Congenital Heart Disease in Adults: Residua, Sequelae, and Complications of Cardiac Defects Repaired at an Early Age

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Nowadays, it is estimated that 85% of the infants born with congenital heart disease (CHD) will survive to adulthood, thanks mainly to surgical or therapeutic procedures performed during infancy or childhood. The clinical profile and disease pattern of adults with CHD is changing. The prevalence of certain adult CHDs, such as tetralogy of Fallot, transposition of the great arteries or univentricular heart, is rising, but these conditions have practically become new diseases as a result of therapy. Most surviving patients present residua, sequelae, or complications, which can progress during adult life. These disorders can present electrophysiological disturbances, valvular disease, persistent shunts, myocardial dysfunction, pulmonary or systemic vascular disease, problems caused by prosthetic materials, infectious complications, thromboembolic events, or extravascular disorders involving multiple organs or systems. In tetralogy of Fallot, the most striking problems that affect long-term prognosis are pulmonary valve regurgitation, right ventricle dysfunction, and atrial or ventricular arrhythmias. The main problems appearing after physiological atrial repair of transposition of the great arteries are related to right ventricular function, since it is structurally unprepared for systemic circulation, and atrial arrhythmias. Surgical repair of univentricular heart using Fontan techniques should be considered a palliative procedure that does not modify the underlying structural disorder and exposes the postoperative patient to severe complications and problems. The increase in the number of patients with CHD who will reach adulthood in the coming decades makes it necessary to carefully consider the new healthcare demands that are being generated, who should be responsible for them, and how and where solutions can be found.

Key words: *Congenital heart disease. Cardiac surgery. Tetralogy of Fallot. Transposition of the great arteries. Univentricular heart.*

Cardiopatías congénitas del adulto: residuos, secuelas y complicaciones de las cardiopatías congénitas operadas en la infancia

Hoy día se estima que el 85% de los niños nacidos con cardiopatías congénitas (CC) sobrevivirá hasta la vida adulta, la mayoría gracias a procedimientos terapéuticos realizados en la infancia. El espectro de CC del adulto se está modificando, y enfermedades como la tetralogía de Fallot, la transposición de grandes vasos o el corazón univentricular están emergiendo como enfermedades prácticamente nuevas, transformadas por los procedimientos terapéuticos. Casi todos los pacientes que sobreviven presentan lesiones residuales, secuelas o complicaciones que pueden tener un carácter evolutivo durante la vida adulta. Estas lesiones se pueden manifestar como alteraciones electrofisiológicas, enfermedad valvular, cortocircuitos persistentes, disfunción miocárdica, lesiones vasculares, problemas derivados de materiales protésicos, complicaciones infecciosas, fenómenos tromboembólicos o alteraciones totalmente extravasculares que afectan a múltiples órganos o sistemas. En la tetralogía de Fallot operada, los problemas de mayor impacto sobre la longevidad se relacionan con insuficiencia de la válvula pulmonar, disfunción del ventrículo derecho y arritmias auriculares o ventriculares. En la transposición de grandes vasos con corrección fisiológica auricular, los problemas más graves se relacionan con la función del ventrículo derecho, que no está estructuralmente preparado para soportar la circulación sistémica, y las arritmias auriculares. La cirugía de Fontan, para la corrección del corazón univentricular, debe considerarse como una técnica paliativa que no modifica la alteración estructural básica y expone al paciente postoperatorio a graves complicaciones y problemas. El incremento del número de CC que llegarán a la edad adulta durante las próximas décadas demanda una cuidadosa consideración sobre qué nuevas necesidades asistenciales se están generando, quién debe responsabilizarse de ellas y cómo y dónde se pueden encontrar soluciones.

Palabras clave: *Cardiopatías congénitas. Cirugía cardíaca. Tetralogía de Fallot. Transposición de grandes vasos. Corazón univentricular.*

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The main intention of this article is to report how the congenital heart diseases (CHD) are increasing progressively in adults and how a new disease is emerging, configured by the residual injuries,

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ABBREVIATIONS

CHD: congenital heart disease.
ASD: atrial septal defect.
VSD: ventricular septal defect.
TF: tetralogy of Fallot.
TGV: transposition of great vessels.
ACHDU: adult congenital heart disease unit.

sequelae, and complications of CHDs treated surgically in childhood. Undoubtedly, the impressive progress of cardiac surgery and advances in pediatric cardiology achieved in recent decades have been responsible for this evolution.[1]

HISTORICAL PERSPECTIVE

From 1938, when Robert Gross, a pediatric surgeon of Boston, performed the first ligation of a ductus arteriosus in a 7 1/2 year old girl,[2] to 1981, when Norwood[3] devised a systematic approach to the surgical correction of aortic atresia, surgical techniques have been designed to correct, or at least palliate, any type of CHD not associated with unviable chromosomal or systemic anomalies (Table 1). The first achievements in this endeavor were made by Clarence Crafoort, who conceived the idea for the surgical correction of aortic coarctation,[4] Alfred Blalock, who performed the first connection of the left subclavian artery to the ipsilateral pulmonary artery in cyanotic patients with pulmonary stenosis or atresia,[5] and Richard Brock, who carried out the first pulmonary valvulotomy using a closed technique.[6] At the beginning of the 1950s, Gibbon perfected a machine for extracorporeal circulation,[7] which made it possible to operate directly on the heart.

The main achievements of the 1950s were the repair of ventricular septal defect (VSD) and tetralogy of Fallot[8] (TF); of the 1960s, atrial physiological correction of transposition of the great vessels[9] (TGV) and the interposition of conduits between the right ventricle and pulmonary artery;[10] and in the 1970s, the techniques of Fontan[11] and Jatene[12] for the reconstruction of single-ventricle heart and TGV, respectively. The progressive improvement in cardiopulmonary bypass techniques, and the use of methods for cerebral[13] and myocardial protection,[14] have made the surgical repair of most CHDs possible at a progressively earlier age, obtaining excellent short and long-term results. The first successful heart transplantation in newborns was carried out at the Loma Linda university medical center in 1985.[15] Since then, many centers in the world have offered this therapeutic alternative for infants with CHD unsuitable for surgical reconstruction or in which surgery has failed.

The initial contribution of pediatric cardiology was the morphological analysis of all the cardiac malformations. A select group of cardiologists and anatomists — notably Van Praagh[16] in the U.S., Anderson[17] in Great Britain, and Quero-Jiménez[18] in Spain — dedicated considerable effort to the sequential analysis, nomenclature, classification, and diagnostic and therapeutic approach to CHD. The second advance was the use of cardiac catheterization and angiocardiography techniques in the pathophysiological and anatomic assessment of CHD.[19,20] In the 1980s, the hemodynamic and morphological assessment of CHD with non-invasive techniques began, and included techniques such as Doppler echocardiography,[21] radionuclide angiography,[22] and magnetic resonance imaging,[23] thus making possible a broad array of therapeutic interventions in the catheterization laboratory. The first intracardiac therapeutic procedure carried out with a catheter was atrial balloon septostomy, which was made by Rashkind in 1966,[24] and eventually led to

Table 1. **Development of cardiac surgery in congenital heart diseases**

Year	Author	Surgical technique
1938	Gross	Ductus arteriosus ligation
1944	Crafoort	Aortic coarctation
1945	Blalock	Subclavian-pulmonary fistula
1948	Brock	Pulmonary valvulotomy
1953	Lillehei	VSD closure
1955	Kirklin	Fallot correction
1964	Mustard	Physiological TGV correction
1967	Rastelli	Prosthetic conduits
1971	Fontan	Atriopulmonary connection
1975	Jatene	Anatomical TGV correction
1981	Norwood	Hypoplastic left ventricle
1985	Fricker	Heart transplantation in children

Table 2. **Therapeutic procedures in congenital heart disease**

Atrial balloon septostomy
Atrial blade septectomy
Embolization of arteriovenous fistulas
Extraction of intravascular foreign bodies
Pulmonary or aortic valvuloplasty
Angioplasty and stenting of a native coarctation or re-coarctation
Angioplasty and stenting of pulmonary arteries
Dilation of caval or pulmonary veins
Angioplasty and stenting of intra-atrial baffles
Occlusor device for ductus arteriosus, ASD, and VSD
Percutaneous pulmonary prosthesis

the development of the present therapeutic arsenal available to pediatric cardiologists[25,26] (Table 2). The latest contribution of pediatric cardiology is prenatal diagnosis with fetal echocardiography[27] that, without doubt, is an extraordinary advance in the knowledge of morphological and functional disturbances of the heart from an early gestational age.

DEMOGRAPHIC IMPACT

The major development experienced by pediatric cardiology and cardiovascular surgery in recent decades has made possible an impressive recovery program for children who once were condemned to die. The demographic impact of this advance has been reviewed in recent publications. In 1992, Moller and Anderson[28] reviewed the present state of 1000 consecutive unselected children with CHD who were initially evaluated between 1952 and 1963. After a follow-up of 26 to 37 years, 285 patients had died, but 712 (71%) remained alive, most of them in an excellent or good clinical situation. In 1993, the findings of a prospective study on the long-term evolution of pulmonary stenosis, aortic stenosis, and VSD were published.[29] After more than 25 years of follow-up, 97% of the patients with pulmonary stenosis,[30] 87% of the patients with aortic stenosis,[31] and 85% of the patients with VSD32 remained alive, most of them with a good or excellent functional assessment. The patients who underwent surgery for uncomplicated atrial septal defect (ASD) in the first two decades of the life had a long-term survival similar to that of the general population.[33] The survival of patients with TF 30 years after surgery is 86%.[34]

Long-term follow-up studies of patients operated for complex heart diseases are less definitive, but in a recent study of 216 patients with tricuspid atresia, corrected with Fontan technique and followed-up for 25 years, the overall survival was 79%.[35] Nowadays, it is estimated that 85% of the children born with CHD survive until adulthood and it is estimated that this percentage will increase even more over the next two decades, due to the continuous improvement in surgical and therapeutic techniques.[36] In industrialized countries with a low birth rate, the number of adults with CHD now equals that of children with cardiac malformations.[37] A conservative estimate of the number of patients with CHD who have survived to adulthood in the U.S. yields the figure of 787 800 cases for the year 2000, of which 117 000 had severe CHD and 302 000 CHD of moderate severity.[38] By extrapolating these findings to the Spanish population, it is estimated that there are more than 100 000 adults with CHD in the country.

