

Single-Stage Fontan Procedure: Early and Late Outcome in 124 Patients

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Introduction and objectives. The Fontan procedure was designed to palliate complex congenital heart disease with univentricular physiology. A retrospective study was made to document the determinants of early (≤ 30 days) and late (≥ 31 days) mortality with the modified Fontan procedure performed in one-stage over a 22-year period.

Material and methods. Between 1978 and 2000, 102 atriopulmonary, 16 cavopulmonary, and 6 Kawashima type anastomoses were performed to palliate complex congenital heart defects in 124 patients with a mean age of 7.3 ± 4.7 years. Forty-five patient and procedure-related variables were analyzed in relation to mortality. All events were verified.

Results. There were 29 early (23%) and 20 late (16%) deaths. Estimated survival at 30 days, 2 years, 5 years, and 20 years was 78, 75, 66, and 50%, respectively. Subaortic stenosis, protein-losing enteropathy, and arrhythmia were observed in 8, 5 and 33 patients, respectively, after surgery. Univariate and multivariable analysis indicated that left ventricular end-diastolic pressure (≥ 13 mmHg), mean pulmonary pressure (≥ 19 mmHg), mitral stenosis/atresia, atrioventricular valve regurgitation, visceral heterotaxia, absence of fenestration, risk factors criteria, duration of extracorporeal circulation, and operative technique were associated with early mortality. Reoperation, arrhythmia, and pacemaker implantation were predictors of late death. Forty percent remained free from surgical or catheter reintervention after Fontan operation at 20 years.

Conclusions. The outcome of Fontan procedure is profoundly affected by patient-related variables (ventricular function and pulmonary circulation). Postoperative arrhythmia and reoperation shortened the lifespan of the Fontan circulation model in patients with atriopulmonary connections. Total cavopulmonary anastomosis improves the physiology of univentricular circulation. In the light of our findings, the modified Fontan procedure (one or two stages) should be performed early in life to better preserve ventricular and pulmonary vascular function.

Key words: *Heart defects. Congenital. Fontan procedure. Cavopulmonary anastomosis.*

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Operación modificada de Fontan o variantes efectuadas en un solo tiempo quirúrgico. Determinantes de la mortalidad

Introducción y objetivos. El procedimiento de Fontan está concebido para paliar cardiopatías congénitas complejas con fisiología univentricular. Analizamos los determinantes de mortalidad temprana (≤ 30 días), tardía (≥ 31 días) con esta operación efectuada en un solo tiempo quirúrgico durante un período de 22 años.

Material y métodos. En el período 1978-2000 fueron realizadas 102 conexiones atriopulmonares, 16 bicavopulmonares y 6 tipo Kawashima en 124 niños operados con una edad de $7,3 \pm 4,7$ años. Se analizaron 45 variables dependientes del enfermo y del procedimiento quirúrgico; el resultado se tipificó como variable dependiente y los eventos se acreditaron en toda la serie.

Resultados. Se registraron 29 muertes inmediatas (23%) y 20 tardías (16%), siendo la supervivencia a los 30 días, a los 2, 5 y 20 años del 78, el 75, el 66 y el 50%, respectivamente. En el postoperatorio 8 niños desarrollaron estenosis subaórtica, 5 síndrome pierdeproteína, y en 33 apareció arritmia cardíaca. La presión diastólica ventricular (≥ 13 mmHg) y media de arteria pulmonar (≥ 19 mmHg), tiempo de circulación extracorpórea, atresia/estenosis mitral, heterotaxia, situs inversus, insuficiencia atrioventricular, ausencia de fenestración, criterios de riesgo, la técnica y el calendario quirúrgico se asociaron a la mortalidad inmediata. Las reoperaciones, la arritmia tardía y el implante de marcapaso determinaron el resultado tardío. El 40% de los niños está libre de reintervenciones quirúrgicas o por catéter a los 20 años.

Conclusiones. La preservación preoperatoria de la función ventricular y de la fisiología circulatoria pulmonar es esencial para el éxito de la cirugía de univentricularización tipo Fontan. La aparición de arritmia postoperatoria y las reoperaciones limitan la longevidad de este modelo circulatorio; la técnica cavopulmonar ofrece ventajas respecto de la atriopulmonar.

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ABBREVIATIONS

MPAP: median pulmonary artery pressure
SPAP: systolic pulmonary artery pressure
FDVP: final diastolic ventricular pressure
apR: arteriolar pulmonary resistance
CPB: cardiopulmonary bypass
AV: atrioventricular

Palabras clave: *Defectos cardíacos. Congénitos. Fontan. Anastomosis cavopulmonar.*

INTRODUCTION

The surgical procedure conceived and performed by Fontan in 1971 continues to create a fascinating and growing field of interest in pediatric cardiology. Initially carried out on patients with tricuspid atresia and subsequently used for various defects with a single, univentricular atrioventricular connection, it is also applicable to other complex cardiac malformations with 2 ventricles –complete or incomplete– when biventricular surgery is not possible. Thanks to innovative surgeons, the original technique has evolved throughout the years and undergone various modifications with the goal of decreasing surgical mortality and prolonging the longevity of this special circulatory system. In spite of these contributions and possibly because of them, the literature embraces the generic term «Fontan» to describe the procedure itself as well as variants of it and all surgical modalities that use a circulation model characterized by the channeling of the venous return towards the vasculopulmonary outlet without the help of an immediate ventricular impulse, a model which indeed could be described as the Fontan principle but also as simple total univentricular circulation.¹⁻⁷

Innovations in the procedure include reducing the time between previous palliative procedures and the actual surgery, the implantation of an extracardiac conduit with or without bypass, fenestration between the systemic venous reservoir and the atrium that receives the pulmonary veins, and the ability to configure the definitive stepped univentricular model into 2 well-differentiated surgical stages. Prominent researchers in comprehensive series have demonstrated the impact of various factors associated with immediate and/or late mortality that affect surgical success. Disagreement among such

researchers is understandable given the nature of the studies and progressive incorporation of various medical-surgical strategies.⁸⁻¹⁷

The objective of this study is to identify the factors that determine overall, early, and late mortality in a series of 124 patients undergoing the Fontan procedure and variations in one-stage surgery over a period of 22 years in the same hospital. Other objectives of the study were to compare our observations with those described in the literature, to propose methods of reducing adverse events in order to decrease mortality, and, finally, to use the information as a reference for comparing other surgical strategies.

MATERIALS AND METHODS

Between June 1978 and February 2001, 166 modified Fontan procedures and variants of same were performed in our hospital: 131 one-stage and 35 two-stage (31 with bidirectional Glenn shunt and 4 with previous unidirectional Glenn shunt). Of the 131 children who underwent one-stage surgery, 7 were excluded due to the presence of severe anomalies (discontinuation of the pulmonary branches [n=2], severe organic mitral insufficiency requiring prosthetic valve [n=2], and anomalous pulmonary venous drain [n=3]). We studied 124 patients who had surgery between 1978 and 2000. The indication for the Fontan procedure was established before surgery in 120 patients; in the remaining 4 the procedure was chosen during surgery due to inability to successfully perform the planned procedure, bidirectional Glenn shunt anastomosis in 2 cases and biventricular correction in the other 2.

Surgery was performed patients with a mean age of 7.3 years±4.7 years (0.06 to 35 years), a median weight of 22 kg±11.6 kg (3.5 to 90 kg); the male to female ratio was 1:47. There were 294 pre-operative catheterizations registered in the series with a mean of 2.4 per patient (1 to 5), and another 51 were carried out in 40 patients post-operatively. Of the pre-Fontan catheterizations, 252 were diagnostic and 42 were therapeutic (balloon septostomy in 36, knife and balloon in 4, and implant of pulmonary branch stent in 2), and 18 of the 51 post-Fontan catheterizations had interventions.

Figure 1 shows the various anatomical substrates and associated anomalies identified on pre-operative angiography and echocardiography, as well as in the surgical notes where necessary. The left ventricle was the principle chamber in approximately 70% of the patients; the right ventricle or a ventricle of

Fig. 1. Anatomical diagnosis. TA indicates tricuspid atresia; SLV, single left ventricle; PA+IS, pulmonary atresia with intact septum; SRV, right ventricle; SindV, single indeterminate ventricle; 2 VENT, heart disease with 2 complete ventricles (1 hyperplastic); AV, atrioventricular.

