make any statistical correlations between these items.

Second, you were asking about biventricular versus univentricular and when to perform the latter even in patients with two ventricles but highly complex intracardiac anatomy.

Although the long-term survival seems similar, we didn’t do any exercise testing to see if the capacity of those patients is really similar.

To the best of my knowledge, there is a paper from Japan or Korea that showed similar exercise test function in these patients. However, we believe that probably two ventricles are better than one, but we still have to make some more refined testing to unravel any difference between these patients.

Now, what to do? I think that the best way to decide if we do a bi- or univentricular repair is only a question of surgical experience. I mean, if the surgeon feels clear and easy with this biventricular repair, just do it. If not, he should favour univentricular repair because the overall results could be the same.

**Dr T-J Yun** *(Seoul, Korea)*: I have two questions. What is your technique of TAPVD repair in patients with right atrial isomerism and TAPVD?

**Dr Serraf**: The technique of TAPVD repair is almost the same as in a normal heart. I mean, just isolate the common vein and try to make a large anastomosis between the common atrium and the left atrium.

**Dr Yun**: And when you are doing biventricular repair for right atrial isomerism, did you find any morphological difference of AVSD between right heterotaxy syndrome and other isolated AVSD patients?

**Dr Serraf**: We didn’t in our institution.