

Risk Factors Associated With Arterial Switch Operation for Transposition of the Great Arteries

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Introduction and objectives. The present study was undertaken to determine the risk factors for early mortality following an arterial switch operation.

Patients and method. From January 1994 through October 2003, 78 pediatric patients underwent surgical repair. Simple transposition was present in 48 patients (61.5%), 29 (37.2%) had an associated ventricular septal defect, and one had a Taussig-Bing anomaly. The risk factors analyzed were: the patient's age and weight at the time of the intervention, repair of a coexisting ventricular septal defect, coronary artery anatomical pattern, duration of cardiopulmonary bypass, duration of aortic cross-clamping, and duration of circulatory arrest. All factors were evaluated for strength of association with the duration of mechanical ventilation, the length of intensive care unit stay, and mortality.

Results. Overall, the early mortality rate was 9% (7/78). Some 14 patients (17.9%) underwent simultaneous repair of a ventricular septal defect. Patients with an intramural coronary artery (n=3, 3.8%) or a single coronary ostium (n=5, 6.4%) were the only ones who had a significant ($P<.05$) mortality risk, at 50% (4/8). Circulatory arrest was implemented in 53 (68%) patients. There were significant correlations between the duration of circulatory arrest and the ventilator support time ($r=0.3$, $P<.05$) and the duration of stay in the intensive care unit ($r=0.3$, $P<.05$).

Conclusions. The risk of early death was increased when more complex coronary artery anatomical variants were present. As the period of circulatory arrest lengthened, the mechanical ventilation time and duration of intensive care unit stay increased.

Key words: Congenital heart disease. Transposition of the great arteries. Cardiopulmonary bypass. Nitric oxide.

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Factores de riesgo de la corrección anatómica para la transposición de grandes arterias

Introducción y objetivos. Este estudio se realizó para determinar los factores de riesgo que pueden influir en la mortalidad precoz después de la corrección anatómica.

Pacientes y método. Entre enero de 1994 y octubre de 2003 intervenimos a 78 pacientes; 48 (61,5%) eran transposiciones simples, 29 (37,2%) presentaban asociada una comunicación interventricular y 1 tenía una anomalía de Taussing-Bing. Se analizaron la edad y el peso en el momento de la intervención, el cierre o no de la comunicación interventricular, la anatomía coronaria y los tiempos de circulación extracorpórea, la anoxia miocárdica y la parada circulatoria. Evaluamos la relación entre estas variables con los tiempos de ventilación mecánica, la estancia en la unidad de cuidados intensivos pediátricos y la mortalidad.

Resultados. De los 78 niños fallecieron 7 (9%). En 14 (17,9%) se cerró, además, una comunicación interventricular. Los que presentaron una arteria coronaria intramural (n = 3, 3,8%) o tenían un orificio coronario único (n = 5, 6,4%) fueron los que tuvieron una mayor mortalidad (4/8, 50%) ($p < 0,05$). En 53 niños (68%) se realizó parada circulatoria; el tiempo de parada se correlacionó de forma directa tanto con las horas de ventilación mecánica ($r = 0,3$; $p < 0,05$) como con los días de estancia ($r = 0,3$; $p < 0,05$).

Conclusiones. Las variantes más complejas en la anatomía coronaria se asociaron con un mayor riesgo de muerte precoz. La duración de la parada circulatoria influyó en los tiempos de ventilación mecánica y en la estancia en cuidados intensivos.

Palabras clave: Cardiopatías congénitas. Transposición de grandes arterias. Circulación extracorpórea. Óxido nítrico.

ABBREVIATIONS

VSD: ventricular septal defect.
TGA: transposition of the great arteries.
ICU: intensive care unit.

INTRODUCTION

If transposition of the great arteries (TGA) is left untreated, 95% of the patients die in the first year of life. Anatomic repair, according to the technique described by Jatene et al¹ with the Lecompte modification, is still the surgical treatment of choice. Elective anatomic repair during the neonatal period was first carried out by Castañeda et al² in the year 1983.

In view of the variability of coronary artery anatomy associated with this type of congenital heart defect,³ the main difficulty associated with the procedure is coronary artery switching. The development of new surgical techniques has facilitated anatomic repair,^{4,5} even in the least favorable anatomical variants.