In order to attend this increasing demand, in recent years clinical units specialized in adult CHD (ACHDU) have been created in major health centers in the world. Spain, particularly the La Paz University Hospital of Madrid, has participated in this development. This center harbors a very active nucleus of pediatric cardiology and cardiac surgery, which has been functioning for more than 35 years. In this time, thousands of children with CHD have been studied and treated in the children´s hospital and many of them are now adult patients under clinical follow-up in the general hospital. According to mutual agreement between pediatric and adult cardiologists, in 1987 it was decided to unify the clinical follow-up
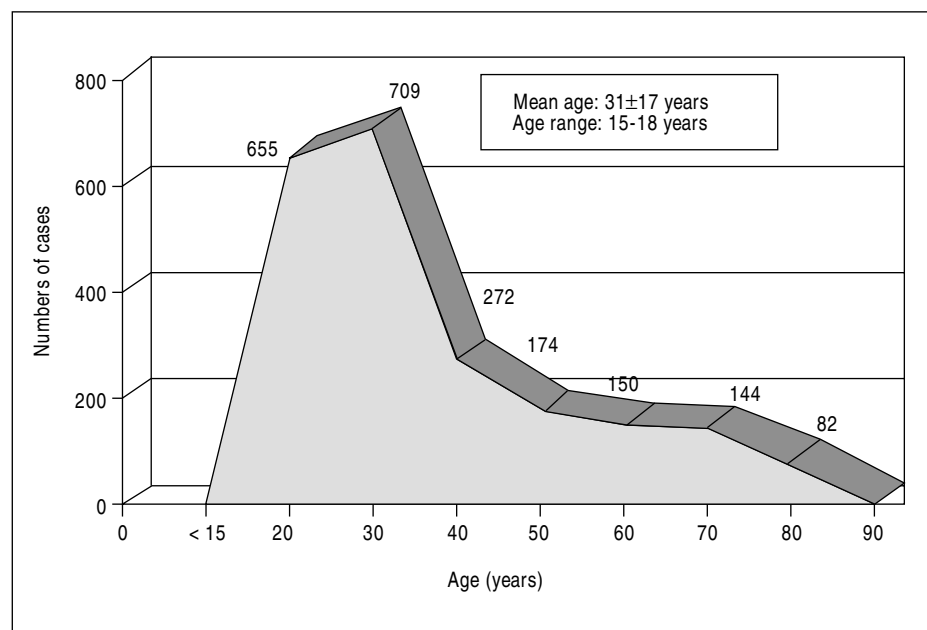

Fig. 1. Distribution by age groups of 2169 patients followed up in the Adult Congenital Heart Disease Unit the La Paz Hospital between 1990 and 2000.
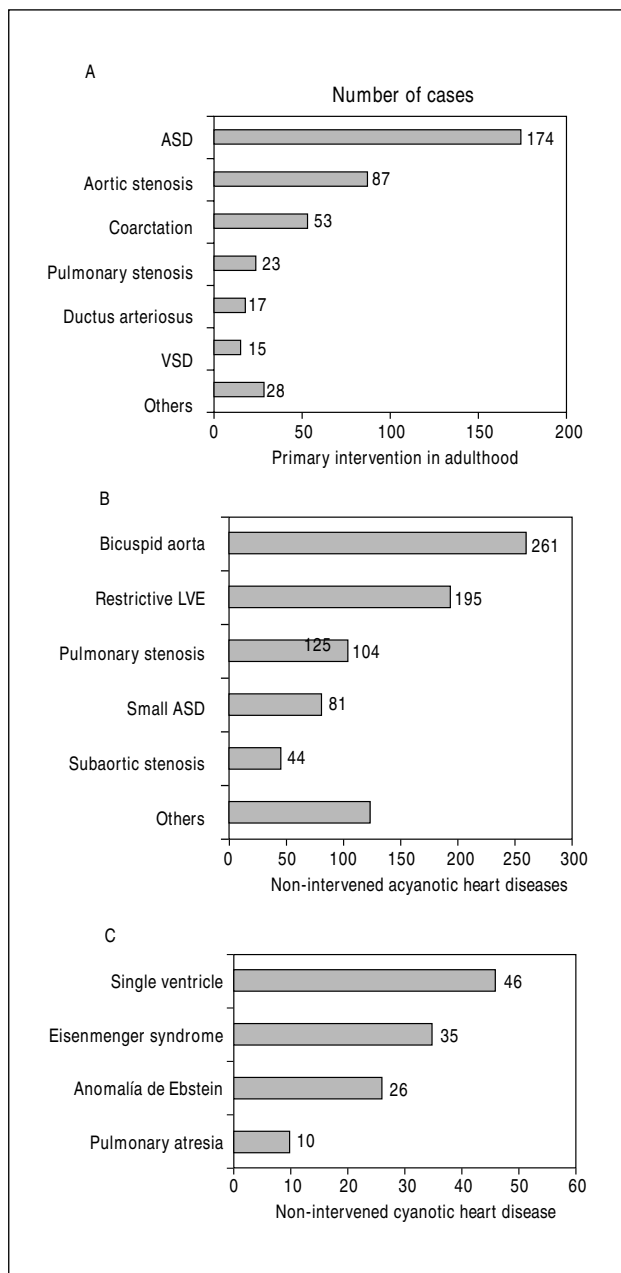
Fig. 2. Main diagnostic groups of congenital heart diseases with natural survival until adulthood. *A)* Heart diseases that require primary intervention during adulthood. *B)* Acyanotic heart diseases that do not require intervention. *C)* Cyanotic heart diseases not intervened.

of these patients in an ACHDU. Between 1990 and 2000, 2169 adults with CHD were cared for in this unit. As can be seen in Figure 1, the number of patients over the age of 40 years who are cared for has remained stable, but there has been an avalanche of new cases in patients between the ages of 15 and 40 years, the majority coming from the children´s hospital. The analysis of this population is the main objective of this article.

CLINICAL FORMS OF SURVIVAL

The population of adult patients with CHD currently includes two large groups: *a)* CHD with natural survival[39] and *b)* CHD with some type of therapeutic intervention[40] (surgery or a percutaneous procedure) carried out in childhood. Cases of CHD with a natural survival until adulthood can be classified in three subgroups:[41]

1. CHDs that require a primary therapeutic intervention in adulthood.
2. CHDs that do not require therapeutic intervention but do need monitoring and continuous clinical follow-up.
3. CHDs that are currently inoperable, can only be treated by transplantation, or in patients in which the surgical risk is greater than the risk of the natural evolution (Table 3).

In Figure 2A are shown the main CHDs of the series of the La Paz Hospital that required a primary intervention during adulthood. Without doubt, ASD continues to be the most frequent disorder in this group, followed by valvular or subvalvular aortic stenosis, and uncomplicated aortic coarctation. Other CHDs, like pulmonary stenosis, ductus arteriosus, and VSD, are now treated surgically in adults with much less frequency. In fact, except for aortic stenosis, which can continue to evolve throughout life, most patients in this group must undergo surgery before reaching adulthood, which is why the number of primary interventions of CHD in older patients is decreasing.

Figure 2b shows acyanotic CHDs that have not required any intervention in our series. This group is numerous and important, and is prominently represented by patients with bicuspid aortic valve, restrictive VSD, and mild pulmonary stenosis. They are asymptomatic patients with mild heart diseases that do not require treatment but are exposed to serious complications, such as infectious endocarditis or progressive valve degeneration (stenosis or insufficiency).

In Figure 2c are shown the cyanotic CHDs in our series that have a natural survival until adulthood. In this group, Eisenmenger syndrome, single-ventricle heart, Ebstein anomaly, and pulmonary atresia with VSD are noteworthy. These patients are symptomatic

TABLE 3. **Classification of adult congenital heart diseases**

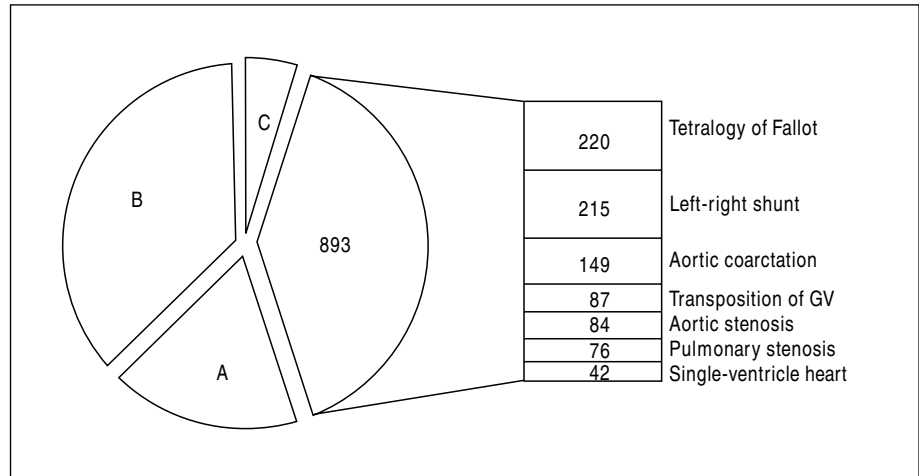| Natural survival	Operation in adulthood
	Follow-up without surgery
	Inoperable except for organ transplantation
Operation in childhood	

Fig. 3. Main diagnostic groups of 893 adult patients with congenital heart disease who underwent surgery in childhood. A, B, and C refer to the groups in Figure 2.

220	Tetralogy of Fallot
215	Left-right shunt
149	Aortic coarctation
87	Transposition of GV
84	Aortic stenosis
76	Pulmonary stenosis
42	Single-ventricle heart

and have serious heart diseases, but cannot be undergo surgery with a reasonable risk. In some cases, cardiopulmonary transplantation, or isolated pulmonary transplantation with correction of the cardiac anomaly are the only possible options, but the risks of these therapeutic alternatives are almost always higher than those of the natural evolution.[42] These patients can present serious complications: hemorrhage (profuse hemoptysis), infection (endocarditis, cerebral abscess), arrhythmia (atrial flutter or fibrillation), or thromboembolism. However, these patients generally remain relatively stable, with intolerance to effort, frequent symptoms of hyperviscosity, but few signs of cardiac insufficiency. In our experience, most complications occur during pregnancy, intercurrent disease, surgical interventions, impaired hydration, excessive exercise, or medical interventions. These patients need strict cardiological control to prevent high-risk situations and ensure that immediate treatment will be provided if complications arise: embolization of bleeding vessels, surgical drainage of cerebral abscesses, arrhythmia ablation, and others.