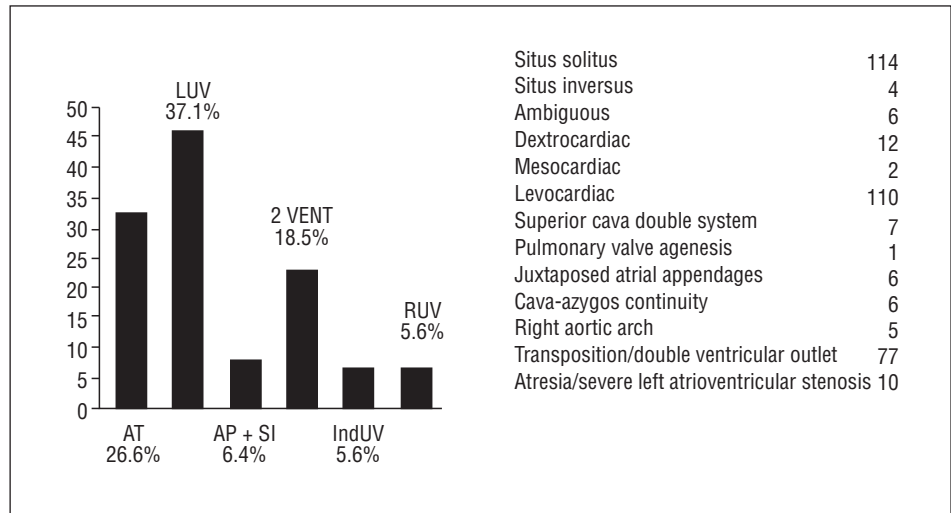
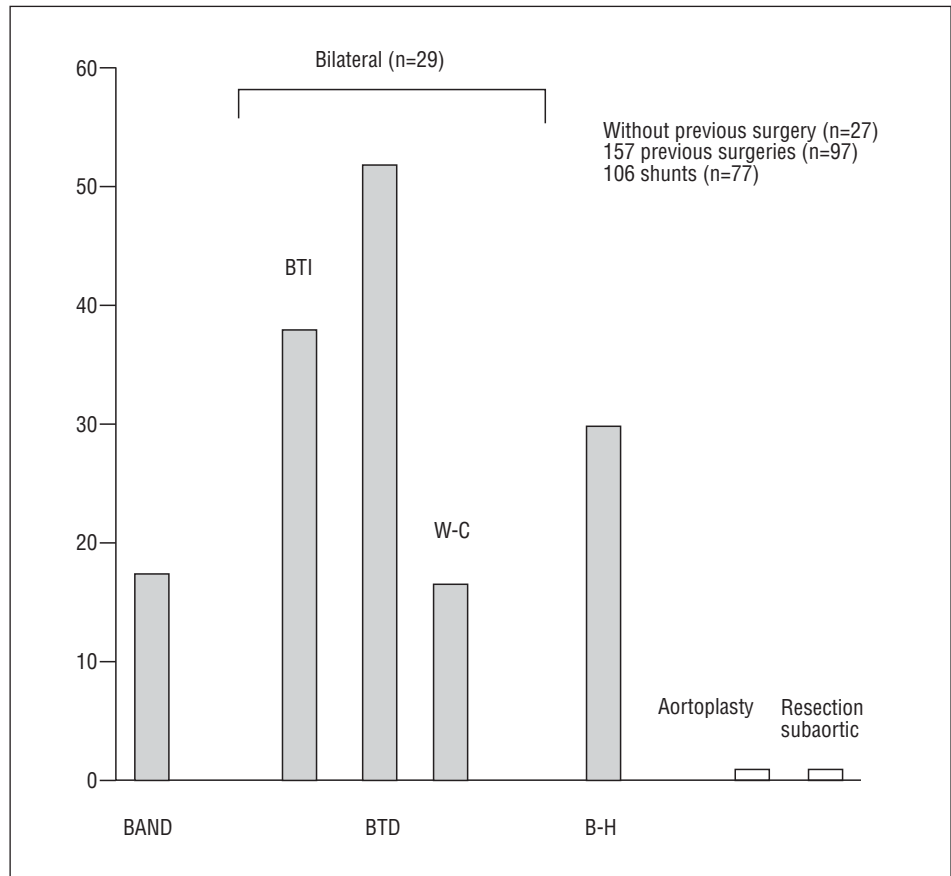


Fig. 2. Previous surgeries. BAND indicates pulmonary banding; BTL and BTR, Blalock-Taussig left and right; W-C, Watterston Cooley; B-H, Blalock-Hanlon.



indeterminate morphology in 12% of patients, and 2 complete ventricles shared the support of the circulation system in 18% of the cases regardless of ventricle size.

The number and types of surgery performed prior to the Fontan procedure are shown in Figure 2. Of 124

patients, 97 had 157 surgical procedures (78%) and only 27 (22%) had not had previous surgery. The procedures were banding of the pulmonary artery (18), systemic pulmonary shunts (87 Blalock-Taussig [36 left and 51 right] and 19 Watterston-Cooley; 29 of the total were bilateral), septectomies of the interatrial

central separation by Blalock-Hanlon technique (31), and finally aortoplasty had to be performed in 2 children to correct a coarctation of the aorta in 1 case and widening of a restrictive interventricular defect in the other.

There were 102 atriopulmonary connections performed, of which 69 were anastomosis between the right atrial appendage and the pulmonary artery (1 with valve conduit) and 33 were between the ceiling of the right atrium and the adjacent portion of the superior vena cava with the right pulmonary artery; in 4 of the 102 a Glenn bidirectional shunt was performed (double in 1 case) as part of the atriopulmonary connection. Sixteen cavopulmonary connections were performed (13 intracardiac and 3 extracardiac); in 12 of 16 a Glenn bidirectional shunt (double in 2 cases) was performed as part of the procedure, while in the remaining 4 the original superior vena cava connection with the right atrium was preserved during performance of the cavopulmonary technique. Finally, the Kawashima technique was used in 6 patients, connecting the superior vena cava to the homolateral pulmonary artery (in 1 child associated contralateral Glenn shunt was performed) as they were all missing the suprahepatic portion of the inferior vena cava and connection of this vessel with the superior vena cava by means of the azygos; in 4 of the 6 patients the suprahepatic veins were not incorporated into pulmonary circulation, while in 2 they were incorporated by means of an intracardiac Gore-Tex® conduit to the right pulmonary artery. In 17 of the 124 patients, 1 or 2 bidirectional Glenn shunts constituted part of the Fontan procedure or a variation of it.

In 22 of 124 children, a 14 mm to 22 mm diameter (mean 19 mm) conduit was implanted in the distinct

connections between the venous system return and the pulmonary arteries. In 13 of 124 cases the tricuspid valve was closed, isolating the right atrium from the single ventricle. Along with univentricularization surgery any homolateral stenosis of the pulmonary branch present was corrected; plasty of the contralateral branch was carried out in only 3 cases, and, finally, in 1 child, stenotic lesions in both branches were repaired. The pulmonary artery was resected or tied off in 104 of 124 patients, concurrently occluding systemic pulmonary shunts in 67 of the 74 children in whom these were obviously permeable. In 7 of the 124 patients a systemic pulmonary shunt was left as an additional source of pulmonary flow, either due to technical difficulties or in the creation of what were significant hypofunctions; in 3 cases these were closed with coils in a post-operative catheterization. In addition, in 2 children other techniques were combined (1 mitral valvuloplasty, 1 pacemaker implantation, and small ligature of the right superior vena cava in 1 patient and left superior vena cava in 1 patient).

In this series all the children underwent cardiopulmonary bypass (CPB) for 108 minutes±36 minutes (27 to 230). In 7 children the Fontan procedure was performed without aortic cross-clamp; it was necessary in 117 patients; median time was ±2 min (9 to 127 minutes). Rectal temperature was 26±4.6 °C (16 to 36). As shown in Table 1, intervention was necessary in 49 patients, 33 patients had 47 surgeries to correct residual hemodynamic lesions or rhythm disorders, and 18 therapeutic catheterizations were performed in 16 patients. Another 13 children underwent 15 immediate minor operations for hemorrhage (n=6), tamponade (n=4), phrenic paralysis (n=3), and mediastinitis (n=2). Six of these 13 children are included in the list of the 33

TABLE 1. Post-Fontan re-intervention in 49 children for repair of hemodynamic or anatomic sequelae or PALIAR disorder of the cardiac rhythm

45 surgical procedures in 33 patients		18 catheterizations in 16 patients	
Residual CIA occlusion	9	Pulmonary branch stent	5
Subaortic resection	5	Pulmonary branch angioplasty	4
Fontan de-obstruction	5	S-P shunt coils 3	
Tricuspid occlusion	5	AD-AP stent connection	1
S-P shunt	2	Conduit valvuloplasty	1
Fenestration	2	AD-AP Union angioplasty	1
Pulmonary artery occlusion	2	Rashkind device in residual CIA	1
Contralateral Glenn	1	VCS stent	1
Cardiac transplant	1	EEF+ablation	1
Pacemaker implant	13		

IAI indicates interatrial communication; S-P, systemic pulmonary; RA-PA, right atrium-pulmonary artery; SVC, superior vena cava; EPS, electrophysiological study.

requiring relevant surgical procedures. Six patients required ≥ 3 procedures, 13 required 2, and the remainder underwent 1 re-operation.

Follow-up data was obtained from all patients. In those who survived more than 31 days, the information was documented at the last clinical visit or obtained by telephone contact (with parents, cardiologists, and/or the pediatricians involved) during the last 6 months before the end of the study (February 28, 2001).

GETTING VARIABLES

Appendices 1 and 2 detail the 45 variables studied, noting the periods of observation where applicable and the corresponding abbreviations. The anatomic diagnoses were classified into 6 subtypes (Figure 1), while principal ventricular morphology was qualified as left, right, indeterminate, or with 2 ventricles when both chambers were observed to be complete. The systolic and median pulmonary artery pressure (SPAP and MPAP, respectively) were measured in all but 8 patients, in 5 of whom the MPAP was obtained by measuring the buried pulmonary vein pressure. The ratio of systemic flow to pulmonary flow was obtained by the Fick method ($n=74$), and arteriolar pulmonary resistance (apR) was calculated when MPAP and pulmonary flow were determined concomitantly ($n=55$). Final ventricular diastolic pressure (FVDP) was noted in 121 patients, and aortic oxygen saturation was noted in 100 of 124 patients. Given the difficulty in measuring the absolute diameter of pulmonary arteries, particularly on older angiographies, we preferred to determine the ratio of the caliber of each estimated at the predivision branch level with the corresponding diaphragm aorta. Stenosis located in the pulmonary branch was considered present when the decrease in the vascular lumen was greater than or equal to 50%; similarly, atrioventricular valve insufficiency was considered present when it was moderate or severe. The diastolic size of the ventricle and its systolic function were both classified in a qualitative manner with dichotomic qualification from observation of angiographic images.