Our hospital has been performing the procedure since 1985,⁶ initially in children with TGA and ventricular septal defects (VSD). Currently we systematically operate on neonates with TGA with or without VSD. Other groups in Spain have also gained experience in the operation and have obtained good short-term outcomes in recent years.^{7,8} The impact of this surgical technique on long-term survival is not well defined, as defects in coronary artery anatomy due to stenosis or occlusions of the main branches are currently being reported.⁹ Therefore, before repeat intervention in adults who have undergone repair of this type of congenital heart defect, aortography or selective coronary angiography should be done to determine the state of the coronary arteries.¹⁰

The risk factors which might influence morbidity and mortality after surgery, such as the anatomy of the congenital defect, the surgical technique, or the postoperative period in the intensive care unit (ICU) have still not been identified in sufficient detail. Some authors have related mortality to a series of variables, such as low weight at the time of the intervention, presence of additional congenital defects, right ventricular hypoplasia, residual obstruction after aortic arch surgery or prolonged extracorporeal circulation time, myocardial anoxia, or circulatory arrest. Yet unfavorable coronary artery anatomy has not been considered a risk factor.^{11,12} Other authors, in contrast, have found that more complex variants of coronary artery anatomy, such as intramural coronary arteries or a single coronary artery are the main determinant of mortality.^{13,14}

The objective of this study was to analyze in detail a series of variables to identify the risk factors that might influence the postoperative course and early in-hospital mortality of the patients. We have also compared the most significant findings of the present study with those obtained in a preceding study conducted between 1988 and 1993 in a population of 21 children with TGA and small or no VSD, given that the present study was a continuation of this previous one.⁶

PATIENTS AND METHOD

Description of the Population, Variables Analyzed, and Data Collection Method

Between January 1994 and October 2003, 78 children underwent the Jatene procedure in our hospital. Of these, 48 children (61.5%) had been diagnosed with TGA without VSD, 29 (37.2%) had TGA associated with VSD of varying sizes, of whom 4 also presented aortic coarctation, and 1 child was diagnosed with the Taussig-Bing anomaly.

In all cases, the diagnostic and treatment protocols described below were followed. These protocols covered the preoperative, perioperative, and postoperative periods. The variables analyzed were age and weight at the time of surgery, coronary artery anatomy, whether or not the VSD was closed, need for total circulatory arrest and its duration, duration of extracorporeal circulation and myocardial anoxia, time on mechanical ventilation, and length of stay in the ICU (Table 1). Age and weight were recorded at the time of surgery. Variables related to the surgical procedure were obtained from verbal information and from the log sheet filled out by the surgeon, while variables related to the postoperative period were taken from the monitoring done in the ICU. A database was set up using the SPSS program version 12.0 that allowed us to carry out a statistical analysis to determine the possible association between the variables described and mechanical ventilation times, length of stay in the ICU, and mortality.

TABLE 1. Variables Analyzed in the Study*

1. Age when the procedure was performed
2. Weight when the procedure was performed
3. Surgical closure of VSD
4. Coronary artery anatomy
5. Duration of extracorporeal circulation
6. Duration of myocardial anoxia
7. Use of circulatory arrest
8. Duration of circulatory arrest
9. Hours on mechanical ventilation
10. Days stay in ICU

*VSD indicates atrial septal defect; UCI, intensive care unit.

Preoperative Management

Once diagnosis of TGA had been established, we started perfusion with prostaglandin E₁. We then performed a Rashkind atrioseptostomy in all patients in the catheterization laboratory or in the ICU under echocardiographic control if the patient was in such a poor condition that he or she could not be moved. If the child was still hypoxemic after these measures, pulmonary hypertension was suspected and, if confirmed, treated with inhaled nitric oxide. The day before surgery, we administered methylprednisolone intravenously (10 mg/kg) in order to attenuate the inflammatory response to extracorporeal circulation. Surgery in patients with TGA but without VSD was preferably indicated at around the first week of life and we tried to avoid procedures once the baby was more than 2 weeks old. Patients with TGA and VSD associated with significant shunting could undergo the operation when they were older and heavier, though surgery was not delayed excessively because of the risk that the patient might develop irreversible pulmonary hypertension.