CHANGES IN THE SPECTRUM OF CONGENITAL HEART DISEASE IN ADULTS

Currently, the most numerous group of patients with CHD who reach adulthood is formed by patients who have undergone some type of therapeutic intervention during childhood. This fact is greatly changing the spectrum of CHDs that cardiologists see in adults, which underlines that cardiologists should be prepared to recognize this new disease. In the series of La Paz Hospital, 56% of adults under the age of 40 years pertained to this group. In Figure 3 are shown the main CHDs treated surgically in childhood in our series. Without doubt, the most frequent CHD in this

group is TF. This disease had disappeared almost completely from general cardiology clinics and now has reappeared with a much greater prevalence, but in the form of a postoperative disease. We are also observing the appearance in our clinics of diseases that are practically unknown to us, like TGV. Complete transposition is an unviable CHD outside the first months of life and must be repaired by surgery. Nevertheless, most children with this malformation now reach adult life, although in a state modified by different surgical techniques. Patients with an anatomically or functionally unique heart constitute another large group of patients that are seen in our clinic. Most of them arrive after undergoing surgical palliation or partial correction, which enables survival but does not modify the basic structural disturbance and adds structural changes introduced by surgery.

In spite of the previous intervention, the patients in this group rarely reach adulthood with a fully normal anatomy, physiology, and cardiovascular function. Few therapeutic interventions are totally curative. The ligation of a ductus arteriosus, closure of an ostium secundum type ASD at an early age, or closure of a VSD by transatrial approach can be totally curative. In most cases, surgical or interventional procedures are only reparative and in other cases are just palliative in nature. This means that almost all patients with CHD who were operated during childhood present residual injuries, sequelae, or complications that can have a progressive character during adulthood.

RESIDUA, SEQUELAE, AND COMPLICATIONS

Table 4 offers a classification of residual lesions, sequelae, and complications of CHD in adults, modified from the Perlof and Warnes classification.[43] These injuries can manifest as electrophysiological disturbances, valve disease, persistent shunting,

Table 4. **Classification of the residual lesions, sequelae, and complications of congenital heart disease**

Electrophysiological disturbances	Permanent electrophysiological changes Arrhythmias and conduction defects
Cardiac valve disease	Intrinsic valve malformation Sequelae of previous interventions Hemodynamic effects on normal valves
Persistent shunts	Uncorrected residual lesions Sequelae of therapeutic procedures
Myocardial dysfunction	Structural disturbances Hypertrophy and remodeling Perioperative ischemia
Vascular disorders	Congenital or acquired stenoses Pulmonary or systemic hypertension Aneurysm, dissection or rupture
Prosthetic materials	Patches, valves, or conduits
Infectious complications	Cardiac valves or mural endocardium Arterial vessels or fistulas Extravascular structures (cerebral abscess)
Thromboembolic phenomena	Intravascular thrombosis Pulmonary or systemic thromboembolism
Extravascular disturbances	Mental and physical development Sense organs Osteomuscular structure Central nervous system Teeth Other organs and systems

myocardial dysfunction, vascular lesions of the pulmonary or peripheral system, problems derived from prosthetic materials, infectious complications, thromboembolic phenomena, or extravascular disturbances that affect multiple organs and systems. In general, these problems can be caused by intrinsic malformations, the effects of therapeutic procedures, secondary hemodynamic changes, or unexpected complications. Residual lesions are anomalies that are deliberately left uncorrected during surgical repair. Examples of residual lesions are a restrictive VSD associated with a repaired aortic coarctation, or mitral insufficiency due to a cleft anterior leaflet that was not repaired during the surgical closure of an ostium primum type ASD. Neurological or systemic abnormalities that remain after the intervention are also residual lesions. Sequelae are new cardiovascular disturbances that occur as a necessary consequence of repair. Pulmonary failure secondary to the surgical correction of TF with a transannular patch, or persistent electrophysiological anomalies after right ventriculotomy are common examples. In contrast,

complications are undesired cardiovascular or systemic disturbances that may be related to therapeutic procedures or appear spontaneously in the course of the natural evolution. Postoperative AV block, myocardial dysfunction due to insufficient protection of the cardiac muscle during ischemia, or the consequences of infectious endocarditis are complications that can have a major impact on survival and morbidity in adulthood. This review does not allow an exhaustive analysis of the residual lesions, sequelae, and complications of CHDs operated in childhood.[44] However, in the following sections we will review the main residual disorders and the most frequent complications of patients with TF, TGV, and single-ventricle heart, three CHDs that have emerged in the context of adult heart disease as modified conditions that manifest as practically new diseases.

TETRALOGY OF FALLOT

TF is the most frequent cyanotic CHD in children.[45] Fewer and fewer patients with this CHD reach adulthood by natural survival, but a growing number of adults have TF in postoperative follow-up. The estimated survival rate 30 years after surgery is 86%.[34] Surgical correction consists of VSD closure and enlargement of the right ventricular outflow tract. For this reason, the surgeon often must use a transannular patch that can reach the pulmonary bifurcation and, sometimes, a prosthetic conduit between the right ventricle and pulmonary artery. It is not uncommon that the pulmonary branches have to be enlarged if there is congenital stenosis or stenosis induced by previous surgical fistulas.

Obstruction of the outflow tract

When they reach adulthood, most patients maintain an effective correction. In more than 60% of our series, the systolic pressure of the right ventricle is less than 50 mm Hg and there is no significant residual gradient, although 10% to 15% present moderate or severe obstruction of the outflow tract with a right ventricular systolic pressure that is more 70% greater than systemic pressure.[44] The obstruction can be subvalvular, valvular, or supravalvular, although it is most frequently located in the branches of the pulmonary artery. This raises serious diagnostic problems in adults because the pulmonary branches are poorly evaluated by conventional or transesophageal Doppler echocardiography. Nevertheless, vascular magnetic resonance imaging is a high-resolution non-invasive technique for the anatomic assessment of the main pulmonary branches (Figure 4). The surgical treatment of stenosis of the pulmonary branches also

Fig. 4. Three-dimensional reconstruction of the vascular magnetic resonance imaging of the pulmonary artery in the anteroposterior (left) and lateral (right) views of a patient with tetralogy of Fallot treated with a transannular patch to the pulmonary bifurcation. It can be seen that the left pulmonary branch is straddling and there are stenoses at the distal insertion of the patch and right pulmonary branch.
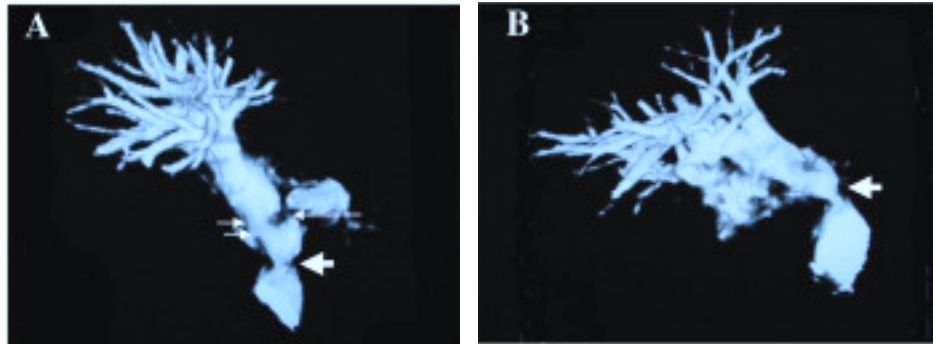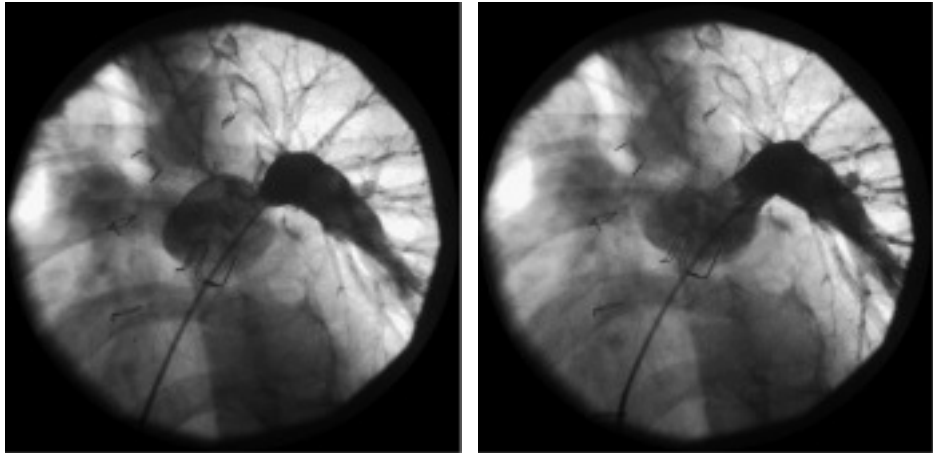

Fig. 5. Angiography of the left pulmonary artery in a patient with operated tetralogy of Fallot and a pulmonary prosthesis. The stenosis of the left pulmonary branch before (left) and after (right) insertion of an intravascular stent.

has serious difficulties, but percutaneous procedures using stents are very effective[46,47] (Figure 5). In patients who have undergone correction with a conduit or valve prosthesis, restenosis is the rule and many patients need to be reoperated several time in the course of their lives. Dilation with stent placement[48] and later percutaneous implantation of a valve prosthesis is a new procedure that shows great promise in these patients.[49]

Persistent shunts

Residual shunts are not infrequent. Thirty percent of the patients in our series have a persistent shunt, in most cases small and of scant clinical importance.[44] The most frequent location is the interventricular patch, although some patients have an extracardiac shunt related with surgical fistulas or unligated aortopulmonary collateral vessels. Some of our patients have a permeable foramen ovale or an ASD not closed in the correction. This has been cause of paradoxical embolism in some cases, which could have been avoided if more attention had been given to the interatrial septum during surgery. Most residual interatrial or aortopulmonary shunts can be treated with percutaneous procedures.