Post-operatively, we recorded the amount of time (in days) in the intensive care unit, the administration of inotropic or inodilator drugs, connection to a ventilator, amount of time thoracic drains were in place, and total time hospitalized. Other risk factors with recognized clinical impact as noted in other

TABLE 2. Risk factors

Arrhythmia	
Age ≤ 3 years	
LPB/Ao and RPB/Ao ≤ 0.75	
MPAP ≥ 16 mmHg	
FVDP ≥ 13 mmHg	
ApR $\geq 2.1 \mu/m^2$	
Pulmonary branch stenosis ($\geq 50\%$)	
AV valve insufficiency (moderate-severe)	
Subaortic obstruction (≥ 20 mm Hg gradient)	
Decreased systolic ventricular function	
Ratio number of criteria/number of patients	
0	42 (34%)
1	49 (40%)
2	23 (18%)
≥ 3	10 (8%)

LPA indicates left pulmonary artery; RPA, right pulmonary artery; Ao, aorta; MPAP, median pulmonary artery pressure; FVDP, final ventricular diastolic pressure; apR, arteriolar pulmonary resistance; AV, atrioventricular.

studies were explored in a dichotomic manner, noting at what point in time they were recorded: left atresia or atrioventricular (AV) valve stenosis in situs habitual, or right atresia or AV valve stenosis in the context of situs inversus; subaortic stenosis by restrictive interventricular communication or another type of obstruction with Doppler gradient or by catheter of ≥ 20 mm Hg; cardiac arrhythmia with rapid or slow disorders of the cardiac rhythm or absence of sinus rhythm; and pacemaker implant. The detection of an atrial short circuit by means of cardiac catheterization or color Doppler echocardiography post-Fontan (by residual defect in 21 cases, by reopening the tricuspid valve which drives systemic venous blood in diastole to the principal ventricle in 5, or because of both conditions in 1 case), this was termed fenestration and considered involuntary ($n=25$) if not intentionally created by the surgeon, or voluntary if decided upon by the surgeon ($n=2$). Protein-loss enteropathy was proven when there was hypoproteinemia with hypoalbuminemia and positive proof in Δ -trypsin deposits; finally, the number and type of post-Fontan re-operations were noted in detail, with special attention paid for statistical purposes to those needed to modify or optimize the univentricular circulatory system (hemodynamic or electrical); simple immediate re-interventions were therefore excluded. A variable called «criteria» was developed which defines the risk factors present in each of the children in the series, using as a reference the Choussat catalogue along with the most recently published modifications. More than two-thirds of the patients had 1 or more risk factors at the time of

Fontan surgery (Table 2).¹⁸⁻²⁰

Statistical analysis

Continuous variables were expressed as mean, standard deviation, and range. The median values of the survivor and deceased subgroups were compared by the Wilcoxon non-paired data test; when the hemodynamic data pre- and post-Fontan surgery were compared, the paired Wilcoxon test was used. The Fisher χ^2 or binomial test was used to compare proportions, and appropriate contingency tables were also created. Different variables were analyzed, such as continuous or categorized, categorizing deaths, whether attributable to Fontan surgery or not, as immediate death (≤ 30 days), late death (≥ 31 days), and both conjointly were qualified as dependent. As certain independent variables could be related in a different way to mortality ≥ 30 days, the possible influence of each variable was analyzed using non-conditional logistic regression, and the corresponding odds ratio (OR) with its 95% confidence intervals. For investigation of determining factors in late mortality, early deaths were excluded from the analysis; also as the more recent cases may not have clinical antecedents or relevant interventions, different variables were analyzed for those patients who had been for ≥ 5 years. Dummy variables were created for the pacemaker implant and the appearance of arrhythmia to discern the impact of each according to the time period in which it was recorded (pre-, immediately post-, or later). By means of the Cox regression method and its corresponding 95% CI, we determined the relative risk of the variables so that only those that could have a potential clinical influence on surgical outcome were selected. A retrospective strategy was used in the construction of the multivariable models only with those that would have appeared $1 P < .1$ in the univariable analysis; first the possibility of co-linearity between variables was eliminated by applying the corresponding test. Curves reflecting survival rates and those patients free of surgical procedures were constructed by the Kaplan-Meier method, the CI being calculated by the Greenwood method; this methodology was also used to create MPAP and FDVP, and various cut-off points were established as appropriate. Using the same observation method, we explored the association of the number of risk factors present in each patient and the type of univentricular surgery carried out with overall mortality. All levels of $P < 5\%$ were considered significant. The PRESTA statistical packet was the

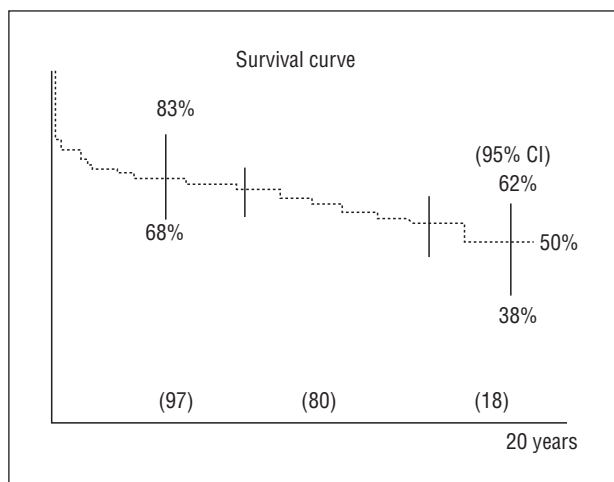


Fig. 3. Global survival curve with Fontan surgery and variants, with corresponding 95% confidence intervals. Notice that like initial mortality, the obit continues to progressive through the years. The number of patients being followed appears in parenthesis.

basis for all analytical explorations carried out.²¹

RESULTS

Overall mortality

The manner and cause of death in the 49 deceased patients is shown in Table 3. Immediate death ($n=29$) occurred between the operating room and 28 days post-operatively, with a mean of 3.6 ± 7.6 days, while late death ($n=20$) varied between 0.12 and 13 years, with a median of 2.6 ± 4.5 years. Essentially, in more than 60% of patients the cause of death was related to

TABLE 3. Manner and/or cause of death in each subgroup

	≤ 30 days	≥ 31 days
Did not survive CPB	6	–
Low output/ARI	10	–
+post-ECMO	1	–
Re-operation	2	3
Sepsis+re-operation	1	2
Neurological	1	–
Thromboembolism	1	1
Protein-loss Syndrome	–	1
+re-operation	–	1
Sudden	3	2
+Previous arrhythmia	–	5
Cardiac insufficiency	–	3
Not known	4	2
Total	29	20

CPB indicates cardiopulmonary bypass; ARI, acute renal insufficiency; PP, protein-loss; ECMO: CPB maintained with membrane oxygenation.

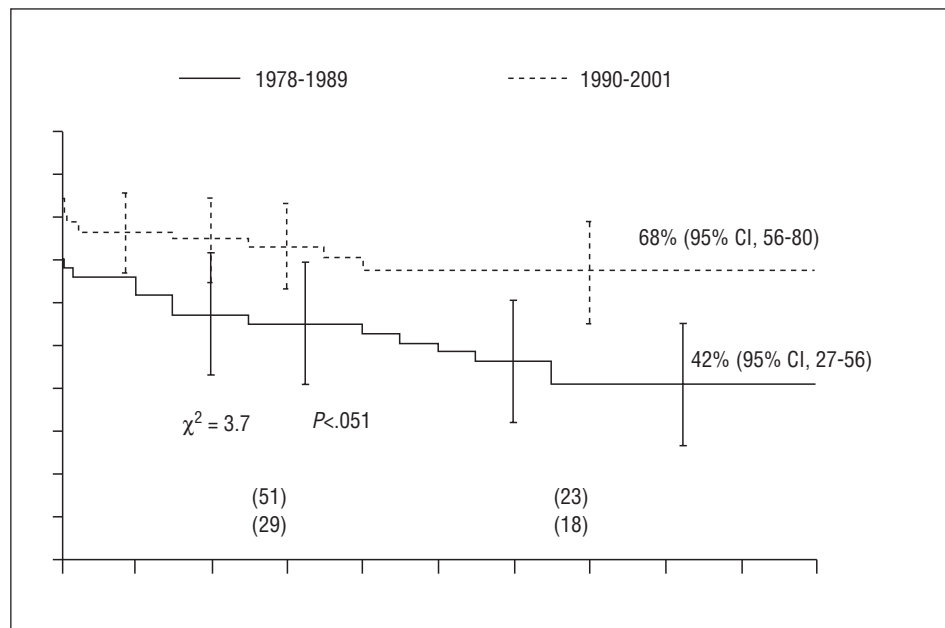


Fig. 4. Survival curve according to the surgical calendar: patients operated on between 1978 and 1989, and between 1990 and 2000. Differences are noted from the immediate post-operative period.

ventricular dysfunction, re-operations to optimize the univentricular circulatory system, or a consequence of an inappropriate procedure. Sudden death related to previously known arrhythmia occurred in 20% of patients, while the remaining factors included thromboembolism, protein-loss syndrome, neurological disorder, sepsis, and death of unknown origin.

Overall survival at 30 days, 2, 5, and 20 years following the Fontan procedure were 78%, 75%, 66%, and 50%, respectively (Figure 3). Follow-up of the 75 survivors varied between 0.41 and 20 years, with a mean of 8.4 ± 4.6 years; different clinical aspects of this important subgroup will be analyzed in another paper.

Univariate analysis comparing the mean values of continuous variables between those who died and the survivors is shown in Table 4. The differences in MPAP, FDVP, and the thoracic drainage time between both subgroups are significant, although the median value is affected by the short course of the thoracic drain implant in those children who died early. Although not of statistical significance, the median values of body weight, apR, and the amount of time in intensive care show a tendency to be lower in the live subgroup with respect to the dead subgroup.

The date of surgery shows a slight relationship with overall mortality. In effect, 57% (27 of 47) of those undergoing surgery 1978 and 1989 died, vs 29% (22 of 77) of those who had surgery between 1990 and 2000 ($\chi^2=9$; $P<.003$), although it is true that there is a strengthening effect on the differences in mortality

TABLE 4. Comparison of mean values

	Alive	Dead	P
Age	7.9±5.5 [1.5-35]	6.4±3 [0.06-14]	NS
Weight	23±13 [9-92]	20±9 [3.5-60]	.07
SPAP	20±5 [10-30]	21±5 [12-35]	NS
MPAP	13±3 [7-20]	15±4.7 [7-29]	.04
apR	0.95±0.5 [0.2-2.7]	1.32±0.79 [0.35-3.2]	.09
FDVP	9.3±2.3 [6-16]	11.2±2.2 [11-16]	.00
AoSAt	84±4 [77-94]	83±5 [71-94]	NS
PF/SF	1.6±0.9 [0.6-5]	1.5±0.8 [0.5-3.5]	NS
CPB	103±32 [27-220]	115±39 [31-230]	NS
ACC	66±21 [9-120]	71±20 [25-127]	NS
Temperature			
rectal	26±4 [16-36]	25±5 [16-36]	NS
Time in ICU	5.9±4.7 [2-30]	6.8±10 [0.04-58]	.06
Hospitalization			
duration	22±13 [4-69]	21±20 [1-87]	NS
ARM	1,9±3 [0,3-24]	2,1±1,5 [0,5-6]	NS
DRENAJ	14±12 [3-60]	9,6±14 [1-59]	.00
LPB/Ao	1,07±0,18 [0,71-2]	1,08±0,22 [0,65-2]	NS
RPB/Ao	1,07±0,23 [0,72-2]	1,09±0,19 [0,65-2]	NS

SPAP indicates systolic pulmonary artery pressure; MPAP, median pulmonary artery pressure; apR, arteriolar pulmonary resistance; FDVP, final diastolic ventricular pressure; AoSat, arterial oxygen saturation; PF/SF, pulmonary/system flow ratio; CPB, cardiopulmonary bypass; TICU, time in intensive care unit; DRENAJ, drainage; LPB/Ao, RPB/Ao, left and right pulmonary branch, respectively, with respect to the abdominal aorta; ACC, aortic cross-clamp

attributable to the progressive number of patients who died during follow-up. Figure 4 shows the survival curve for patients who had surgery during these 2 observation periods.