Surgical Technique

The surgical technique used was first described by Jatene with the Lecompte maneuver to transpose the pulmonary artery to an anterior position. The procedure was performed under deep hypothermia (18°C) and variable flow of extracorporeal circulation. Circulation was arrested on closure of the VSD or when we implanted a single cannula in the right atrium. Both venae cavae could be cannulated with small cannulas in older and heavier children with a larger right atrium, leaving the atrium free so that we could close the septal defects with greater ease, and without the need for circulatory arrest. This was possible more often in children with TGA and large VSD because, as we mentioned earlier, these children underwent the operation when they were older.

Once repair was complete, and after extracorporeal circulation had been finalized, a controlled ultrafiltration was done with two aims: to eliminate fluid and prevent it from accumulating in the extracellular space, and to purify the body of intermediate products (cytokines). If this measure proved insufficient and edema was severe and associated with hemodynamic instability, we opted to defer closure of the sternotomy until the patient was in the ICU. We also inserted a peritoneal dialysis catheter to allow appropriate management of fluids in the postoperative period.

Postoperative Management

Postoperative management was based on treatment of left ventricular failure. We maintained sedation and analgesia with midazolam and fentanyl for the first

night after the operation, and only resorted to neuromuscular paralysis when the patient had difficulty adapting to the ventilator. We started the process of weaning from the ventilator the following day by reducing the dose of sedative and analgesic, and we used pressure-support ventilation, which facilitates spontaneous breathing and digestive tolerance. The same day, we started transpyloric enteral nutrition, preferably with breast milk or hydrolyzed proteins, and we avoided parenteral nutrition as far as possible.

Analytical monitoring included both arterial and venous blood-gas analysis on admission and every 6 hours, and whenever indicated by the clinical state of the patient. We measured oxygen saturation (SaO₂) noninvasively by pulse oximetry and exhaled carbon dioxide (CO₂) by capnography. We also monitored heart rate, the electrocardiographic trace, blood pressure, central venous pressure, and diuresis. The patients underwent echocardiography immediately after the operation to assess left ventricular function. The echocardiographic findings also indicated whether closure of the VSD was satisfactory and whether supra-aortic or pulmonary stenosis and mitral, tricuspid, aortic, or pulmonary valve regurgitation were present.

Statistical Analysis

Qualitative variables were analyzed descriptively with absolute and relative frequencies. Quantitative variables were not normally distributed (Kolmogorov-Smirnov test), and so they were described with the median (interquartile range). The χ^2 test was used for comparison of qualitative variables and the Mann-Whitney U test for quantitative. Association between quantitative variables was determined using the Spearman rank coefficient. All analyses were done with the SPSS program, version 12.0, and *P* values below .05 were considered significant.

RESULTS

The study population was divided into 2 groups (Table 2). Group 1 included children with TGA and no VSD (n=48) and children with TGA and minor VSD (n=16). Group 2 comprised children with TGA and major VSD (n=14) that required surgical closure. The child with the Taussig-Bing anomaly was also included in this second group. Statistical analysis of these groups showed that the quantitative variables did not fit to a normal distribution, and so we calculated medians and produced a percentile distribution. Table 2 presents a breakdown by group of the number of patients, age, and weight at the time of the operation, extracorporeal circulation times and myocardial anoxia, whether circulatory arrest was required and its duration, time on ventilation, length of stay in the ICU in days, and mortality. Children in group 2 underwent

TABLE 2. Distribution of Patients According to Whether They Required Surgical Closure of an Ventricular Septal Defect*

Variables	Group 1 (n=64, 82%)	Group 2 (n=14, 18%)	P
	P ₅₀ (P ₂₅ , P ₇₅)	P ₅₀ (P ₂₅ , P ₇₅)	
Age, days	9 (6-15)	45 (15-216)	<.001†
Weight, kg	3.5 (3-3.7)	3.7 (3.5-8.5)	.002†
ECC duration, min	221 (204-242)	249 (224-316)	.015†
MA duration, min	117 (103-127)	134 (116-152)	.011†
CA duration, min	8 (7-11)	10	.174
Ventilation, h	120 (94.5-192)	144 (82-192)	.773
Stay, days	10 (7-16)	8 (7-10)	.191
CA (n=53), n (%)	50 (78)	3 (22)	<.001†
Mortality (n=7), n (%)	6 (9.4)	1 (7)	.650

*Quantitative variables are expressed as the median (P₅₀) and interquartile range (P₂₅, P₇₅).