Valvular and myocardial dysfunction

Some adult patients with operated TF develop progressive aortic insufficiency. Dilation of the aortic root, lack of support due to a septal defect, and valvular deformation resulting from retraction of the surgical patch are the main causes.[50] Eight patients in our series were operated on as adults for severe aortic insufficiency. Nevertheless, the most frequent valve problem in patients who have undergone surgery for TF is pulmonary valve insufficiency. Approximately half of the patients in our series had grade III-IV pulmonary valve insufficiency due to the use of transannular patches to enlarge the ring, which leave the valve completely incompetent. Pulmonary insufficiency is practically a new disease, which is almost unknown as a natural disease. At present we are learning to recognize and assess it.[51-53] We know that it is clinically well tolerated during decades, but it causes progressive expansion of the right ventricle. When the ventricular dilation is excessive, the increased postload limits cardiac output with exercise and the functional capacity decreases. With time, ventricular function deteriorates and the patient characteristically presents a hypotensive response to effort and a greater functional limitation.[54,55] Right

ventricular dilation and dysfunction causes insufficiency of the tricuspid valve and increased pressure in the right atrium and caval veins. In the terminal stages, signs and symptoms of right heart failure appear.[34]

Arrhythmias and sudden death

Adults with operated TF experience frequent episodes of ventricular tachycardia or atrial tachyarrhythmia (flutter or fibrillation). These arrhythmias sometimes induce syncope or sudden death. A linear incidence of sudden death of 0.4% annually during the first 25 years after the intervention has been estimated, and the incidence grows exponentially from the first 25 years on.[56] The arrhythmia substrate may be related to surgical scars, although the dilation of the right ventricle and atrium induced by the pulmonary and tricuspid insufficiency acts as a trigger factor.[57] It has recently been confirmed that the patients with the greatest risk of atrial and ventricular arrhythmias, including sudden death, are those that have severe pulmonary and/or tricuspid insufficiency and develop a marked cardiomegaly, progressive widening of the QRS complex, and an increase in the dispersion of the QT interval.[58,59] A cardiothoracic index >60%, QRS duration >180 ms and QT dispersion >60 ms are markers of risk that are easy to obtain at the bedside of the patient.[60]

Reintervention in adulthood

Very recent findings suggest that surgical reintervention to correct pulmonary insufficiency with a valvular prosthesis and tricuspid insufficiency by annuloplasty decreases the incidence of atrial and ventricular arrhythmias, especially if surgical repair is accompanied by ablation of the reentry circuit.[61] Unfortunately, we do not yet have trustworthy clinical markers to determine which asymptomatic or minimally symptomatic patients can benefit from early reintervention, but the general impression is that the intervention is usually too late.[62] In most cases, the dilation and systolic dysfunction of the right ventricle do not remit after surgery. In the same way that we know the limits of ventricular size that allow functional normalization in the postoperative period of aortic and mitral insufficiency, we need to know what clinical and echocardiographic data are related to the normalization of right ventricular function after surgery.

Transposition of great vessels

TGV is the most frequent cyanotic heart disease at birth, but natural survival to an adult age is exceptional. This malformation represents 5%-8% of all CHD,[63] but when left to their natural evolution, 30% of the patients die in the first week of life, 50% in the first month, 70% in the first 6 months of life, and 90% in the first year.[64] Only one patient in our series has survived to adulthood without any type of intervention.[65] Atrial septostomy with the Rashkind technique and atrial physiological correction with the Senning or Mustard techniques have radically changed the life expectancy of these patients. In the last decade, anatomical correction (arterial switch) is being used with increasing frequency, although its impact on long-term survival remains to be seen.

Dysfunction of the systemic right ventricle

Patients with TGV have a special anatomic situation in which the right ventricle is connected to the aorta and must bear systemic circulation. The use of the Mustard and Senning techniques for atrial physiological repair over a period of more than 20 years means that many patients have a right ventricle that is surgically connected to the aorta. In the postoperative follow-up, a large number of patients present systolic dysfunction of the right ventricle at rest or after physical exercise.[66,67] As adults life, most of them are clinically well, but have a reduced capacity for effort.[68] Some develop chronic heart failure and the proportion of patients with this complication increases with time. The cause of postoperative right ventricular dysfunction is multifactorial.[69] The factors that may contribute are: *a)* inability of the right ventricle to adapt to its new function as the pump for systemic circulation; *b)* coronary circulation maintained by a right coronary artery that must supply all the blood flow to the systemic ventricle; *c)* myocardial damage produced by sustained severe hypoxia before surgery, and *d)* perioperative damage induced by insufficient myocardial protection.

Cardiac rhythm disorders

The high frequency of postoperative arrhythmias after atrial physiological correction is, along with myocardial dysfunction, one of the main reasons why this intervention is being replaced by arterial switch (Jatene) in many centers. The incidence of significant arrhythmias increases progressively with the time since the intervention. It has been estimated that the probability of maintaining a normal sinusal rhythm is 72% at 1 year of the Mustard operation, 56% at 5 years, and 43% at 13 years.[70] The most frequent rhythm disorders are symptomatic sinus bradycardia, slow nodal rhythms, and paroxysmal or sustained supraventricular tachycardia, principally atrial flutter. The cause lies in the lesion of the sinus
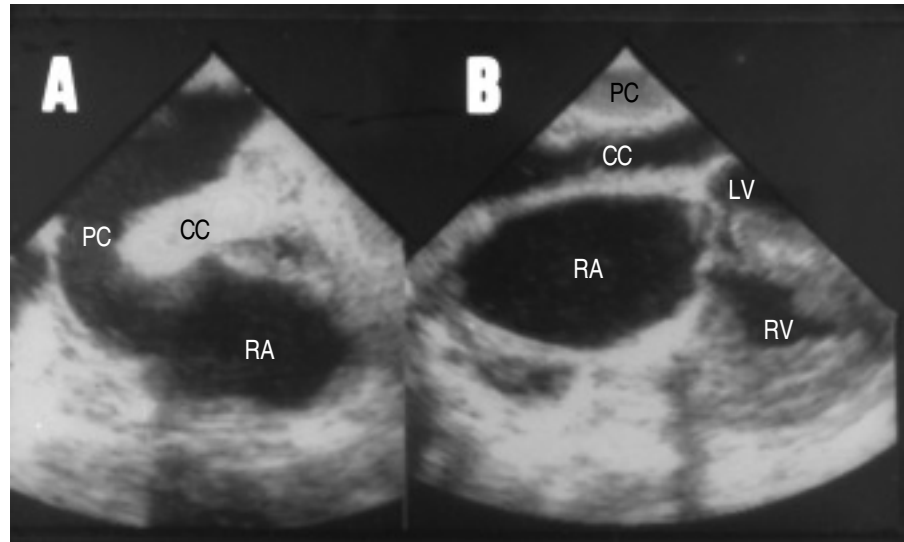
Fig. 6. Transesophageal echocardiogram in a patient with transposition of the great vessels corrected with the Senning technique. *A)* Pulmonary canal (PC) that connects the pulmonary veins to the right atrium (RA) and right ventricle (RV). *B)* Canal of the cavas (CC) which connects both cavas to the left atrium and left ventricle (LV).

node during surgery and the atrial scars that interrupt the preferred internodal conduction pathways, which form the substrate for reentry circuits.[71] The current indications for a permanent pacemaker in patients with TGV are complete AV block, sustained heart rates of less than 30 beats/min, documented Stokes-Adams episodes, severe ventricular systolic dysfunction with bradycardia, and the need to begin treatment with antiarrhythmic drugs that depress sinus function even more. In patients with recurrent atrial flutter, ablation of the arrhythmia may be indicated, although this procedure involves difficulties because the circuit it is located in the pulmonary venous canal in most cases, which makes a retrograde arterial approach mandatory.

Dehiscence and obstruction by baffles

These are the two most frequent mechanical complications that appear after atrial physiological correction with the Mustard or Senning technique. The obstruction can be early, due to an unsuitable reconstruction geometry, but it may also be late, due to retraction and calcification of the baffles and scars on the atrial wall. Dehiscence and baffle obstruction are usually located distal to the inflow tract of the superior vena cava.[72] In small children, these defects can be easily diagnosed by color Doppler echocardiography,[73,74] but in the postoperative adult patient, multiplane transesophageal echocardiography provides more diagnostic information (Figure 6). Obstruction of the inferior vena cava is, fortunately, less frequent, but it can induce Budd-Chiari syndrome, congestive liver disease, and protein-losing enteropathy.[75] Baffle stenosis can be corrected by balloon dilation[76,77] or an intravascular stent.[78,79]

Valvular dysfunction

Insufficiency of the tricuspid valve, which is located on the systemic ventricle, can appear after surgical atrial correction, but it is infrequent in the absence of severe right ventricular dysfunction. This complication is more prevalent in patients with a large VSD that has been closed with a septal patch.[80] Surgical reconstruction with conservative techniques or prosthetic substitution of the valve has yielded relatively unsatisfactory results.[81] Some patients present stenosis of the left ventricular outflow tract of subvalvular location. The obstruction can be anatomic and permanent, due to a membrane or subpulmonary ridge, or functional and dynamic, due to inversion of the curvature of the ventricular septum and the anterior systolic movement of the mitral valve.

Arterial correction

Arterial correction with the Jatene technique is replacing atrial correction in most hospital centers.[82] It can be performed with a relatively low mortality in centers with experience and the intermediate-term results of the patients who survive are excellent.[83,84] The most frequent complication is pulmonary supravalvular stenosis,[85] followed by the less frequent aortic supravalvular stenosis. One reason for long-term concern is the disproportional expansion of the anatomic pulmonary root (aortic neoroot) that some patients have.[86] This dilation can induce annulectasia and, in fact, the incidence of postoperative aortic

insufficiency is too high. However, the main reason for long-term concern after arterial switching is the state of coronary circulation. The transfer of the coronary arteries to the aortic neoroot is a delicate process that must be carried out with extreme care in order to avoid causing immediate catastrophes. However, a relatively high incidence of stenosis or occlusion of main coronary arteries has been detected even in patients who survive the intervention with no apparent perioperative complications.[87-89] The prevalence of sudden death years after surgery is not unappreciable.[90]

SINGLE-VENTRICLE HEART

In Table 5 is shown a list of the main CHDs that do not allow surgical reconstruction while maintaining a normal biventricular physiology. These are generally serious and complex CHDs with scant natural survival to adulthood and cardiologists for adults are not very familiar with them. The pediatric cardiologist sees them as a group of very heterogeneous problems that require an individualized diagnostic analysis and therapeutic approach. Cardiologists who treat adults must approach them as if they were a homogeneous disease. This way, all their anatomic complexity can be simplified by considering them as a single anatomic or functional ventricle. What matters most to cardiologists for adults is whether survival is spontaneous or previous interventions have been carried out in childhood.