Table 5 shows the individuals and percentages that

TABLE 5. Categorized variables (individual and percentages)

		Dead	Alive	P
Dilatation ventricular	Yes	34 (37)	52 (63)	.081
	No	4 (20)	22 (80)	
Function ventricular	Good	33 (34)	65 (66)	NS
	Bad	2 (67)	1 (33)	
Stenosis of branches	Yes	14 (43)	18 (57)	NS
	No	34 (38)	54 (62)	
Insufficiency AV valve	Yes	5 (100)	0 (0)	.017
	No	44 (39)	68 (61)	
Hypoplasia both branches	Yes	3 (100)	0 (0)	.066
	No	44 (39)	68 (61)	

The percentage of patients is in parenthesis.

correspond to the various dichotomic variables. The creation of contingency tables for each did not show an association with mortality, except when evaluating AV valve insufficiency ($P<.017$). A tendency toward that association was observed when compared with the presence of ventricular dilatation ($P<.081$); nevertheless, the qualitative dichotomic methodology used to typify cancels out this observation. Of the 8 children with small pulmonary branches (right branch in 2 and both branches in 3 patients) 70% died compared to 37% of those who died that had normal branches ($P<.057$).

Ventricular morphology was not associated with mortality, either when the original categories were analyzed or when those children with a left ventricle

servicing either as the only ventricle or the principal ventricle are grouped together compared with right or undetermined ventricular morphology. There were no differences observed when the subgroup with 2 ventricles was incorporated into the analysis. The number and type of previous surgeries had no bearing on overall mortality when analyzed with contingency tables. Figure 5 illustrates survival according to the type of surgical technique used. Comparison of the survival curves shows a tendency to differences ($\chi^2=4.8$; $P<.08$); but the analysis is influenced by the small number of patients who underwent the Kawashima technique, which produces an excessive CI for the corresponding curve. Even assuming that the atriopulmonary technique was used more often and is an older technique than the bicavopulmonary one, the comparison of outcomes between the 2 techniques alone is significant when expressed as curves ($\chi^2=4.4$; $P<.03$) as it is when compared via contingency tables ($\chi^2=6.8$; $P<.008$).

Table 6 lists the variables associated with overall mortality as evaluated by the Cox regression method. Univariate analysis demonstrated that MPAP, FDVP, CPB, atresia or mitral stenosis, the criteria, the combined association with situs inversus and viscerotaxia, and AV insufficiency are narrowly associated with mortality; with the exception of AV insufficiency, the other variables remain in the multivariate model.

The impact of MPAP and FDVP on surgical results, expressed as survival curves, is shown in Figures 6 and 7, respectively. For the analysis MPAP, the

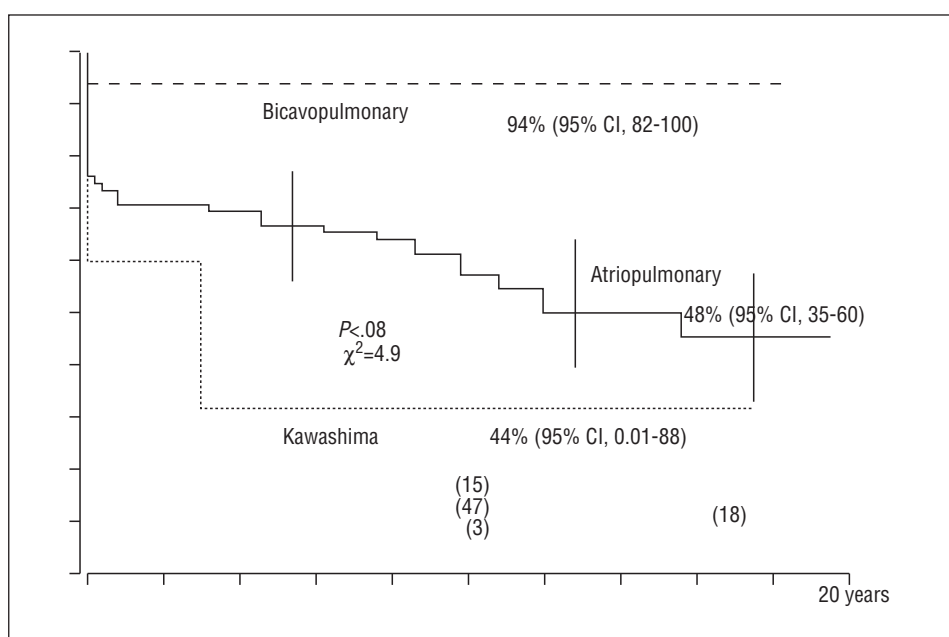


Fig. 5. Survival curve in relation to the surgical technique used. Although the differences between the distinct techniques are appreciable, it must be noted that the bicavopulmonary technique is more recent and has had less time for follow-up.

TABLE 6. Cox regression

	Univariable		Multivariable	
	RR (95% IC)	P	RR (95% IC)	P
MPAP	1.08 (1.01-1.54)	.029	–	–
FDVP	1.26 (1.12–1.41)	.000	1.14 (1.01-1.29)	.018
CPB	1.01 (1.00-1.02)	.011	1.01 (1.00-1.02)	.031
Criteria	1.85 (1.35-2.49)	.000	1.61 (1.16-2.24)	.004
Atresia or AV stenosis AV	2.71 (1.64-4.49)	.000	2.23 (1.33-3.76)	.002
AV insufficiency	4.57 (1.78-11.7)	.001	–	–
<i>Situs inversus</i> + heterotaxia	1.71 (1.07-2.73)	.022	1.74 (1.05-2.87)	.027

MPAP indicates median arteriopulmonary pressure; FDVP, final diastolic ventricular pressure; CPB, cardiopulmonary bypass; AV, atrioventricular; RR, relative risk; CI, confidence interval.

TABLE 7. Nonconditional logistic regression vs mortality at ≤30 days

	Univariable		Multivariable	
	OR (95% CI)	P	OR (95% CI)	P
MPAP	1.08 (1.01-1.54)	.029	–	–
FDVP	1.39 (1.14-1.68)	.000	1.46 (1.18-1.82)	.000
CPB	1.01 (1.00–1.03)	.009	–	–
Fenestration	0.21 (0.05-0.94)	.038	0.07 (0.01-0.52)	.009
Criteria	1.94 (1.22-3.07)	.004	–	–
Atresia or AV stenosis	4.71 (1.65-14.1)	.005	15 (2.65-85.3)	.002
<i>Situs inversus</i>	10.8 (1.08-108)	.040	–	–

FDVP indicates final diastolic ventricular pressure; CPB, cardiopulmonary bypass; OR, odds ratio; CI, confidence interval; MPAP, median arteriopulmonary pressure.

various categories were explored, and it was found that 2 showed major differences between them (≤ 18 vs ≥ 19 mmHg, respectively) ($\chi^2=6.3$; $P<.011$); in the same way, the cut-off point for statistical significance

for FDVP was ≤ 12 vs ≥ 13 mm Hg ($\chi^2=8.9$; $P<.002$).

Figure 8 shows the survival curve for the criteria variables. It was determined that 3 categories most faithfully represented their association with overall mortality; children with 3 or more associated risk

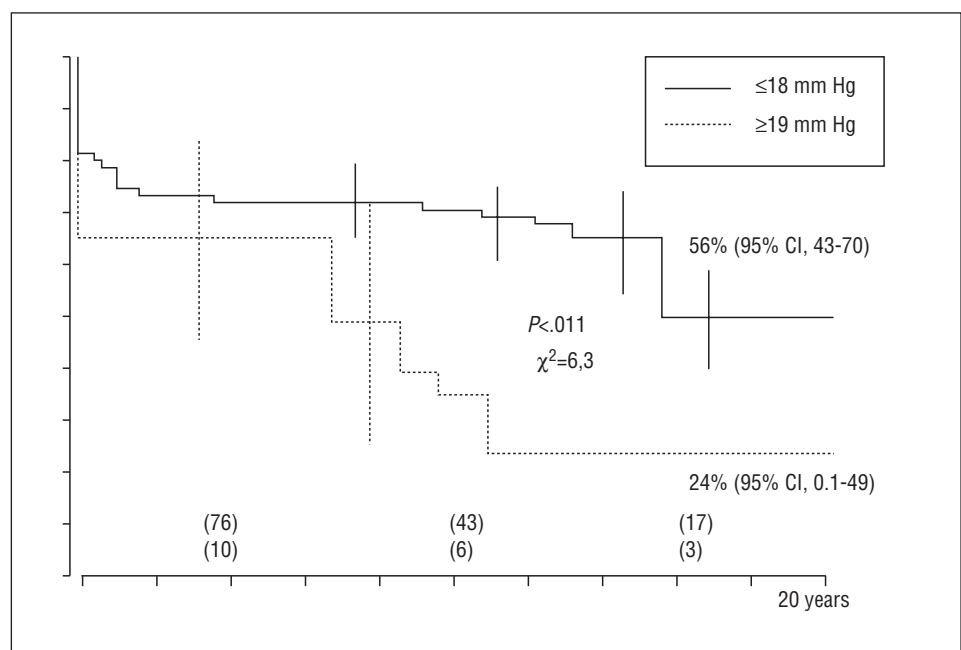


Fig. 6. Survival curve which illustrates the impact in the global evolution of pre-operative median arteriopulmonary pressure; patients with ≥ 19 mm Hg had a worse prognosis.