MA indicates myocardial anoxia; ECC, extracorporeal circulation; VSD, ventricular septal defect; CA, circulatory arrest; P₂₅, 25th percentile; P₅₀, 50th percentile; P₇₅, 75th percentile; TGA, transposition of the great arteries.

†Statistically significant.

Group 1: TGA without VSD or with minor VSD.

Group 2: TGA with major VSD (surgical closure) and Taussig-Bing anomaly.

TABLE 3. Distribution by Group According to Coronary Artery Anatomy and Relationship with Mortality*

Cases	Deaths	P
Group 1 (n=63 [80%])		
Normal (n=38)	2	
Circumflex artery originating from right coronary artery (n=25)	1	
Total	3 (4.7%)	NS
Group 2 (n=4 [5%])		
Inversion of right coronary and circumflex arteries (n=2)	0	
Inversion of right and left coronary arteries (n=1)	0	
Left coronary artery originating from right coronary artery (n=1)	0	
Total	0	NS
Group 3 (n=8 [10%])		
Single coronary artery (n=5) (4 right; 1 left)	2 (right)	
Left intramural coronary artery (n=3)	2	
Total	4 (50%)	<.05
Group 4 (n=3 [5%])	0	NS
Total number of patients, 78		
Total deaths	7 (9%)	

*NS indicates not significant.

surgery when they were older and heavier than those in group 1. The duration of extracorporeal circulation and myocardial anoxia were also longer. We found no significant differences in the duration of circulatory arrest, time on mechanical ventilation, length of stay in the ICU, or mortality. Circulatory arrest was used more often in group 1 than in group 2 (78% vs 22%; $P<.001$) because, in group 2, it was easier to insert 2 cannulas into the venae cavae and close VSD without

having to resort to circulatory arrest.

The coronary artery anatomy of our series varied greatly. For classification of this anatomy, we followed the guidelines of Meyer according to the review done at the Children's Hospital of Boston.¹⁵ The children were divided into 4 groups: group 1, with the greatest number of patients, included those with a normal coronary artery pattern and those with the circumflex artery originating from the right coronary artery; group 2, with few patients, included those with inverted right coronary and circumflex arteries, inverted right coronary and left coronary arteries, and the left coronary artery originating from the right coronary artery; group 3, the least favorable anatomy, included those with a single intramural coronary artery; and group 4, which included patients with coronary artery anatomy that could not be classified according to the previous groups. Table 3 presents this classification by group and the distribution of patients who died according to coronary artery anatomy.

As shown in Tables 3 and 4, 7 out of 78 children died, corresponding to a mortality rate in the ICU of 9%, though this rate has decreased to 7.8% in the last 5 years. This decrease is even more marked, though not statistically significant, when comparing current mortality to that of the previous period (1988 to 1993),⁶ when 3 out of 21 children who underwent the procedure died (14.3%). Of the 7 children who died in this second period, 3 (4.7%) belonged to group 1 (2 with normal coronary artery anatomy and 1 with the circumflex artery originating from the right coronary artery) and 4 (50%) to group 3 (2 with a single right coronary artery and 2 with an intramural left coronary artery). Mortality was much greater (50%) in group 3 compared to the remaining groups and this difference was statistically significant ($P<.05$). In all children, the cause of death was heart failure refractory to treat-

TABLE 4. Analysis of the Variables in Children Grouped by Those Who Survived and Those Who Died*

Variables	Survivors (n=71, 91%)	Deaths (n=7, 9%)	P
Age, days	9.3 (8-20.7)	9 (6-15)	.754
Weight, kg	3.5 (3-3.7)	3.4 (3.3-3.7)	.674
ECC duration, min	238 (49)	239 (56)	.952
MA duration, min	117 (19)	126 (31)	.290
CA duration, min	9 (7-11)	8 (6-44)	.673
Ventilation, h	120 (96-192)	144 (3-216)	.770
Stay, days	10 (7-15)	6 (1-9)	.029†
VSD closure (n=14)	13 (93%)	1 (7%)	.650
CA (n=53)	48 (90%)	5 (10%)	.635

*Age, weight, duration of circulatory arrest, hours on mechanical ventilation, and days of stay are expressed as median (P_{50}) and interquartile range (P_{25} , P_{75}). Duration of extracorporeal circulation and myocardial anoxia are expressed as mean (SD).