From Glenn to Fontan

In 1958, Glenn established the therapeutic basis for eliminating the right side of the heart from the pulmonary circuit as an alternative to systemic-pulmonary fistulas.[91] Glenn´s original intervention consisted of end-to-end anastomosis between the superior vena cava and right pulmonary artery. The technique did not have much initial acceptance due to fear that the venous flow was not sufficient to keep the pulmonary artery permeable, but the long-term clinical

TABLE 5. **Congenital heart diseases that preclude biventricular reconstruction**

Anatomic single ventricle
Tricuspid atresia
Pulmonary atresia with hypoplastic right ventricle
Large or multiple ventricular septal defects
AV valve straddling
Mitral atresia or hypoplasia
AV canal with unbalanced ventricles
Extreme Ebstein anomaly
Syndrome of hypoplastic left heart

experience in many patients has been excellent.[92] The Glenn operation acquired new interest when, in 1971, Fontan and Baudet described a palliative technique for the surgical treatment of tricuspid atresia.[11] The Fontan technique completed the Glenn technique by carrying out a direct connection between the right atrium and pulmonary trunk or the rudimentary right ventricle.

It was soon observed that some of the pathophysiological hypotheses on which the Fontan technique rested were not correct and many technical aspects were modified.[93] The first to disappear were the valvular prostheses at the inlet of the inferior vena cava and atriopulmonary connection. The second concept to be revised was that bloodflow from the lower half of the body (60% of the total) went to the left lung, which is smaller (40% of capacity). This motivated a revision of the Glenn technique, maintaining the central connection of the two pulmonary arteries (bidirectional Glenn).[94] The third concept to be revised was the role of the right atrium as a hydraulic pump. In fact, the contractile function of the distended right atrium ceases at high pressures, which increases the reservoir effect, blood stasis, and atrial arrhythmias. These deleterious effects can be avoided by directly connecting the inferior vena cava to the pulmonary artery by means of an intra-atrial conduit (lateral tunnel) or a completely extracardiac conduit.[95,96] The last concept to be revised was that of watertight compartmentation of the new cavopulmonary circuit. In order to avoid the adverse effects of a sharp rise in venous pressure, partial fenestration of the Fontan technique is used, leaving a transitory residual ASD that allows excess atrial pressure to be relieved in the immediate postoperative period.[97]

Expansion of the Fontan technique

In initial experiences with the Fontan technique, the selection criteria for patients were very strict and are included in the famous decalogue of Choussat et al.[98] In the 1980s, the selection criteria were expanded. The intervention was carried out not only in patients with tricuspid atresia, but also in those with different forms of single ventricle and other complex congenital heart diseases.[99] Age limits were lowered, cardiac rhythm ceased to be a limiting factor, and anatomical and functional criteria became laxer.[100] The result was a wave of moderate optimism which led to the operation of many patients with these techniques. In the 1990s, this optimism was replaced by a more realistic view. Fontan[101] himself has clearly established that, even under the «perfect» conditions of a Fontan without sequelae, there is a progressive decrease in functional capacity and survival that cannot be attributed to anything except the circulatory status of the correction per se. Although longer-term results are still not

available, 5 to 15-year follow-up studies have demonstrated that the 10-year survival is only 60%. In this time, almost one-third of the survivors have had to be reoperated, 20% present cardiac arrhythmias that require antiarrhythmic medication or pacemakers, and 7-10% have hypoproteinemia due to protein-losing enteropathy. At 5 years of the operation, more than one-third have died or have a worse functional state than before surgery.[102]

Obstruction and thrombosis

In Table 6, the main complications of long-term Fontan circulation are described. The atrial or cavopulmonary connections may become obstructed by stenosis or kinking of the pulmonary arteries, retraction of suture lines, intrinsic degeneration of valvular prostheses, neointimal proliferation of conduits, calcification and the rigidity of prosthetic materials, or intraluminal thrombosis. The system created by Fontan surgery is very sensitive to stasis phenomena because venous flow is slow, and thromboembolic complications are common (Figure 7). The high incidence of thrombosis found in some series suggests that most adult patients should receive permanent anticoagulant treatment if no specific contraindications are present.[103] Another long-term complication is the obstruction of the left ventricular outflow tract. Obstruction generally takes place in the VSD or bulboventricular foramen (Figure 8). The subaortic obstruction can be interpreted as a process of myocardial remodeling that occurs in response to changes in ventricular geometry induced by the reduction of the volumetric overload that transforms eccentric hypertrophy into concentric hypertrophy.[104] An infrequent mechanical complication with very somber consequences is obstruction of the drainage of pulmonary veins, which can be partially occluded as a consequence of morphological changes in the right atrium after surgery.[105]

Fig. 7. Transesophageal echocardiogram in a patient with a single-ventricle heart corrected with the Fontan technique. The atriopulmonary connection (large arrow) and a large mural thrombus in the wall of the right atrium (small arrows) are evident. RA indicates right atrium; LA: left atrium.

Persistent shunts and valvular insufficiency

After Fontan surgery, many patients have persistent shunts. These shunts can be produced by dehiscence of patches or lines of suture, neoformation of venous collaterals, distal aortopulmonary anastomoses, or the development of pulmonary arteriovenous fistulas. In some patients with an operated single ventricle, AV valve insufficiency can appear. The insufficiency can appear in very late phases of evolution and may have a progressive nature.[106]

Atrial arrhythmias and congestive heart failure

Atrial arrhythmias, especially atrial flutter and tachycardia due to macroreentry, are frequent after the Fontan procedure, associated with sudden death, and potentially refractory to all types of treatment, including drugs, antitachycardia pacing, and radiofrequency ablation.[107] The prevalence of atrial arrhythmias in the follow-up of adults with Fontan physiology varies from 40% to 60% in different studies.[108,109] Patients with atrial arrhythmia have a greater incidence of heart failure, atrial thrombosis, reoperation for conduit obstruction, AV valve incompetence, and ventricular dysfunction.[110] Many patients with tricuspid atresia and single ventricle have ventricular dysfunction before surgery.[111] Unfortunately, the Fontan intervention does not improve myocardial function in many cases, particularly when the operation is performed in patients over 10 years old.[112]

TABLE 6. **Complications of the Fontan operation**

Anatomic complications
    Obstruction or stenosis of connections
    Atrial thrombosis and thromboembolic phenomena
    Persistent or neoformed shunts
    Pulmonary vein obstruction
    AV valve insufficiency
    Subaortic stenosis

Symptomatic arrhythmias
    Atrial flutter or fibrillation
    Incisional tachycardia
    Ventricular tachycardia
      Ventricular dysfunction
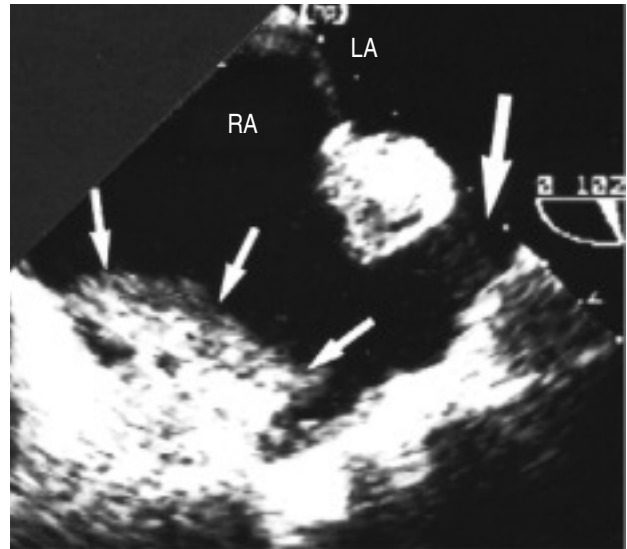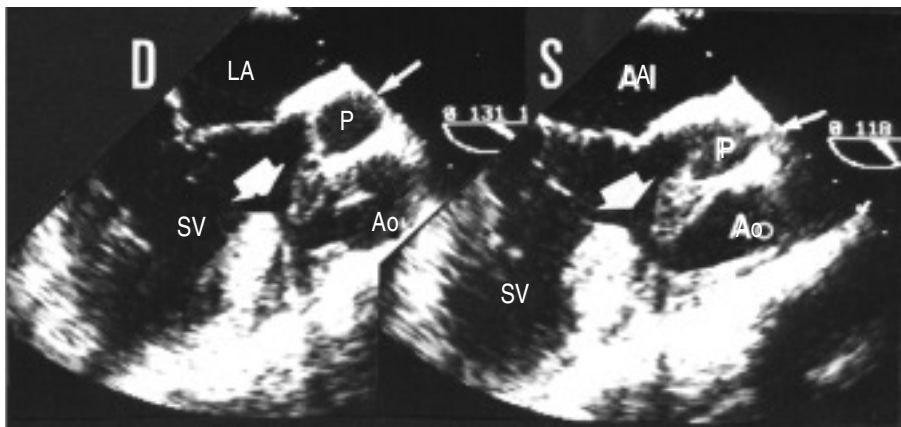   Congestive heart failure
      Protein-losing enteropathy

Fig. 8. Transesophageal echocardiogram in a patient with a single ventricle heart corrected with the Fontan technique. A localized subaortic stenosis can be observed in the bulboventricular foramen (wide arrow). LA indicates left atrium; Ao, aorta; D, diastole; P, pulmonary; S, systole; AV,

Protein-losing enteropathy

One of the worst long-term consequences of the Fontan operation is protein-losing enteropathy, which produces refractory ascites, generalized edema, and massive pleural effusion. The syndrome is infrequent in the first months or years after the operation, but its incidence increases with time.[113] The clinical condition is similar to nephrotic syndrome and, like this condition, is produced by severe hypoalbuminemia. The cause of hypoalbuminemia is a chronic loss of proteins by the digestive system induced by the excessive and persistent increase in the venous pressure of the lower cava and portal system, with secondary lymphangiectasia. The diagnosis is based on the clinical condition, hypoalbuminemia, and the demonstration of increased elimination of α1-antitripsin in stool. The inhibitors of angiotensin-converting enzyme can be effective, but it is sometimes necessary to remove the Fontan connection or induce ASD to relieve central venous pressure.[114] A chance observation has suggested that heparin treatment can be effective in improving hypoalbuminemia and the water-salt retention syndrome.[115]