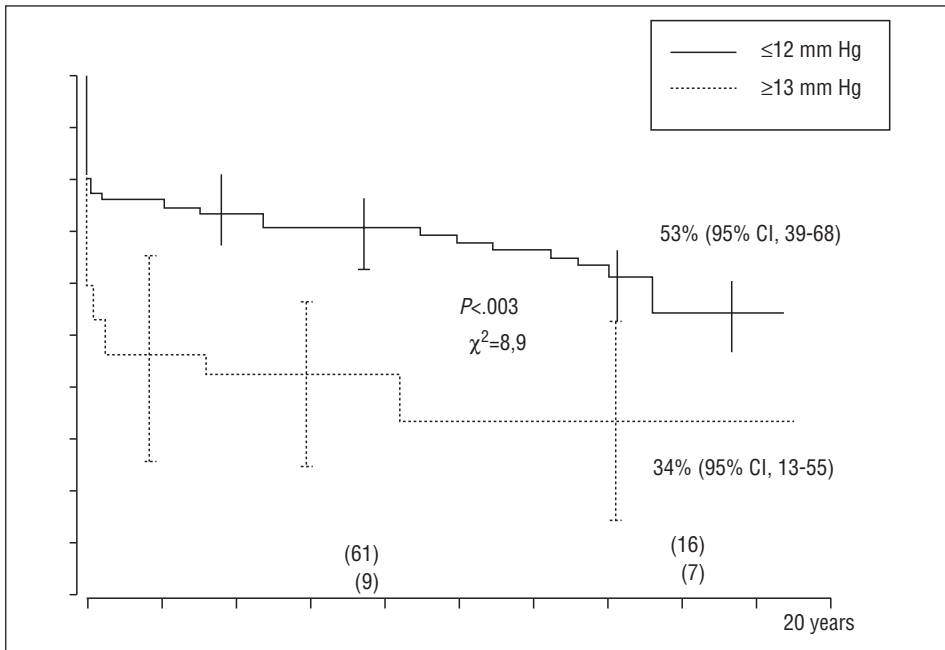


Fig. 7. Survival curve which illustrates the global evolution of patients with ≤ 12 and ≥ 13 .

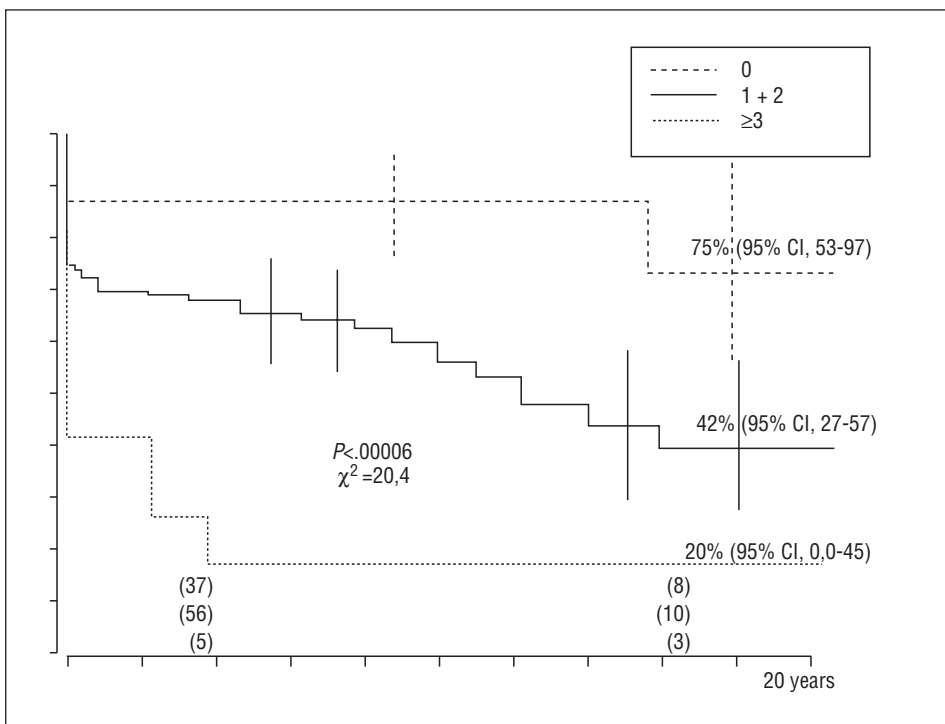


Fig. 8. Survival curve which shows the negative impact on initial and late mortality according to the number of pre-operative risk factors present in each patient.

factors had an essentially worse prognosis ($\chi^2=20.4$; $P<.00006$).

Variables associated with early mortality

The surgical timeline, although without statistical significance, showed a relationship with regard to mortality ≤ 30 days, as it reveals a decrease from 30%

in the period of 1978-1989 to 19% in the period. In the last 3 years, only 1 death has been recorded, which is 8% of early death in this period (1 of 13).

Age at the time of surgery was associated with immediate mortality, as 56% (5 out of 6) of patients younger 3 years of age died early while only 21% (24 of 115) of patients older than 3 years died early ($\chi^2=3.8$; $P<.47$). Body weight was associated with

TABLE 8. Nonconditional logistic regression vs mortality at ≥ 30 days (n=95)

	Univariable		Multivariable	
	OR (95% CI)	P	OR (95% CI)	P
FDVP	1.33 (1.07-1.66)	.010	–	–
PMAP	1.23 (1.05–1.43)	.007	–	–
Criteria	2.63 (1.40-4.92)	.002	2.31 (1.19-4.50)	.013
Re-operation	3.34 (1.63-6.85)	.002	15 (2.65-85.3)	.002
Surgical calendar	0.52 (0.30-0.93)	.025	–	–

MPAP indicates median pulmonary artery pressure; OR, odds ratio; CI, confidence interval.

early death: 47% (8 of 17) of the children who weighed ≤ 13 kg died vs 20% (21 of 107) of those with a weight of ≥ 14 kg ($\chi^2 = 4.6$; $P < .029$). Table 7 shows the other associated variables which were analyzed by non-conditional logistical regression: FDCP, CPB, atresia or mitral stenosis, fenestration, criteria, and situs inversus.

When observed categorically, the impact of CPB and aortic cross-clamping can be appreciated. In effect, 30% (24 of 79) of the children with $CBP \geq 91$ min died vs 11% (5 of 45) of those with ≤ 90 min ($\chi^2 = 4.9$; $P < .02$); in the same manner, 32% (22 of 68) of children with a clamping time of ≥ 61 min died, vs 14% (7 of 51) with a time of ≤ 60 min ($\chi^2 = 4.5$; $P < .03$). The presence of mitral atresia or severe stenosis of the mitral valve was associated with mortality; it was not determined that there was an association due to the coexistence of atrioventricular valve insufficiency, which acts as the only or dominant valve. It is of interest to note that the presence of fenestration is associated inversely with early death; only 75 (2 of 27) of patients with this

TABLE 9. Nonconditional logistic regression in patients with > 5 year follow-up (n=63)

	OR	P	95% CI
Re-operation	3.12	.014	1.24-7.81
Arrhythmia	2.23	.021	1.12-4.47
Late	11.1	.033	1.8-102
Pacemaker	1.87	.032	1.04-3.37
Late	7.2	.026	1.24-41.2

OR indicates *odds ratio*; CI, confidence interval.

diagnosis died, while 28% (27 of 97) of those with no sign of a residual short circuit – either because there was no record of systemic oxygen desaturation or because it was excluded by catheterization and/or echocardiography ($\chi^2 = 3.8$; $P < .042$). The impact of this variable on the immediate outcome is the same even those children who died during surgery were excluded; in these children it was impossible to know whether a residual atrial defect was present. This observation

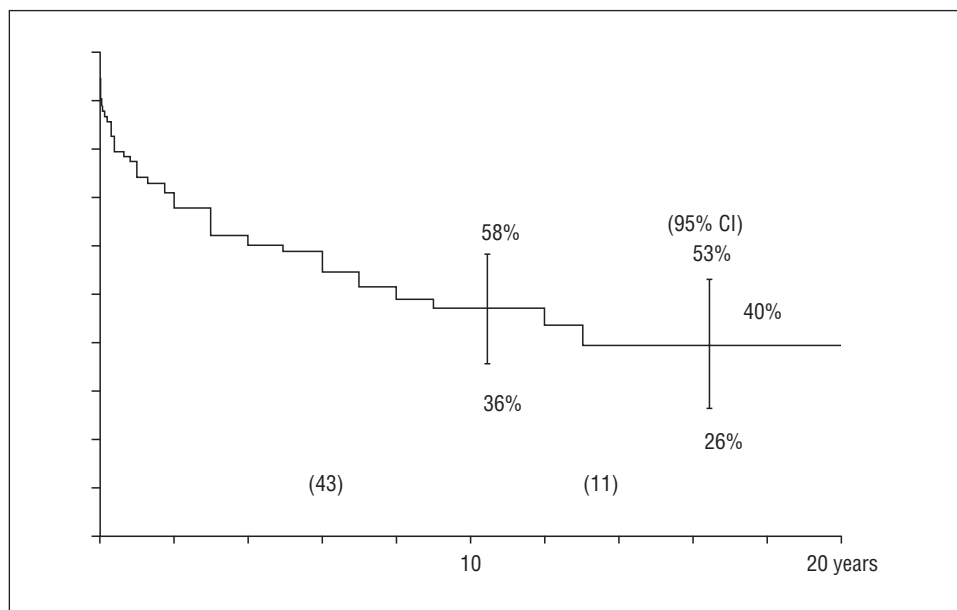


Fig. 9. Survival curve of patients without surgical or catheter re-intervention during the follow-up period. Note that in the first 12 years the procedures are necessary to improve or abolish residual lesions.

means that fenestration has a protective effect on the immediate post-operative outcome.

Other variables (while not reaching statistical significance) that were associated with mortality ≤ 30 days were: AV valve insufficiency (OR=5.3; 95% CI, 0.85-33); the presence of heterotaxia (OR=1.6; 95% CI, 0.70-4.1), and previous systemic pulmonary shunt implant (OR=2.1; 95% CI, 0.88-4.99). With regard to the latter variable, median FDVP in children with shunts was significantly higher than those without shunts (12 vs 9, respectively; $P < .012$). Although the morphology of the principal ventricle did not show a relationship with early death, it must be pointed out that 60% (6 of 10) of the children with situs inversus and heterotaxia died, vs 20% of those with habitual situs viscerotaxial (23 of 114) ($\chi^2=6.1$; $P < .01$). This difference most likely probably reflects a constellation of variables present in children with situs other than the habitual type which supposes a more serious pathology. In the multivariate model, only FDVP, fenestration, and atresia or mitral stenosis were present.