MA indicates myocardial anoxia; ECC, extracorporeal circulation; VSD, ventricular septal defect; CA, circulatory arrest.

†Statistically significant.

ment, precipitated by sepsis with blood cultures positive for *Klebsiella* in 2 patients, by myocardial infarction in 1 patient, and by incessant ventricular tachycardia in 1 patient. The cause was not identified in the 3 remaining patients.

According to our findings, the only variable shown to be a risk factor was coronary artery anatomy (Table 3). The other variables analyzed, except for length of stay in the ICU, did not vary significantly between those who survived and those who died (Table 4). As seen in Table 4, the risk of death was not related to age or weight at the time of the operation, to whether the VSD was closed or not, to use of circulatory arrest or its duration, nor to the duration of extracorporeal circulation or myocardial anoxia. The length of stay in the ICU was significantly longer in the group of survivors compared to the group who died ($P<.05$).

Time on mechanical ventilation and length of stay in the ICU are presented in days in Table 5, which compares the findings from the current period with those from the previous period. The number of days on mechanical ventilation is similar in both groups, but the length of stay in the ICU has dropped appreciably in the second period. In children who underwent circulatory arrest (n=53, 68%), the duration of this procedure correlated directly with the number of hours of mechanical ventilation ($r=0.3$; $P<.05$) and with the length of stay in the ICU in days ($r=0.3$; $P<.05$), that is, children who required longer circulatory arrest needed more hours of ventilation and, as a result, stayed longer in the ICU. The duration of circulatory arrest in the last 9 years, expressed as the median, was 9 minutes—considerably shorter than the duration of 26.5 minutes obtained in the first 6-year period (1988 to 1993). Children who underwent circulatory arrest had a higher incidence of convulsive syn-

drome, although differences between this group and the one in which circulatory arrest was not practiced were not significant (14.3% vs 0%; $P=.094$).

DISCUSSION

Anatomic repair remains the technique of choice for surgical treatment of TGA with or without VSD in our hospital, thanks to the good results obtained since 1985, when we started performing the procedure.⁶

We did not find a statistically significant association between mortality and age at the time of the procedure (Table 4). The age at which the operation is performed in children in group 1 is tending to decrease from the median of 9 days (Table 2), and we now aim for surgery during the first week of life to thus achieve higher left ventricular pressures and reduce the risk of ventricular failure in the postoperative period.¹⁶ Left ventricular volume overload occurs in children in group 2 due to shunting, and so higher pressures are obtained, allowing the procedure to be delayed. Median age of children in group 2 at the time of the procedure was 6 weeks. We should try to reduce this time to 3 weeks to forestall the development of irreversible pulmonary hypertension.¹⁶ In group 2, duration of extracorporeal circulation and myocardial anoxia were significantly longer than in group 1, because the operation was more complex as VSD was also closed. In these patients, the frequency of use of circulatory arrest was significantly lower than in group 1 ($P<.001$) because children were older and heavier when they underwent the operation. It was easier to insert 2 canulas in the venae cavae in such patients and therefore VSD could be closed without needing to resort to circulatory arrest.

Although the progressive decrease in mortality from when we started using the technique is not statistically significant due to the small sample size and the small number of deaths, we believe that the decrease is nevertheless important. A series of factors could have contributed to lower mortality, for example, diagnosis of congenital heart disease is made increasingly early, both preoperative and postoperative treatment has improved, and we have gained experience with the surgical technique.