Revision of the Fontan operation

In patients with symptomatic atrial arrhythmias or severe protein-losing enteropathy that does not respond to medical treatment, revision of the Fontan intervention in adult life can be necessary. If stenosis exists in the connections, prosthetic materials, or pulmonary arteries, surgical reconstruction with enlargement of the obstructive areas may be sufficient. Patients with obstruction of the pulmonary veins or refractory atrial arrhythmias can benefit from complete atrial exclusion with an extracardiac Fontan or lateral tunnel.[116,117] The subaortic obstruction can be corrected by muscular resection or a connection between the proximal pulmonary artery and ascending aorta. If the cause is myocardial dysfunction, the therapeutic alternatives are scant, but the clinical situation of some patients can be improved by undoing the Fontan modifications.[118] Patients in an advanced functional class with no reasonable possibility for surgical reconstruction can still look to heart transplantation as an alternative solution.[119]

NEEDS OF ADULTS WITH CONGENITAL HEART DISEASE

The large increment in the number of patients with CHD who will reach adulthood in the coming decades demands careful consideration of the new needs for care that are being generated, who will be responsible for providing care, and where it will be carried out. The physiology of many previously repaired or palliated CHDs can be difficult to understand for cardiologists without special training in pediatric cardiology. On the other hand, most of the medical problems of adults are beyond the training of pediatric cardiologists. The placement of these patients in wards, outpatient clinics, or examination rooms is also complicated. A pediatric setting is unsuitable for the continued care of older adults, but most cardiology departments are unprepared to handle such patients. The traditional barrier between pediatrics and general practice must disappear because teams are needed in which pediatric cardiologists and heart surgeons work hand in hand with cardiologists and heart surgeons specialized in adult patients. Adult congenital heart disease units (ACHDU) have been created in Europe and North America for this purpose.[120] These units have been created to address a specific need, but it is now evident that their growth and development must be planned.[121]

Each ACHDU should be formed by at least one cardiology specialist and an expert in CHDs, generally from pediatric cardiology, but heart surgeons expert in pediatric and adult problems must also participate, as

well as anesthetists with training and experience in both fields.[121] Invasive (catheterization, electrophysiology) and non-invasive studies (echocardiography, stress techniques, dynamic electrocardiography, radionuclide medicine, magnetic resonance imaging) must be performed preferentially in adult units by specialists who are experts in CHDs. Hospitalization and outpatient care are best handled in hospitals for adults, but care by personnel who are experienced in the assessment and treatment of CHDs must be guaranteed. The ACHDU should also have access to a clinic for high risk pregnancies, a cardiac rehabilitation unit with special knowledge of congenital problems, a psychiatry or support psychology unit for adolescents, and a social services unit with special interest in the social and occupational problems of disabled young people. A fluid relation with the areas of clinical genetics (genetic counseling), hematology (blood dyscrasias), neurology (neurological syndromes), traumatology (skeletal malformations), and other specialized areas is important. The ACHDU must be structured in the setting of a tertiary teaching hospital and must have a close relation with one or more pediatric cardiology departments, which supply the patients and must be considered a natural and complementary extension. Ideally, each ACHDU should also be related with a heart transplantation unit with special experience in patients with CHDs.[122] The American Heart Association has defined the need for ACHDU as one unit per 5-10 million inhabitants. For this reason, in Spain it would be necessary to plan for the development of no more than 4-8 units of this type.[121]

Not all specialized care for adults with CHD can and should be provided in the ACHDU. In these units, only patients with complex heart diseases or serious complications should be followed up. The responsibility for most care inevitably lies with clinical cardiologists who have little training in CHDs. It has been estimated that 45% of adults with CHD do not need routine follow-up in a specialized unit. For another 30%, the responsibility for care must be shared between the specialized unit and clinical cardiologist.[123] Ideally, each adult patient with CHD would have to be examined at least once in an ACHDU and returned to the community if a highly specialized follow-up is not necessary. It is important that there be direct communication between the extrahospital cardiologist and ACHDU, both for referral of patients and to consult on specific problems. Each clinical cardiologist should know the referral center. The referral center, with the support of institutions, should develop programs for continuing education to facilitate the work of cardiology specialists who have not had access to specific training.

Institutions must also reconsider the training of

ACHDU cardiology experts. Experts may come from the pediatric setting (pediatric cardiologists) or adult setting (clinical cardiologists), but in both cases they need additional training. The 23rd Conference of Bethesda has classified this additional training into three levels.[124] Level 1 is acquired by means of accredited courses on the special problems of adults with CHD. It should be part of the training of all residents in cardiology and pediatric cardiology and extend to all clinical cardiologists in the community. Level 2 is acquired by a year of full-time post-residence in an ACHDU and level 3, by two years of continuous work in an ACHDU. Whether similar levels of training will be required in Spain is something that the Sociedad Española de Cardiología (Spanish Society of Cardiology) and healthcare and educational institutions will have to consider.

ACKNOWLEDGMENTS

REFERENCES

1. Emmanouilides GC. The development of pediatric cardiology: Historical milestones. En: Moss A, editor. Heart disease in infants, children, and adolescents. Baltimore: Williams Wilkins, 1995; p. 21-24.
2. Gross RE, Hubbard JP. Surgical ligation of a patent ductus arteriosus: report of first successful case. JAMA 1939;112:729-31.
3. Norwood WI, Lang P, Castaneda AR, Campbell DN. Experience with operations for hyoplastic left heart syndrome. J Thorac Cardiovasc Surg 1981;81:239-44.
4. Crafoord C, Nylin G. Congenital coarctation of the aorta and its surgical treatment. J Thorac Surg 1945;14:347-61.
5. Blalock A, Taussig HB. Surgical treatment of malformations of the heart in which there is pulmonary stenosis or pulmonary atresia. JAMA 1945;128:189-202.
6. Brock RC. Pulmonary Valvulotomy for the relief of congenital pulmonary stenosis. BMJ 1948;i:1121.
7. Kirklin JW, DuShane JW, Patrick RT, Donald DE, Hetzel PS, Harshbarger HG, et al. Intracardiac surgery with the aid of a mechanical pump-oxigenator system (Gibbon-type): report of eight cases. Proc Staff Meet Mayo Clin 1955;30:201-6.
8. Kirklin JW, Payne WS, Theye RA, DuShane JW. Factors affecting survival after open operation for tetralogy of Fallot. Ann Surg 1960;152:485.
9. Mustard WT. Successful two-stage correction of transposition of the great vessels. Surgery 1964;55:469-72.
10. Rastelli GC, Titus JL, McGoon DC. Homograft of ascending aorta and aortic valve as a right ventricular outflow: an experimental approach to the repair of truncus arteriosus. Arch Surg 1967;95:698-708.
11. Fontan F, Baudet E. Surgical repair of tricuspid atresia. Thorax 1971;26:240-8.
12. Jatene AD, Fontes VF, Paulista PP, Souza LC, Neger F,

Galantier M, et al. Anatomic correction of transposition of the great vessels. J Thorac Cardiovasc Surg 1976;72:364-70.

13. Barratt-Boyes BG, Neutze JM. Primary repair of tetralogy of Fallot in infancy using profound hypothermia with circulatory arrest and limited cardiopulmonary bypass. Ann Surg 1973;178: 406-11.

14. Bull C, Cooper J, Stark J. Cardioplegia protection of the child's heart. J Thorac Cardiovasc Surg 1984;88:287-93.

15. Fricker FJ, Griffith BP, Hardesty RL, Trento A, Gold LM, Schmeltz K, et al. Experience with heart transplantation in children. Pediatrics 1987;79:138-46.

16. Van Praagh R. Diagnosis of complex congenital heart disease: morphologic-anatomic method and terminology. Cardiovasc Intervent Radiol 1984;7:115-20.

17. Anderson RH, Becker AE, Freedom RM, Macartney FJ, Quero-Jiménez M, Shinebourne EA, et al. Sequential segmental analysis of congenital heart disease. Pediatr Cardiol 1984;5:281-7.

18. Tynan MJ, Becker AE, Macartney FJ, Quero-Jiménez M, Shinebourne EA, Anderson RH. Nomenclature and classification of congenital heart disease. Br Heart J 1979;41:544-53.

19. Bargeron LM, Elliot LP, Soto B, Bream PR, Curry GC. Axial Cineangiography in congenital heart disease. I: Concept, technical and anatomic considerations. Circulation 1977;56:1075-83.

20. Elliot LP, Bargeron LM, Bream PR, Soto B, Curry GC. Axial Cineangiography in congenital heart disease. II: Specific lesions. Circulation 1977;56:1084-93.

21. Gutgesell HP, Huhta JC, Latson LA, Huffines D, McNamara DG. Accuracy of two-dimensional echocardiography in the diagnosis of congenital heart disease. Am J Cardiol 1985;55: 514-8.

22. Treves ST, Newberger J, Hurwitz R. Radionuclide angiocardiography in children. J Am Coll Cardiol 1985;5:120S-7S.

23. Irsik RD, White RD, Robitaille PM. Cardiac magnetic resonance imaging. En: Moss-Adams, editor. Heart disease in infants, children, and adolescents. Baltimore: Williams & Wilkins, 1995; p. 206-23.

24. Rashkind WJ, Miller WW. Creation of an atrial septal defect without thoracotomy: a palliative approach to complete transposition of the great arteries. JAMA 1966;196:991-2.

25. Rashkind WJ. Transcatheter treatment of congenital heart disease. Circulation 1983;67:711-6.

26. Mullins CE, O'Laughlin MP. Therapeutic cardiac catheterization. En: Moss-Adams, editor. Heart disease in infants, children, and adolescents. Baltimore: Williams & Wilkins, 1995; p. 439-52.

27. Romero R, Pilu G, Jeanty P, Ghidini A, Hobbins JC. Prenatal diagnosis of congenital anomalies. East Norwalk: Appleton & Lange, 1988.

28. Moller JH, Anderson RC. 1,000 consecutive children with a cardiac malformation with 26 to 37 years follow-up. Am J Cardiol 1992;70:661-7.

29. O'Fallon WM, Crowson CS, Rings LJ, Weidman WH, Driscoll DJ, Gersony WM, et al. Second natural history study of congenital heart defects. Materials and methods. Circulation 1993; 87(Suppl):I4-I15.

30. Hayes CJ, Gersony WM, Driscoll DJ, Keane JF, Kidd L, O'Fallon WM, et al. Second natural history study of congenital heart defects: results of treatment of patients with pulmonary valvar stenosis. Circulation 1993;87(Suppl):I28-I37.