Variables associated with late mortality

We analyzed 95 patients who lived ≥ 31 days. The variables associated with late mortality are shown in Table 8, and were MPAP, FDVP, re-operation, criteria, and surgical timeline. We also determined that both the protein-loss syndrome (OR=5.01; 95% CI, 0.90-28) and subaortic stenosis (OR=2.17; 95% CI, 0.96-4.91) had an appreciable negative impact on late mortality, even when it did not reach the required statistical significance. In the multivariate model, only the criteria variables and re-operation were left. Figure 9 shows the survival curve for patients without post-Fontan re-operations or catheter re-intervention, excluding those procedures not associated with repair of hemodynamic sequelae or cardiac rhythm; there is a progressive need to correct alterations throughout follow-up. Only those patients with ≥ 5 year follow-up (9.7 ± 3.5 years; between 5 and 20) were analyzed in an attempt to avoid bias which assumes the inclusion of those with a brief follow-up period in the group of patients most recently undergoing surgery. It can be seen that, in addition to the re-operation variable, late appearing arrhythmia and late pacemaker implant are associated with mortality at ≥ 5 years (Table 9).

Other observations of clinical interest

Subaortic stenosis

Ten children (8%) were included in this subgroup with a subaortic gradient of between 20 and 100 mm Hg and an overall mortality rate of 40%. In 8 of 10 the obstruction was detected after the Fontan procedure. Banding (60% vs 11%) ($\chi^2=14$; $P < .0002$) and ventriculoarterial discordance (100% vs 61%) ($\chi^2=4.4$; $P < .033$) had a significant association with subaortic stenosis with respect to those who did not have the condition. Six children underwent surgical repair: 1 before univentricular surgery and 5 as re-interventions in the post-Fontan period (between 3 and 9 years later); 1 of the latter patients required 2 procedures to alleviate the obstruction and ultimately died 7 years post-Fontan, after being rejected for cardiac transplant because of the number of prior surgeries. Of those in whom no surgery was considered to alleviate the subaortic obstruction (4/10), 2 children died post-Fontan procedure (1 late and 1 immediately); another 2 survived, although 1 of them developed protein-loss syndrome and is currently in excellent clinical condition after a successful cardiac transplant performed 6 years post-Fontan procedure.

Protein-loss syndrome

Five children (4%) developed protein-loss syndrome; 2 (40%) died, 1 from hepatitis contracted months after 2 re-operations (repeat Fontan and diaphragmatic kink) and the other died suddenly of known arrhythmia. In the 3 surviving patients, re-operations were carried out from 2 to 12 years post-Fontan: 1 closure of a residual short circuit, 1 cardiac transplant, and 1 arteriopulmonary closure. In addition, no pre- or post-operation hemodynamic variable was associated with protein-loss syndrome.

Arrhythmia

This subgroup was made up of 41 children (33%). The rhythm disorder was detected in the pre-Fontan period in 8 patients (19.5%); in the immediate post-operative period in 12 (29%), and during the procedure in 21 (51%). Atrial flutter, paroxysmal tachycardia, and advanced AV block were the most frequent arrhythmias found. Thirteen children died (32%), 2 during the post-operative period of ≤ 30 days. Twenty-seven percent (11 of 41) died during follow-up (7 suddenly), a significantly different number than the 11% late mortality rate in the patients without previously known arrhythmia ($P < .022$). In 13 of the 41 patients various re-interventions were necessary, 12 involving pacemaker implantation. Pre-operative

MPAP was higher in patients with arrhythmias as compared to those who did not have arrhythmias (15 vs 13.7; $P<.02$); when patients with pre-operative rhythm disorders were excluded, the MPAP lost its significance as a possible factor in inducing arrhythmia. Previous interatrial septectomy (Blalock-Hanlon) was also not associated with post-Fontan arrhythmia; on the other hand, it was observed that the atriopulmonary technique showed a marked tendency to be associated with an altered post-operative rhythm with the cavopulmonary technique (19 vs 2, respectively; $P<.07$).

Thromboembolism

The presence of systemic venous thrombosis was evident on transthoracic echocardiography (TTE) in 5 patients (4%). Early demise was noted, preceded by confirmed pulmonary thromboembolism, and 3 patients died later (of jugular vein thrombosis and superior vena cava thrombosis), all within the context of re-operations to optimize circulation. All the patients who died had undergone the atriopulmonary technique. In 1 survivor an inferior vena cava thrombosis was detected immediately post-operatively, which disappeared with heparin treatment. Thromboembolism was suspected, but not definitively confirmed, in 2 children who died in the early period (probably of pulmonary embolism) and later (probably from systemic embolism in the presence of fenestration).

DISCUSSION

Our series and its limitations

The current study analyzes and describes in detail our experience in a large series of children operated on with one-stage Fontan surgery or a variant thereof performed at the same center over a period of 22 years. The study population consisted primarily of cases similar to those in the first large studies published in the literature, which involved patients operated on in the 80's and in which the predominant technique of choice was atriopulmonary connection. Our series –some years later– extended well into the 90's; only in the later years –from 1992 on– have we gradually included the bicavopulmonary technique.²²⁻²⁸

Given the changes in strategy for patient selection and choice of appropriate surgical technique over the years, and because it is retrospective, the current study has design limitations which must be considered when

interpreting the information detailed in the discussion. Given the well known hemodynamic considerations, therefore, we have chosen not to include information gleaned from two-stage surgical univentricularization, although this last group of patients will be documented in a future paper.

Because of ethical considerations and limitations of the surgery, it is essentially impossible to randomize homogenous subgroups which allow the clear perception of factors that contribute to surgical failures and the lack of durability of this circulatory system. Even with these precedents, we believe this study is broad for a single center and that it yields relevant interesting data for both the clinician and the surgeon that effect allows the Fontan principle to be examined from different perspectives. The study also serves to inform as it highlights the results of new strategies that we are currently applying.

Mortality

Overall mortality in our series was 39% (49 of 124 patients) in a follow-up of up to 20 years (8.4 ± 4.6), with survival of 30 days (78%), 2 years (75%), 5 years (66%), and 20 years (50%) post-surgery (Figure 3). At the Mayo Clinic, of 352 Fontan surgeries between 1973 and 1984, 16% died within a month, 23% within a year, and 40% at 10 years; in a multicenter study of 334 children operated on during the 1980s, 33% died early and 13% later.^{24,29}

Our overall mortality with this one-stage surgery is high, including for those cases that occurred in the 1990s. This may be due to an initial prodigal attitude regarding palliative techniques, and to performance of a technique that was not sufficiently established and that had a high incidence of re-operations, all factors which we know cause deterioration of ventricular function. Since the immediate mortality rate has dropped to 8% in recent years, 22% (29 of 124) is a high rate; in similar series carried out in the 1980s and 1990s, between 15% and 31% of children died in <30 days. In more recent studies, mortality drops to between 0% and 10%, increasing survival to more than 80% at 10 years.^{8,22,30-35}

Risk factors related to the patient

Ventricular function and its enemies

Since the ventricle acts as a pump and the univentricular system is the only energy source to support 2 serial resistances, good function is indispensable for the success, both immediate and

later, of the Fontan operation. In this circulatory model, 90% of ventricular energy is dissipated in the blood flow impulse through recurrent systemic vascular resistance in the best cases, and the remaining 10% by its own diastolic suction power overcomes pulmonary vascular resistance; therefore any decrease in ventricular function, no matter how small, could be critical to a loss of the energy needed for blood flow to easily cross the pulmonary vascular circuit.^{13,14}

Ventricular function in malformations in which there is only 1 useful ventricle can deteriorate for many reasons, the primary one probably being the substrate of the myocardial myoarchitecture as described by Sánchez Quintana, other reasons being the natural course of the disease or the surgical modification. Initial pre-operative ventricular blood volume tends to more than double what is considered normal in biventricular hearts. The numerous systemic pulmonary shunts –inevitable in the majority of cases– (in our series 106 in 77 of the 124 patients) produce a pulmonary hypervascularity which favors good initial oxygen saturation in these patients, but also increases the already excessive ventricular overload that is present and that often is reinforced with atrioventricular valve(s) insufficiency of varying grades.^{36,37}

The chronic volume overload produces a geometry which progresses to dilatation. If the volume to mass ratio does not balance with progressive compensatory parietal hypertrophy or the dilatation is excessive, changes in systolic and even diastolic function can result that affect the ventricular suction power. Although it is difficult to predict when such changes are irreversible, it seems logical to correct the volume overload as soon as possible, avoiding shunts if possible or implanting the smallest caliber possible, or by performing Glenn anastomosis or Fontan surgery, or both, early on. In light of this considering that the latter surgery induces a rapid geometric change, the relative predominance of hypertrophy in these conditions can lead to a loss of myocardial elasticity, with resultant diastolic dysfunction during the first pre-operative days or months. These effects are evinced in study by the fact that previous shunt implant and ventricular dilation, with its consequent influence on final diastolic pressure, had a tendency to be associated with a worse surgical outcome.³⁸⁻⁴⁴

In the same manner, in anatomical substrates post-operative geometric change facilitates subaortic obstruction (by reducing the size of the interventricular communication) or favors AV valve regurgitation because of valve redundancy. At least

20% of patients with a single ventricle have systemic obstructive lesions that cause a pressure overload and ventricular hypertrophy that alters diastolic function. In these patients there is often an associated anterograde pulmonary hyperflux due to the absence of protective pulmonary stenosis; the inevitable need to control pulmonary flow with banding produces or increases subaortic stenosis, changing ventricular function even more. In our series, as is well known, we also observed a narrow relationship between banding, ventriculoarterial discordance, and the appearance of subaortic stenosis.⁴⁵⁻⁵⁰

The preceding effects would result in severe ventricular dysfunction immediately post-surgery, with consequent patient death; therefore the concept of the two-stage Fontan principle has become more and more refined so that changes relating to the mass to volume ratio have progressed, which we have also noted in recent years. It remains to be seen if this strategy results in lower surgical mortality rates and, at the same time, greater longevity of the circulatory system. In any case, since function of the only impulse pump is essential in the physiology of the univentricular model; it seems evident that many of the deleterious forces that act upon it can affect, and also exhaust the limits of its reserve function. In the majority of studies, as well as in ours, ventricular dysfunction is the principle cause of early and late death, from the Fontan dismounting or from cardiac transplant. Given this, it is not surprising that indices of ventricular function performance, such as FDVP, ejection fraction, hypertrophy grade, and cardiomegaly are universally recognized as risk factors.^{22,22,34,51}