One of our priorities in preoperative management is to achieve acceptable oxygenation, so we resort, in cases of pulmonary hypertension, to the administration of inhaled nitric oxide.¹⁷ We administer a methylprednisolone bolus 12 hours before surgery to reduce the inflammatory response triggered by extracorporeal circulation that might cause vascular patency disorders and generalized edema. Corticosteroids have been shown to have a therapeutic effect on the lung, as they improve the levels of oxygenation in the first 24 hours after surgery¹⁸ and shorten the time needed on mechanical ventilation.¹⁹ Once surgi-

TABLE 5. Days on Mechanical Ventilation and Stay in the Intensive Care Unit in the 2 Periods*

	1988-1993 P ₅₀ (P ₂₅ , P ₇₅)	1994-2003 P ₅₀ (P ₂₅ , P ₇₅)	P
Mechanical ventilation, days	5.5 (4-9)	6 (4-9)	NS
Stay in ICU, days	13 (9-22)	9 (7-15)	NS

*NS indicates not significant; P₂₅, 25th percentile; P₅₀, 50th percentile; P₇₅, 75th percentile; ICU, intensive care unit.

cal repair is complete and before the pump is withdrawn, we also perform a ultrafiltration of plasma for the same reason, that is, to reduce the interstitial edema induced by extracorporeal circulation.²⁰ Only in cases of edema sufficiently severe to compromise hemodynamic function when the chest is closed do we leave the sternotomy open for 48 hours to 72 hours. We then close the sternotomy in the ICU when the clinical state of the patient so allows.

We base postoperative treatment in the ICU on hemodynamic support with inotropic and vasodilator drugs. After 24 hours, we start transpyloric enteral nutrition with breast milk or with an elemental formula, avoiding as far as possible parenteral nutrition because of the risk of infection. Transpyloric enteral nutrition has been useful in children who have undergone operations for congenital heart defects, particularly when mechanical ventilation is required and/or when they receive high doses of sedatives and/or muscle relaxants.²¹ The process of weaning from the ventilator is in pressure-support mode, which encourages spontaneous breathing, reduces respiratory work²² and oxygen consumption, and indirectly improves cardiac output.²³

We found a statistically significant association between mortality and coronary artery anatomy. This variable was therefore the only one that was shown to be a risk factor. Of the 8 children included in group 3, that is, the group with the least favorable anatomy, 4 died (50%), 2 of whom had a single right coronary artery and 2 had a left intramural coronary artery. The increased mortality among patients with abnormal coronary artery patterns, and in particular among those with a single coronary artery or with an intramural artery, has been described elsewhere.^{13,14} The difficulties the surgeon faces to switch these arteries and the poor outcomes obtained in doing so are the reasons for the higher mortality. The development of new techniques for surgical management of the least favorable variants will probably decrease mortality and improve prognosis for this type of congenital heart defect.^{4,5} Other authors, in contrast, do not consider complex anatomical variants as a risk factor for mortality.^{11,12} The remaining variables analyzed showed no statistically significant differences between groups of survivors and those that died, except for length of stay in the ICU (Table 4).

In children who have undergone operations to correct congenital heart defects, weaning from mechanical ventilation often presents a series of difficulties, particularly if the heart defects lead to increased pulmonary flow. The surgical technique itself, with the use of extracorporeal circulation, often accompanied by total circulatory arrest under hypothermia, causes pulmonary parenchymal injury of a severity directly proportional to the duration of arrest.^{24,25} In our series, the duration of extracorporeal circulation did not affect mortality or the number of hours on mechanical ventilation, but was significantly associated both with the number of hours on ventilation and with the number of days spent in the ICU in children who required total circulatory arrest (n=53, 68%). We have managed to reduce the duration of circulatory arrest during the current period compared to the previous period (Table 5) because it has become possible to close VSD without the need for circulatory arrest. Outcomes have therefore improved.

CONCLUSIONS

1. The decrease in hospital mortality obtained over a 15-year period with 99 patients encourages us to continue with surgical repair of TGA with or without VSD with the same diagnostic and treatment protocol.

2. In our hospital, the factor that has most affected mortality is coronary artery anatomy. We should work to improve surgical management of the least favorable anatomical variants.

3. Prolonged circulatory arrest delays weaning from mechanical ventilation and therefore extends the time spent in the ICU.

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