31. Keane JF, Driscoll DJ, Gersony WM, Hayes CJ, Kidd L, O'Fallon WM, et al. Second natural history study of congenital heart defects: results of treatment of patients with aortic valvar stenosis. Circulation 1993;87(Suppl):I16-I27.

32. Kidd L, Driscoll DJ, Gersony WM, Hayes CJ, Keane JF, O'Fallon WM, et al. Second natural history study of congenital heart defects: results of treatment of patients with ventricular septal defects. Circulation 1973;87(Suppl):I38-I51.

33. Murphy JG, Gersh BJ, McGoon MD, Mair DD, Porter CJ, Ilstrup DM, et al. Long-term outcome after surgical repair of isolated atrial septal defect. N Engl J Med 1990;323:1645-50.

34. Murphy JG, Gersh BJ, Mair DD, Fuster V, McGoon MD, Ilstrup DM, et al. Long term outcome in patients undergoing surgical repair of tetralogy of Fallot. N Engl J Med 1993;329:593-9.

35. Mair DD, Puga FJ, Danielson GK. The Fontan procedure for tricuspid atresia: early and late results of a 25-year experience with 216 patients. J Am Coll Cardiol 2001;37:933-9.

36. Moller JH, Taubert KA, Allen HD, Clark EB, Lauer RM, a Special Writing Group from the Task Force on Children and Youth, American Heart Association. Cardiovascular health and disease in children: current status. Circulation 1994;89:923-30.

37. Webb GD, Williams RG. 32nd Bethesda Conference. Care of the adult with congenital heart disease: introduction. J Am Coll Cardiol 2001;37:1166-9.

38. Warnes CA, Liberthson R, Danielson GK, Dore A, Harris L, Hoffman JIE, et al. 32nd Bethesda Conference. Task Force 1: The changing profile of congenital heart disease in adult life. J Am Coll Cardiol 2001;37:1170-5.

39. Kaplan S. Natural adult survival patterns. J Am Coll Cardiol 1991;18:311-42.

40. Perloff JK. Pediatrics congenital cardiac becomes a postoperative adult: The changing population of congenital heart disease. Circulation 1973;47:606-19.

41. Child JS, Perloff JK. Natural survival patterns: a narrowing base. En: Perloff JK, Child JS, editors. Congenital heart disease in adults. Philadelphia: WB Saunders, 1991.

42. Hopkins WE. Severe pulmonary hypertension in congenital heart disease: a review of Eissenmenger syndrome. Curr Opin Cardiol 1995;10:517-23.

43. Perlof JK, Warnes CA. Challenges posed by adults with repaired congenital heart disease. Circulation 2001;103:2637-43.

44. Oliver J. Cardiopatías congénitas del adulto. Cambios en el espectro de las malformaciones cardíacas durante la vida adulta y análisis de las lesiones residuales, secuelas y complicaciones a largo plazo. Un estudio de 1.500 pacientes consecutivos. [Tesis Doctoral]. Madrid: Universidad Autónoma, 1997.

45. Report of the New England Regional Infant Cardiac Program. Pediatrics 1980;65:375-461.

46. O'Laughlin MP, Slack MC, Grifka RG, Perry SB, Lock JE, Mullins CE. Implantation and intermediate-term follow-up of stents in congenital heart disease. Circulation 1993;88:605-14.

47. Benito F, Oliver J. Dilatación con *stent* de la estenosis de la arteria pulmonar en el adulto con cardiopatía congénita. Rev Esp Cardiol 2000;53:583-6.

48. Powell AJ, Lock JE, Keane JF, Perry SB. Prolongation of RV-PA conduit life span by percutaneous stent implantation. Circulation 1995;92:3282-8.

49. Bonhoeffer P, Boudjemline Y, Qureshi SA, Le Bidois J, Iserin L, Acar P, et al. Percutaneous insertion of the pulmonary valve. J Am Coll Cardiol 2002;39:1664-9.

50. Pome G, Rossi C, Colucci V, Passini L, Morello M, Taglieri C, et al. Late reoperations after repair of tetralogy of Fallot. Eur J Cardiothorac Surg 1992;6:31-5.

51. Redington AN, Oldershaw PJ, Shinebourne EA, Rigby ML. A new technique for the assessment of pulmonary regurgitation and its application to the assessment of right ventricular function before and after repair of tetralogy of Fallot. Br Heart J 1988;60: 57-65.

52. Rebergen SA, Chin JG, Ottenkamp J, van der Wall EE, de Roos A. Pulmonary regurgitation in the late postoperative follow-up of tetralogy of Fallot. Volumetric quantitation by nuclear magnetic resonance velocity mapping. Circulation 1993;88:2257-66.

53. Chang AC, Vetter JM, Gill SE, Franklin WH, Murphy JD, Chin

AJ. Accuracy of prospective two-dimensional Doppler echocardiography in the assessment of reparative surgery. J Am Coll Cardiol 1990;16:903-12.

54. Rowe SA, Zahka KG, Manolio TA, Horneffer PJ, Kidd L. Lung function and pulmonary regurgitation limit exercise capacity in postoperative tetralogy of Fallot. J Am Coll Cardiol 1991;17: 461-6.

55. Carvalho JS, Shinebourne EA, Busst C, Rigby ML, Redington AN. Exercise capacity after complete repair of tetralogy of Fallot: deleterious effects of residual pulmonary regurgitation. Br Heart J 1992;67:470-3.

56. Nollert G, Fischlein T, Bouterwek S, Bohmer C, Klinner W, Reichart B. Long-term survival in patients with repair of tetralogy of Fallot: 36-year follow-up of 490 survivors of the first year after surgical repair. J Am Coll Cardiol 1997;30:1374-83.

57. Zahka KG, Horneffer PJ, Rowe SA, Neill CA, Manolio TA, Kidd L, et al. Long-term valvular function after total repair of tetralogy of Fallot: relation to ventricular arrhythmias. Circulation 1988;78:III14-9.

58. Gatzoulis MA, Till JA, Somerville J, Redington AN. Mechanoelectrical interaction in tetralogy of Fallot: QRS prolongation relates to right ventricular size and predicts malignant ventricular arrhythmias and sudden death. Circulation 1995;92:231-7.

59. Gatzoulis MA, Till JA, Redington AN. Depolarization-repolarization inhomogeneity after repair of tetralogy of Fallot: the substrate for malignant ventricular tachycardia? Circulation 1997;95:401-4.

60. Gatzoulis MA, Murphy DJ. The adult with tetralogy of Fallot. Armonk: Futura Publishing Company, Inc., 2001.

61. Therrien J, Siu SC, Harris L, Dore A, Niwa K, Janousek J, et al. Impact of pulmonary valve replacement on arrhythmia propensity late after repair of tetralogy of Fallot. Circulation 2001;103: 2489-94.

62. Therrien J, Siu SC, McLaughlin PR, Liu PP, Williams WG, Webb GD. Pulmonary valve replacement in adults late after repair of tetralogy of Fallot: are we operating too late? J Am Coll Cardiol 2000;36:1670-5.

63. Carlgren LE. The incidencie of congenital heart disease in children born in Goteborg, 1941-1950. Br Heart J 1959;21:40.

64. Liebman J, Cullum L, Belloc NB. Natural history of transposition of the great arteries: anatomy and birth an death characteristics. Circulation 1969;40:237-62.

65. Gallego P, Oliver JM, Benito F, Mesa JM, Sanz E, Moreno I, et al. Unusual longevity without surgical intervention in complete transposition of the great arteries. Pediatr Cardiol 1998;19:358-60.

66. Hagler DG, Ritter DG, Mair DD, David GD, McGoon DC. Clinical, angiographic, and hemodynamic assessment of late results after Mustard's operation. Circulation 1978;57:1214-20.

67. Kato H, Nakono S, Motsada H, Hirose H, Shimazaki Y, Kawashima Y. Right ventricular myocardial function after atrial switch operation for transposition of the great arteries. Am J Cardiol 1989;63:226-30.

68. Reybrouck T, Dumoulin M, Van der Hauwaert LG. Cardiorespiratory exercise testing after venous switch operation in children with complete transposition of the great arteries. Am J Cardiol 1988;61:861-5.

69. Hurwitz RA, Caldwell RL, Girod DA, Mahony L, Brown J, King H. Ventricular function in transposition of the great arteries: evaluation by radionuclide angiocardiography. Am Heart J 1985;110:600-5.

70. Kirklin JW, Barrattt-Boyes BG. Complete transposition of the great arteries. En: Cardiac Surgery. 2nd ed. White Plains: Churchilll Livingstone, 1993; p. 1383-467.

71. Gillete PC, Kugler JD, Garson Ajr, Gutgesell HP, Duff DF, McNamara DG. Mechanisms of cardiac arrhythmias after the Mustard operation for transposition of the great arteries. Am J Cardiol 1980;45:1225-30.

72. Abbruzzese PA, Issenberg H, Cobanoglu A, Garcia C, Nunley D, Starr A. Superior vena cava obstruction after Mustard repair of D-transposition of the great arteries. Scand J Thorac Cardiovasc Surg 1984;18:5-7.

73. Chin AJ, Sanders SP, Norwood WI, Castañeda AR. Two-dimensional echocardiographic localization of residual atrial shunts after the Senning procedure. Am J Cardiol 1985;55:1238-9.

74. Chin AJ, Sanders SP, Williams RG, Lang P, Norwood WI, Castañeda AR. Two dimensional echocardiographic assessment of caval and pulmonary venous pathways after the Senning operation. Am J Cardiol 1983;52:118-26.

75. Kirk CR, Gibbs JL, Wilkinson JL, Wilson N, Dickinson DF, Qureshi SA. Protein-losing enteropathy caused by baffle obstrction after Mustard's operation. Br Heart J 1988;59:69-72.

76. Benson LN, Yeatman L, Laks H. Balloon dilation for superior vena cava obstruction after the Senning procedure. Cathet Cardiovasc Diagn 1985;11:63-8.

77. González Barrero AJ, Santos de Soto J, Descalzo Señorans A. Angioplastia de lesiones residuales tras cirugía correctora de transposición de grandes vasos. Rev Esp Cardiol 1997;50:42-7.

78. Chatelain P, Meier B, Friedli B. Stenting of the superior vena cava and inferior vena cava for symptomating narrowing after repeated atrial surgery for D-transposition of the great vessels. Br Heart J 1991;66:466-8.