In our series FDVP is a determinant of mortality during any stage of the study and the greatest impact on prognosis; so that we can be certain that an $FDVP > 12$ mm Hg indicates a negative surgical outcome, as shown in Figure 7, even though the survival curves in those patients with ≤ 12 and ≥ 13 mm Hg tend to be close on follow-up. We also observed that ventricular dilatation, which in spite of its dichotic determination can be considered imprecise, tends to be associated with overall mortality ($\chi^2=2,8$; $P<.08$). In light of this data it is essential to try to preserve the maximum ventricular function reserve from the neonatal period on; therefore we believe it is necessary to have a new strategy of early intervention and avoid palliative surgery as much as possible by trying to control pulmonary flow when by early implantation of bidirectional Glenn anastomosis or Fontan surgery when or variant thereof when it is inevitable and, when necessary, optimize hemodynamics by

configuring total two-stage univentricularization. The future will reveal whether this assertion is true; we would not hesitate to consider cardiac transplant if ventricular function has deteriorated considerably.^{12,13,17}

Atrial valve insufficiency. Atrial valve insufficiency is a known risk factor for immediate and overall mortality in Fontan surgery; the 5 children with this condition died (Table 5). Its association with the presence of a common or unique AV valve was evident every time this valve morphology was present in 3 of them, who also had viscerotaxial heterotaxia. In a series of 500 cases undergoing Fontan surgery, the Mayo Clinic identified AV insufficiency as an immediate post-surgical risk factor; this association is confirmed—this time with overall mortality rates—in 352 surgical cases between 1973 and 1984. Kaulitz et al, in a study of 72 children with cavopulmonary surgery, also recognized AV insufficiency as a significant risk factor. In fact, it is associated with an increased risk of death in visceral heterotaxia syndromes with or without abnormal connections of pulmonary or system veins, malformations in which only 1 AV valve is frequently present.^{24,37,52-55}

These observations are not surprising considering the fact that 1 morphologically normal functionally competent valve is essential for good system function. As long ago as 1977 the absence of mitral insufficiency was requirement number 9 on the list of the 10 requirements of Choussat, and even of those at least 5 seem to have currently lost importance, this continues to be fundamental in the success of univentricular surgery. It is not unusual to encounter cases of a mitral prosthesis in a Fontan series; nevertheless, few know the later outcome of these patients. Speaking from our own experience, it is recommended that mitral valvuloplasty be performed before any major insufficiency occurs. Although the methods we used to typify the grade of regurgitation differs from that described by Imai et al, the authors made similar recommendations, and even when discussing the immediate and late risk of this condition, they recognized a reduction in valve competence through annuloplasty in those patients with a pre-operative regurgitation grade higher than 2.^{18,37}

Ventricular morphology. Although there is not a definitive consensus on the impact of ventricular morphology on mortality in Fontan surgery, many researchers consider right and/or indeterminate morphology to be prognostic factors in terms of both mortality and morbidity. The failure of the chamber

in question to achieve normal aerobic capacity with exercise in children and adults who undergo surgery is established, supporting the findings of abnormal diastolic function and deficient functional reserve. In our study we did not observe this finding, but perhaps this is due to a potential problem because of the small number of patients with this type of morphology. On the other hand, we did observe that the constellation associated conditions related to the AV connection or to visceral situs, among others, is greater in those cases with a dominant right or indeterminate ventricle.^{17,30,56-59}

Mitral valve stenosis/atresia. Mitral valve stenosis or atresia is a determining factor for mortality in our series; 8 of the 10 children (80%) with this anomaly died. Many mechanisms are suspected in this anomaly such as: *a)* pulmonary venocapillary congestion and passive hypertension over several months and even years, exacerbated by the coexistence of previous hyperflux, which would alter the extrauterine maturation of the pulmonary vasculature (3 old cases in our series); *b)* balloon and/or knife atrial septostomy, and the need for Blalock-Hanlon septectomy (7 out of 10 of our patients) could be the cause of additional interventions that could induce arrhythmias and, in turn, difficult later surgeries and the atriopulmonary connection in the presence of mitral stenosis or atresia necessitate oblique and wide patch implantation, with long suture lines that not only increase CPB time but also potentiate the appearance of arrhythmias. Currently, since the cavopulmonary technique—intra- or extracardiac—is the technique of choice at most centers, this last mechanism is less important; we recognize that to achieve early atrial communication would soften the impact of the two first points.^{48,60,61}

Systemic obstructions. Aortic coarctation and aorto prior to Fontan surgery have also been identified as overall mortality risk factors in a multivariate model for the Boston group. If this is confirmed by other studies, the physiopathologic mechanism may be related to parietal hypertrophy of the ventricle, although pulmonary hypertension cannot be ruled out in cases with hyperflux, which is also common in these children. In our series only 1 patient required pre-Fontan aortoplasty, and they survived surgery.³⁰

With respect to subaortic stenosis, 4 of our 10 children (40%) with this condition died. Although there was a tendency of subaortic stenosis to be associated with late mortality, the negative impact of the obstruction was very evident when we include in the subgroup the only patient who developed protein-

loss syndrome associated with the subaortic obstruction and who survived cardiac transplant. The Mayo Clinic group established a strong association between the subaortic gradient and mortality in Fontan surgery; mortality can reach 67% if the gradient is more than 40 mm Hg, or be as low as 17% if the defect is widened first, and is less than 10% with a gradient of less than 25 mm Hg. In most of our patients this condition appeared post-Fontan surgery; for this reason it is essential to determine the pre-operative sub-aortic gradient where there is an anatomical tendency, as the latent obstruction could be circumvented at the time of or before Fontan surgery.^{48,51}

Situs inversus and viscerotaxial heterotaxia viscerotaxial

Whether individually or in combination, *situs* other than habitual is a known mortality risk factor. In our series 4 of the 6 children with heterotaxia died (67%, 3 immediately post-surgery and 1 later), and 3 of the 4 with *situs inversus* (75%, all in ≤ 30 days). In the Mayo Clinic experience, heterotaxia is a determinant of poor prognosis both in those undergoing the atriopulmonary technique and the cavopulmonary technique. Marcelletti also observed that heterotaxia increased surgical risk in patients with extracardiac conduit surgery. An early Glenn strategy to repair valvular insufficiency, which frequently occurs in these cases, could benefit the course of these children; but even so it must be determined whether this complicated subgroup has a good long-term prognosis with Fontan surgery.^{34,54,56,62}

Arrhythmias. An arrhythmia can occur pre-, post-surgery, or immediately, it is difficult to clearly determine the impact of a rhythm disorder on patients who undergo Fontan surgery or variants thereof. In our series, we observed that only late-appearing arrhythmia was associated with mortality in children who followed more than 5 years. In fact, 5 of the 7 who died had a history of recognized arrhythmia. There is no consensus on whether rhythm disorders occur less frequently in extracardiac tunnel procedures with respect to the atriopulmonary technique in the long-term. In any case different factors can induce arrhythmia. As we noted, we also observed an association of pacemaker implant and late mortality; the Mayo Clinic group found that this is greater in children requiring pre-Fontan pacemaker implant, while the Boston group noted its impact on children who underwent intracardiac tunnel technique and

pacemaker implant pre- and post-surgery. What does seem evident is that the presence of rapid or slow rhythms or that are congenital or occur post-surgically can affect ventricular function and, in turn, lead to frequent re-operations that worsen the prognosis for these children. Aggressive correction of rhythm disorders is desirable, and the hemodynamic or electrical situation of each patient must be taken into consideration, and the disorder must be treated aggressively with medication or possible reversion by the atriopulmonary or cavopulmonary technique along with anti-arrhythmia surgery if necessary.⁶²⁻⁷⁰

Pulmonary circulation and vascular anatomy: the last barrier to overcome. Arteriolar pulmonary resistance which is dependent on adequate anatomy and physiology of its vascular model must necessarily be low for Fontan surgery or its variants to be successful. We point out that, in most cases, the ventricular impulse only has 10% of the available energy to cross the pulmonary vascular barrier. Therefore, any increase in resistance, no matter how slight, can have disastrous effects on the fragile Fontan principle. There are many factors in the patients' natural history and the surgical modifications that can increase resistance; these factors are physiological (long-term pulmonary hyperflux, obstructive systemic lesions), as well as anatomical secondary to vessel distortion, amputation of secondary branches or arterial stenosis resulting from shunts, occlusion of ducts in some cases, or occlusion of the pulmonary artery. All these conditions may restrict the capacity of the vascular pulmonary tree, and it is no surprise that these physiological or morphologic changes have been defined as risk factors. In our series, MPAP has a clear impact on the prognosis; when greater than 18 mm Hg pre-operatively, there was a negative survival curve (Figure 7). We have proved, furthermore, that with more than 15 mm Hg of median AP pressure, the prognosis worsens. There are a number of reasons for the influence of apR on surgical outcomes such as the errors inherent in the surgical method in cases where this could be determined, and the small number of indications used to perform the surgery. Two of the 3 cases that exceeded the 2.5 u/m^2 died (67%). We have also explored other contraindications, such as those described by Mair and Knott-Craig, related to different hemodynamic variables in pulmonary and systemic flow, MPAP, and apR. We have noted its association with immediate and overall death but, given that its predictive value was not greater than that of MPAP, we did not report it in this article.^{62,71,72}

In the Boston group an apR $>2 \text{ u/m}^2$, MPAP $>15 \text{ mm}$

Hg, and the distortion of the pulmonary arteries constituted clear risk factors. Kirklin also established that this last variable is associated with overall mortality. In a combined multicenter study, it was recommended that successful surgery required the absence of deformities of the pulmonary vascular tree, and Nakata and McGoon indexes greater than 250 mm²/m² and 1.5. Although these data have been questioned by other researchers who argue that the continuous non-phasic flow characteristic of this univentricular circulatory model makes it unnecessary to attain those values. In our series, when both branches are small (≤ 0.75 as related to the abdominal artery), the surgical result is worse (3 patients with this condition died). The influence of stenosis of the branches on the outcome was not evident. Repair of same during surgery without excessive CPB prolongation or later catheter intervention neutralizes its potentially negative effect.^{18,24,30,34,62,73-75}

Other extrapulmonary and extracardiac factors

Younger age (<4 years) and lower body weight (<15 kg) tended to increase the risk in surgical treatment of congenital heart disease. There are many reasons for this such as the greater complexity of heart disease, the smaller margin of error in the technique, or difficulties in post-operative management, among others. Although several researchers have also highlighted the importance of age and weight as determinants of mortality in univentricular palliation (both in atriopulmonary surgery and with placement of conduits), most surgeons believe that technological advances and improved techniques cancel out the negative impact of these factors. In fact, in a series from the 1980s and in more recent series it was determined that age was not a risk factor for mortality; it was determined that Fontan surgery could be performed safely at 3 years or younger. Given that our group had successfully undergone cavopulmonary surgery—in 1 or 2 stages—and based on our own observations, we established an age of about 3 years and a body weight of about 13-15 kg as appropriate.^{28,76,77}

