EDITORIAL

Optimal Outcome of Treatment for Right Isomerism: An Elusive Goal!

Resultados óptimos del tratamiento del isomerismo derecho. Un objetivo esquivo!

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The International Society for Nomenclature of Paediatric and Congenital Heart Disease (ISNPCHD) has established the International Paediatric and Congenital Cardiac Code (ipccc.net) which was introduced for the first time during the historic 4th World Congress of Pediatric Cardiology and Cardiac Surgery in Buenos Aires, Argentina in 2005. According to the ISNPCHD **heterotaxy is** defined as an abnormality where the internal thoraco-abdominal organs demonstrate abnormal arrangement across the left-right axis of the body. **Heterotaxy is** synonymous with "**visceral heterotaxy**" and "**heterotaxy syndrome**". (1) The heterotaxy syndromes are characterized by a high incidence of complex cardiovascular malformations of extreme heterogeneity. Because of the occurrence of several simultaneous cardiac malformations, the surgical management of these patients is extremely challenging. In general, patients fall within one of two syndromes, right isomerism or left isomerism with a characteristic constellation of cardiac anomalies in each syndrome.(2,3) Although within each syndrome there is still tremendous variability, there is a characteristic pattern in the majority of patients. Splenic abnormalities are frequent with asplenia more common in the right isomerism syndrome of heterotaxy.

The surgical options depend on the precise constellation of anatomical cardiac malformations, including anomalies of systemic and pulmonary venous connections. Because of the presence of significant ventricular hypoplasia or the extreme complexity of biventricular repair in two-ventricle hearts, the majority of patients will undergo single ventricle palliation and ultimately be managed by the Fontan/Kreutzer operation, especially in the right isomerism syndrome.(4) The presence of a common atrioventricular junction with the potential for atrioventricular valve regurgitation, with a negative impact on ventricular function, implies that the type and timing of surgical palliation in early life is extremely important. Furthermore, an accurate and complete understanding of the systemic and pulmonary venous anatomy is an absolute prerequisite for the successful performance of the Fontan/Kreutzer operation. The significant challenges in the surgical treatment of heterotaxy syndromes are evident by the poor long-term survival reported by the Hospital for Sick Children in Toronto. (5,6) In a series of 91 consecutive patients with right isomerism over a 26-year period, the overall mortality was 69 % and the 1 month, 1 year and 5 year survival rates were 71 %, 49 % and 35 % respectively. [5] Management of pulmonary venous obstruction was identified as a serious problem. Although long-term survival was better for patients with left isomerism in a series of 163 patients from the same institution, the mortality was still significant. (6)

I read the article by Lafuente and associates (7) on "Clinical Presentation and Outcome of Right Isomerism" with great interest. This retrospective study on 72 patients with right isomerism, with asplenia in 53 patients, seen between 1997 and 2011, is a large contemporary series of patients treated at a single institution, the Hospital Nacional de Pediatria "Professor Dr. Juan P. Garrahan". This study is important as it sheds light on the current presentation and outcomes for this challenging group of patients in an advanced country, Argentina, and in a large and sophisticated world-class city, Buenos Aires, equipped with modern and up to date cardiac care. Of note is the neonatal presentation of more than 90 % of the patients, dominated by cyanosis. As in previous series with right isomerism/asplenia, the majority of the patients had single-ventricle physiology. The dominant anatomi-

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cal features in this series were bilateral superior vena cava in 30 patients, a common atrioventricular junction in 56 patients, pulmonary outflow obstruction in 67 patients (with pulmonary atresia in 25) and conotruncal anomalies in 71 patients (double outlet right ventricle in 27 and transposition in 44 patients). Although the incidence of ventricular hypoplasia is not clear, one can imagine the monumental surgical challenge in these patients and why biventricular repair was not achieved in any patient. However, perhaps the most challenging feature when present was total anomalous pulmonary venous connection in 43 patients, obstructed in 14. This often complicates the neonatal palliation and any residual or recurrent pulmonary venous obstruction is potentially lethal. Furthermore in the surviving patients the presence of pulmonary venous obstruction increased the risk of the subsequent stages of palliation.

Surgical treatment was performed in 55 patients and not surprisingly 15 were considered inoperable, mainly because of total anomalous pulmonary connection, most often obstructed. A surgical single-ventricle pathway was considered in 40 patients. Cavopulmonary anastomosis (Glenn shunt) was performed in 17 patients with 29 % mortality, with all 5 deaths undergoing bilateral anastomoses. In four of the 12 survivors contraindications to the completion Fontan/Kreutzer operation developed due pulmonary vein stenosis, pulmonary hypertension and severe AV valve regurgitation. Finally the Fontan/Kreutzer operation was performed in 23 patients with 21.8 % mortality. Only one patient in the entire series had a 1 and half ventricle repair. Higher mortalities have also been observed in heterotaxy patients undergoing the Glenn shunt or the Fontan/Kreutzer operation in a large North American multiinstitutional series, when compared to patients without heterotaxy undergoing the same operations. (8)

So what do we learn from this large series? We already knew that right isomerism type of heterotaxy has been a monumental surgical treatment challenge with the overwhelming number of patients only candidates for single ventricle palliation and very few isolated cases achieving biventricular repair. This contemporary series clearly demonstrates that these malformations remain a huge surgical treatment challenge. The anatomic factors that probably contributed to the high mortality and inoperability in a large number of these patients are the presence of total anomalous pulmonary venous connection, atrioventricular valve regurgitation and myocardial dysfunction, and possibly the presence pulmonary hypertension. Surprisingly the presence of bilateral vena cava was associated with a significantly higher mortality, an anatomic feature that one should be able to mitigate with modern surgical techniques.

Where do we go from here in order to significantly improve the outcome of these patients? I have no doubt that in many parts of the world a fetal diagnosis of the possibility of right isomerism may lead to the choice of termination of pregnancy, further decreasing the surgical exposure and experience with these challenging patients. However, if we are to make significant impact and improve survival, then the following areas need to be focused on. Early referral and an absolutely accurate diagnosis of all the anatomic features are of paramount importance. Prompt repair of the total anomalous pulmonary connection with unobstructed anastomosis is essential not only to achieve immediate survival, but also to ensure that the surviving patients remain optimal candidates for the next stages of the single ventricle pathway. More recently described surgical techniques using a sutureless pulmonary venous repair and a pericardial well technique should be considered.(9, 10) And these techniques might in the future prove to be superior. At the time of neonatal palliation the type and location of systemic pulmonary shunts should be carefully considered, in order to avoid causing inaccessible hilar branch pulmonary artery stenoses. The presence of a common atrioventricular junction with the potential for atrioventricular valve regurgitation and a negative impact on ventricular function implies that the type and timing of surgical palliation in early life is extremely important. Preservation of atrioventricular valve and myocardial function are therefore of utmost importance. Careful follow-up and monitoring of atrioventricular valve regurgitation and ventricular function is necessary in order to ensure early intervention in the event of deterioration. Atrioventricular valve repair should be undertaken at the time of the cavopulmonary anastomosis, when additional procedures are best tolerated. Finally, at the time of the Fontan/Kreutzer operation precise knowledge of the course of the systemic and pulmonary veins is essential in order to achieve unobstructed systemic and pulmonary venous pathways. Routine fenestration should be considered.

I congratulate the authors for publishing an excellent, although sobering series. They remind us that despite spectacular advances in the treatment of so many complex cardiac malformations, optimal outcome of many patients with right isomerism remains an elusive goal.

Conflicts of interest

None declared.

(See authors' conflicts of interest forms in the website/Supplementary material).

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