79. Benito F, Sánchez C, Oliver J. Implantación de stent en la obstrucción al drenaje venoso sistémico tras la cirugía tipo Mustard en el adulto. Rev Esp Cardiol 1997;50:904-5.

80. Penkoske PA, Westerman GR, Marx GR, Rabinovitch M, Freed MD, Norwood WI, et al. Transposition of the great arteries and ventricular septal defect: results with the Senning operation and closure of the ventricular septal defects in infants. Ann Thorac Surg 1983;36:281-8.

81. Carrel T, Serraf A, Lacour-Gayet F, Bruniaux J, Demontoux S, Touchot A, et al. Transposition of the great arteries complicated by tricuspid valve incompetence. Ann Thorac Surg 1996;61: 940-4.

82. Turley K, Verrier ED. Intermediate results from the period of the Congenital Heart Surgeons Transposition Study: 1985 to 1989. Congenital Heart Surgeons Society Database. Ann Thorac Surg 1995;60:505-1.

83. Norwood WI, Dobell AR, Freed MD, Kirklin JW, Blackstone EH. Intermediate results of the arterial switch repair. A 20-institution study. J Thorac Cardiovasc Surg 1988;96:854-63.

84. Kirklin JW, Blackstone EH, Tchervenkov CI, Castaneda AR. Clinical outcomes after the arterial switch operation for transposition. Patient, support, procedural, and institutional risk factors. Congenital Heart Surgeons Society. Circulation 1992;86:1501-15.

85. Yacoub MH, Bernhard A, Radley-Smith R, Lange P, Sievers H, Heintzen P. Supravalvular pulmonary stenosis after anatomic correction of transposition of the great arteries: causes and prevention. Circulation 1982;66(Suppl):I193-7.

86. Hourihan M, Colan SD, Wernovsky G, Maheswari U, Mayer JE Jr, Sanders SP. Growth of the aortic anastomosis, annulus, and root after the arterial switch procedure performed in infancy. Circulation 1993;88:615-20.

87. Tanel RE, Wernovsky G, Landzberg MJ, Perry SB, Burke RP. Coronary artery abnormalities detected at cardiac catheterization following the arterial switch operation for transposition of the great arteries. Am J Cardiol 1995;76:153-7.

88. Bonhoeffer P, Bonnet D, Piechaud JF, Stumper O, Aggoun Y, Villain E, et al. Coronary artery obstruction after the arterial switch operation for transposition of the great arteries in newborns. J Am Coll Cardiol 1997;29:202-6.

89. Tanel RE, Wernovsky G, Landzberg MJ, Perry SB, Burke RP. Coronary artery abnormalities detected at cardiac catheterization following the arterial switch operation for transposition of the

great arteries. Am J Cardiol 1995;76:153-7.

90. Tsuda E, Imakita M, Yagihara T, Ono Y, Echigo S, Takahashi O, et al. Late death after arterial switch operation for transposition of the great arteries. Am Heart J 1992;124:1551-7.

91. Glenn WWL. Circulatory bypass of the right side of the heart. II: Shunt between the superior vena cava and distal right pulmonary artery: report of a clinical application. N Engl J Med 1958;259:117-20.

92. Trusler GA, Williams WG, Cohen AJ, Rabinovitch M, Moes CA, Smallhorn JF, et al. William Glenn lecture. The cavopulmonary shunt. Evolution of a concept. Circulation 1990;82(5 Suppl):IV131-8.

93. Castaneda A. From Glenn to Fontan. A continuing evolution. Circulation 1992;86(Supl II):II80.

94. Mazzera E, Corno A, Picardo S, Di Donato R, Marino B, Costa D, et al. Bidirectional cavopulmonary shunts: clinical applications as staged or definitive palliation. Ann Thorac Surg 1989; 47:415-20.

95. Cetta F, Mair DD, Feldt RH, Puga FJ, Schaff HV, Danielson GK. Improved early mortality after modified -Fontan operation for complex congenital heart disease. Am J Cardiol 1993;72: 499.

96. Laschinger JC, Redmond JM, Cameron DE, Kan JS, Ringel RE. Intermediate results of the extracardiac Fontan procedure. Ann Thorac Surg 1996;62:1261-7.

97. Lemler MS, Scott WA, Leonard SR, Stromberg D, Ramaciotti C. Fenestration improves clinical outcome of the Fontan procedure. Circulation 2002;105:207-12.

98. Choussat A, Fontan F, Besse P, Vallot F, Chauve A, Bricuad H. Selection criteria for Fontan procedure. En: Anderson FH, Shinebourne EA, editors. Pediatric cardiology. White Plains: Churchill Livingstone, 1978; p. 599-66.

99. Mayer JE Jr, Helgason H, Jonas RA, Lang P, Vargas FJ, Cook N, et al. Extending the limits for modified Fontan procedures. J Thorac Cardiovasc Surg 1986;92:1021-8.

100. Puga FJ, Chiavarelli M, Hagler DJ. Modifications of the Fontan operation applicable to patients with left atrioventricular valve atresia or single atrioventricular valve. Circulation 1987;76: III53-60.

101. Fontan F, Kirklin JW, Fernández G, Costa F, Naftel DC, Tritto F, et al. Outcome after a «perfect» Fontan operation. Circulation 1990;81:1520-36.

102. Driscoll DJ, Offord KP, Feldt RH, Schaff HV, Puga FJ, Danielson GK. Five-to fifteen-year follow-up after Fontan operation. Circulation 1992;85:469-96.

103. Shirai LK, Rosenthal DN, Reitz BA, Robbins RC, Dubin AM. Arrhythmias and thromboembolic complications after the extracardiac Fontan operation. J Thorac Cardiovasc Surg 1998;115: 499-505.

104. Donofrio MT, Jacobs ML, Norwood WI, Rychik J. Early changes in ventricular septal defect size and ventricular geometry in the single left ventricle after volume-unloading surgery. J Am Coll Cardiol 1995;26:1008-15.

105. Fogel MA, Chin AJ. Imaging of pulmonary venous pathway obstruction in patients after the modified Fontan procedure. J Am Coll Cardiol 1992;20:181-90.

106. Moak JP, Gersony WM. Progressive atrioventricular valvular regurgitation in single ventricle. Am J Cardiol 1987;59:656-8.

107. Balaji S, Johnson TB, Sade RM, Case CL, Gillette PC. Management of atrial flutter after the Fontan procedure. J Am Coll Cardiol 1994;23:1209-15.

108. Gelatt M, Hamilton RM, McCrindle BW, Gow RM, Williams WG, Trusler GA, et al. Risk factors for atrial tachyarrhythmias after the Fontan operation. J Am Coll Cardiol 1994;24:1735-41.

109. Foster E, Graham TP Jr, Landzberg MJ, et al. Complications and morbidity in adults with Fontan physiology: a multicentre study. Circulation 1999;100(Suppl I):I669.

110. Ghai A, Harris L, Harrison DA, Webb GD, Siu SC. Outcomes of late atrial tachyarrhythmias in adults after the Fontan

operation. J Am Coll Cardiol 2001;37:585-92.

111. Kirklin JK, Blackstone EH, Kirklin JW, Pacifico AD, Bargeron LM. The Fontan operation: ventricular hypertrophy, age and date of operation as risk factors. J Thorac Cardiovasc Surg 1986;92:1049-64.

112. Sluysmans T, Sanders SP, van der Velde M, Matitiau A, Parness IA, Spevak PJ, et al. Natural history and patterns of recovery of contractile function in single left ventricle after Fontan operation. Circulation 1992;86:1753-61.

113. Davis CA, Driscoll DJ, Perrault J, Greenwood DH, Schaff HV, Puga FJ, et al. Enteric protein loss after the Fontan operation. Mayo Clin Proc 1994;69:112-4.

114. Mertens L, Dumoulin M, Gewillig M. Effect of percutaneous fenestration of the atrial septum on protein-losing enteropathy after the Fontan operation. Br Heart J 1994;72:591-2.

115. Kelly AM, Feldt RH, Driscoll DJ, Danielson GK. Use of heparin in the treatment of protein-losing enteropathy after Fontan operation for complex congenital heart disease. Mayo Clin Proc 1998;73:777-9.

116. McElhinney DB, Reddy VM, Moore P, Hanley FL. Revision of previous Fontan connections to extracardiac or intraatrial conduit cavopulmonary anastomosis. Ann Thorac Surg 1996;62: 1276-82.

117. Marcelletti CF, Hanley FL, Mavroudis C, McElhinney DB, Abella RF, Marianeschi SM, et al. Revision of previous Fontan connections to total extracardiac cavopulmonary anastomosis: a multicenter experience. J Thorac Cardiovasc Surg 2000;119: 340-6.

118. DeLeon SY, Ilbawi MN, Idriss FS, Muster AJ, Gidding SS, Berry TE, et al. Persistent low cardiac output after the Fontan operation. Should takedown be considered? J Thorac Cardiovasc Surg 1986;92:402-5.

119. Stamm C, Friehs I, Mayer JE Jr, Zurakowski D, Triedman JK, Moran AM, et al. Long-term results of the lateral tunnel Fontan operation. J Thorac Cardiovasc Surg 2001;121:28-41.

120. Perloff JK, Miner PD. Specialized facilities for the comprehensive care of adults with congenital heart disease. En: Perloff JK, Child JS, editors. Congenital heart disease in adults. Philadelphia: WB Saunders, 1998; p. 9-12.

121. Landzberg MJ, Murphy DJ Jr, Davidson WR Jr, Jarcho JA, Krumholz HM, Mayer JE Jr, et al. Task Force 4: Organization and delivery systems for adult with congenital heart disease. J Am Coll Cardiol 2001;37:1187-93.

122. Foster E, Graham TP Jr, Driscoll DJ, Reid GJ, Reiss JG, Russell IA, et al. Task Force 2: Special health care needs of adults with congenital heart disease. J Am Coll Cardiol 2001;37:1176-83.

123. Webb CL, Jenkins KJ, Karpawich PP, and the Congenital Cardiac Defects Committee of the American Heart Association Section on Cardiovascular Disease in the Young. Collaborative Care for Adults With Congenital Heart Disease. Circulation 2002;105:2318-23.

124. Child JS, Collins-Nakai RL, Alpert JS, Deanfield JE, Harris L, McLaughlin P, et al. Task Force 3: Workforce description and educational requirements for the care of adults with congenital heart disease. J Am Coll Cardiol 2001;37:1183-7.