The variable criteria consisted of 10 cardiac, pulmonary, and age factors. In our series, the 10 factors that reflected ventricular function, pulmonary vascular situation, and age had a strong impact on early, late, and overall mortality, as can be seen in the corresponding tables. When survival is compared with the number of factors present in each child, it is

evident that children with 3 or more criteria had a worse survival curve (Figure 8). Other authors have developed similar significant criteria that are useful in determining risk for future patients.²⁴

The protein-loss syndrome is an undesirable complication of the survivors of Fontan surgery. The rate of 4% in our series is similar to that described in a multicenter study by Mertens et al. This condition has a poor prognosis, and its actual mechanism is not well understood, although it is accepted that systemic subdiaphragmatic venous congestion can trigger the condition, although median cavopulmonary pressure does not tend to be elevated in these cases, as in our experience. The success of re-operations to repair significant residual lesions in these children is lower in the study of Mertens et al; however, we believe it is necessary to treat these lesions surgically or with catheterization, as we were able to do in 2 of our patients. Cardiac transplant is also an option when re-intervention to correct functional anatomic alterations is not possible, or when the clinical picture does not change despite recent heparin treatment (1 child in our series).⁷⁸⁻⁸⁰

Thromboembolism is another condition that increases mortality in Fontan surgery. The observation in our own patients of a very slow flow parallel to the wall of a dilated wall and a hypocontractile right atrium on post-surgical angiography or evidence of significant autocontrast on echocardiography in this chamber and in the venas cavae are a result of changes in multiple thrombogenic factors (anatomofunctional and biochemical) that pose a thromboembolic risk. We were able to identify early signs of thrombosis using transthoracic and transesophageal echocardiography, and aggressively treating this hematological change.⁸¹

Factors determining mortality depending on time and technological progress

Date of surgery

As is proven in our series, the surgical timeline has a strong impact on immediate, late, and overall mortality. We observed not only the loss of patients over the years, but also a reduction in immediate mortality to 8% over the last 3 years. The year surgery is performed is also an omnipresent factor in all the large series that span many years, and this is attributable to the learning curve, the advent of new technologies, and the disparate course that results from different surgical techniques. As a result, the date of surgery is universally considered to be a determining

factor in mortality. This finding is not new, but it confounds the detection of other contributing factors of greater importance.

Fontan technique

As this is the oldest, the atriopulmonary technique is a determinant of mortality; the overall rate in our series of 102 cases was 44% and only 6.3% in those cases who underwent cavopulmonary surgery. Figure 5 shows the lowest survival rate in those children undergoing on the Kawashima and atriopulmonary techniques. This study, however, is not optimal for studying these techniques, as it does not take into account the tenuous relationship between late mortality and amount of time of follow-up. Also, as we have shown in our own series, patient selection has improved drastically over the years: the percentage of children without risk factors has increased from 29% with the atriopulmonary technique to 68% with the bicavopulmonary technique ($P<.04$). Balaji et al also observed that the cavopulmonary technique reduces overall mortality from 37% to 15%, and they point out that the incidence of arrhythmias is lower with respect to established surgical techniques. Although various authors have also noted the advantages of the cavopulmonary model, others have not documented such differences. These discrepancies, therefore must be attributed to the difficulty of carrying out comparative study series simultaneously and with the same follow-up, although the conventional wisdom is that the cavopulmonary technique has appreciable advantages.^{32-35,51,52,63,82}

Cardiopulmonary bypass time

As in many other series, we found that prolonged CPB time affected early and overall mortality rates. When CPB was >90 min, mortality increased from 34% to 42%. This was also apparent with aortic cross-clamping (31% vs 44% when >60 min). Although both variables are subject to multiple intraoperative variables, their deleterious effects on endothelial myocardial and pulmonary function are established, especially the damage on univentricular circulation since this depends on good diastolic and ventricular function and low pulmonary resistance. We and other researchers believe that aortic cross-clamping and even cardiopulmonary bypass must be avoided whenever possible in Fontan surgery. Although we could only avoid aortic cross-clamping in 7 cases, we

followed this guideline in the last patients who underwent surgery.^{30,83-85}

Fenestration

Hypertension in the cavopulmonary circuit or low systemic output is frequently combined in the immediate post-operative period of univentricular surgery. Fenestration alleviates this hypertension and increases cardiac output at the cost of decreasing systemic saturation. This is a safety measure that allows time for adaptation to the new circulatory model, and in particular neutralizes the temporary deleterious effects of the surgical techniques on the cardiopulmonary system. This can be applied selectively in the presence of risk factors, or as a survival alternative when the previous MPAP is ≥ 19 mm Hg, or the intra-operative cavopulmonary gradient-FDVP is elevated. Our group did not habitually practice elective fenestration. In fact, it was elective in only 2 of 27 cases; the remainder were involuntary, with decreased early mortality in this subgroup (7.5%) being judged as more important with respect to those who did not have fenestration (29.8%). Bridges et al showed that, when subgroups with and without fenestration are compared, the latter have a lower early mortality rate, lower cavopulmonary pressures, and also less time with the thoracic drain in place. Other groups have also advised fenestration of children with risk factors, arguing that the decrease in systemic oxygen saturation is compensated by the increase in cardiac output which ultimately actually brings more oxygen to the tissues. Some of these, however, do not detect these differences, and there are published studies that emphasize systemic paradoxical embolisms produced by fenestration. It appears that maintaining a short circuit between the pulmonary venous reservoir and the systemic atrium, therefore, provides a more satisfactory post-operative course with less initial mortality in children with risk factors or with elevated cavopulmonary pressures during surgery.^{11,86-88}

Re-operation

Re-operations have been as frequent as 50% in survivors in older series; in the more recent series, re-operation frequency was not more than 15%, and was greater in children who underwent atriopulmonary surgery vs cavopulmonary surgery. The incidence of re-intervention in our series, in both surgical procedures and catheterizations, is elevated, which is

APPENDIX 1. Variables analyzed

Demographic

Age, years

Weight, kg

Preoperative

Systolic pulmonary artery pressure (SPAP), mm Hg

Median pulmonary artery pressure (MPAP), mm Hg

Arterio-pulmonary resistance (apR), U/m²

Arterial oxygen saturation, %

Ratio of pulmonary/systemic flow

Final diastolic ventricular pressure (FDVP), mm Hg

Ratio of caliber of right pulmonary branch/abdominal aorta

Ratio of caliber of left pulmonary branch/abdominal aorta

Stenosis localized in pulmonary branches*

Atrioventricular valve insufficiency (moderate-severe)*

Ventricular dilatation*

Ventricular function (good/bad)

Principal ventricular anatomic and/or morphologic diagnostic (6 categories)

Other anatomic variables: left atrioventricular (AV); atresia/stenosis; heterotaxia; situs inversus; ventriculoarterial discordance

Previous palliative surgeries (5 categories)

*Categorized yes/no.

APPENDIX 2. Variables analyzedPeri-operative^a

Surgical technique

Cardiopulmonary bypass (CPB) time

Aortic cross-clamping time

Rectal temperature

Post-operative^b

Amount of time in intensive care unit

Amount of time of inotropic/inodilator pharmacological infusion

Amount of time on ventilator

Amount of time thoracic drains in place

Length of hospitalization

Other^c

Cardiac arrhythmia (pre-, peri-, and post-operative)

Pacemaker implant (pre-, peri- and post-operative)

Presence of fenestration post-Fontan

Surgical calendar (1978-1989/1990-2001)

Subaortic stenosis

Re-operations

Protein-loss syndrome

Criteria

^aMinutes; ^bdays; categorized as yes/no.

likely due to the 23-year history of this type of surgery. Figure 9 points shows that only 40% of the children were free of re-interventions. Thirty-five percent of the 95 survivors of the surgery required re-operation; the most frequent cause was hemodynamic (principally, residual short circuit, subaortic stenosis, obstruction or stenosis of the atrial anastomosis, cavopulmonary stenosis, and tricuspid damage), and the second most common cause was arrhythmia (pacemaker implant). In the subgroup of 33 re-

operated patients, late mortality reached 36.3% (12 out of 33), while reaching only 13% (8 of 62) in those who were not re-operated. Therefore, re-operation is a determining mortality factor in our series. We believe that this could be avoided by eliminating where possible the shunts or other palliative procedures prior to a bidirectional Glenn or Fontan surgery, and perfecting a technique that prevents residual lesions or resorting to interventional catheterization.⁸⁹⁻⁹¹

CONCLUSIONS

Surgery to achieve a univentricular circulatory model is palliative and has a questionable quality of longevity. The cavopulmonary technique involves less mortality, but long-term follow-up is too short to differentiate the two. We must find new ways to achieve the Fontan principle or explore other options that improve life expectancy and prognosis in children with univentricular disease. Patient characteristics are the principle determinants of mortality in this study, and therefore we must prepare for this type of surgery in a rigorous manner, preserving the functional reserve of the heart and lungs from the neonatal period on. Choussat was not wrong, and although the limits of what could be called the ideal univentricularization candidate have been amplified, the same criteria still apply. The development of a strict risk index could contribute to more appropriate selection and preparation of patients. Different strategies emerge as key in reducing immediate mortality; among these it is worth mentioning the early use of partial cavopulmonary surgery, reduction or abolition of cardiopulmonary bypass and aortic cross-clamping, performing two-stage Fontan surgery, using fenestration in certain cases and developing a more precise and definitive technique to avoid re-interventions. It remains to be seen whether these proposed safeguards will help reduce early mortality and at the same time result in a more favorable prognosis at 3 or 4 decades follow-up, or on the contrary, result in the reconsideration of other already known partial palliative techniques.⁹²⁻⁹⁸

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NOTE

After this study was finished, we had the late death of 2 adult patients: 1 who underwent the cavopulmonary technique who developed a septic infarct in the anterior descending coronary artery due to bacterial endocarditis, and the other who underwent atriopulmonary surgery and died suddenly in the context of cardiac arrhythmia which required pacemaker implant, ventricular dysfunction, and AV valve insufficiency.

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