
OUTCOMES IN PEDIATRIC CARDIAC SURGERY

Late Outcomes in Patients With Surgically Treated Congenital Heart Disease

Amy H. Schultz and Gil Wernovsky

Optimizing late outcomes should be the end result of improvements in medical and surgical care for congenital heart disease (CHD). In addition to mortality, significant morbidities after surgery for CHD need to be considered. These include the need for reintervention, cardiovascular complications, exercise limitations, neurocognitive morbidities, effects on pregnancy, difficulty obtaining insurance, need for chronic medications, and impaired functional status and quality of life. Long-term outcome studies are difficult to perform, and their interpretation is complicated by intervening changes in management. Specific discussion of long-term follow-up of tetralogy of Fallot, D-transposition of the great arteries, and hypoplastic left heart syndrome illustrates the myriad management changes over the last three decades, the challenges in predicting outcomes for recent patients, and the need for ongoing initiation of long-term follow-up studies.

Semin Thorac Cardiovasc Surg Pediatr Card Surg Ann 8:145-156 © 2005 Elsevier Inc. All rights reserved.

KEYWORDS: Heart defects, congenital, follow-up studies, tetralogy of Fallot, transposition of great vessels, hypoplastic left heart syndrome

Optimal late outcomes are the holy grail of medicine. Although the emphasis of innovation is often initially on short-term measures of success, the ultimate goal of therapy is improved long-term functional status and quality of life (QOL). Review of the table of contents of this issue reveals this underlying theme running directly or indirectly through many of the articles.

The meanings of “late” and “outcomes” have historically been from the perspective of the cardiologist and/or surgeon and rarely from the perspective of the patient or parent. Not infrequently, “late” outcome studies in the literature for congenital heart disease (CHD) span a decade or less, certainly not how a parent (or a child) would envision a truly long-term result. Parents of children with CHD are asking for predictions that span a lifetime and exactly how long that lifetime will be. These data are unavailable. In addition, “outcome” studies most commonly deal with mortality and,

occasionally, reintervention or functional outcomes. Patients’ perspectives and interests are frequently quite different and include lifestyle limitations (eg, exercise restrictions, medication burden, doctor visits), self-image (eg, surgical incisions, growth failure), the ability to work in a normal job, the ability to obtain health and life insurance, and other important health-related QOL issues. Now that it is expected that children with CHD will become adults with surgically managed CHD, these outcomes become paramount.

Evaluating and improving late outcomes is a challenging endeavor. Often, better short-term results lead to and may be a prerequisite for improved long-term results. However, in many instances a therapy that seems beneficial in the short-term has unforeseen long-term implications. Most practitioners would be willing to undertake more complex initial management if it clearly would lead to improved long-term results. Thus, long-term outcome studies are vital. These studies require decades of follow-up, and their interpretation is almost invariably complicated by changes in management in the intervening years. It is in this context that we offer this overview of late outcomes in CHD.

The diversity of cardiac malformations, their natural history, and the surgical procedures devised to treat them make summarizing late outcomes for CHD in one review difficult.

The Cardiac Center at The Children’s Hospital of Philadelphia and the University of Pennsylvania School of Medicine, Philadelphia, PA.

Dr. Schultz is supported in part by NIH Grant T32-HL07915.

Address reprint requests to Amy H. Schultz, MD, Division of Cardiology, The Children’s Hospital of Philadelphia, 34th St. & Civic Center Blvd., Philadelphia, PA 19104.

Table 1 Summary of Major Late Morbidities After Surgery for Congenital Heart Disease

Applicable to many lesions	Late death Reintervention Heart failure/ventricular dysfunction Rhythm disturbances and need for pacemaker Endocarditis Exercise limitations and restrictions Neurocognitive impairment Decreased ability to tolerate pregnancy Difficulty obtaining insurance Need for chronic medications Impaired functional status and health-related QOL
Lesion-specific Tetralogy of Fallot	Sudden death Pulmonary regurgitation Ventricular arrhythmias Ventricular dysfunction
D-TGA after arterial repair	Sudden death Sinus node dysfunction Atrial flutter Systemic ventricular dysfunction Baffle obstruction or leak
D-TGA after arterial switch operation	Supravalvar pulmonic stenosis Coronary occlusion Neo-aortic root dilation
HLHS (includes morbidities seen after the Fontan palliation in other forms of CHD)	Recurrent arch obstruction Sinus node dysfunction Neo-aortic root dilation Atrial flutter Ventricular dysfunction Stroke Thrombosis Protein losing enteropathy

Abbreviations: CHD, congenital heart disease; D-TGA, D-transposition of the great arteries; QOL, quality of life.

We focus on late outcomes of CHD after surgery, first addressing general principles applicable to many forms of CHD and then discussing late outcomes in more depth for three common lesions: tetralogy of Fallot (TOF), D-transposition of the great arteries (D-TGA), and hypoplastic left heart syndrome (HLHS). The major late morbidities are summarized in Table 1.

General Principles in Late Outcomes of Surgically Treated Congenital Heart Disease

Mortality

Mortality associated with CHD has been declining over the past several decades. In a study from the Centers for Disease Control, deaths in which CHD was the underlying or contributing cause of death declined 39% between 1979 and 1997 from 2.5 to 1.5 per 100,000.¹ Mortality from CHD decreased in nearly all age groups, particularly in children

less than 5 years of age. In a population-based study, operative mortality also declined between 1965 and 1989 for TOF, ventricular septal defect (VSD), and D-TGA.² However, long-term follow-up data are insufficient to demonstrate any change in late mortality after surgery for CHD overall.² Sudden late death after surgery for CHD is problematic in certain defects, the most common of which are TOF, coarctation, aortic stenosis (AS), and D-TGA.³ No difference was seen in the rate of late sudden death in TOF, AS, or coarctation when comparing patients operated on before and after 1980. The risk of late death for these three lesions seemed to increase at 20 to 25 years after the initial operation. It cannot be determined if the increased risk of late mortality in CHD is due to the intrinsic CHD, its management in an earlier era, or a combination of factors.

Reoperations

A significant fraction of patients requires reoperation after initial repair or palliation of CHD. In many cases this need is predictable, such as in staged reconstructive procedures, conduit or prosthetic valve placement in small children re-

quiring replacement as the child grows, or bioprostheses with limited functional lifespan. In other instances, reoperation is required for residual defects after an initial procedure (eg, mitral valvuloplasty after repair of atrioventricular septal defect), to treat late rhythm disturbances (eg, pacemakers for sinus node dysfunction), or to treat unanticipated consequences of surgical strategies (eg, aortic valve replacement after the arterial switch operation). Additional common examples include pulmonary valve replacement after TOF repair and Fontan revisions with Cox-Maze procedures.⁴

Ventricular Dysfunction and Heart Failure

Patients with surgically treated CHD have a variable predisposition to ventricular dysfunction and heart failure. Mechanisms contributing to ventricular dysfunction include long-standing pressure or volume load, ventriculotomy, inadequate myocardial protection during ischemic cross-clamping, and coronary injury. It has been suggested that patients with isolated atrial septal defect (ASD) or VSD repaired at a young age have low risk of late heart failure;^{5,6} however, among patients with ASD repaired at >24 years of age between 1956 and 1960, heart failure occurred in 25%. Heart failure and ventricular dysfunction are common in adults with D-TGA after the Mustard procedure, congenitally corrected transposition, and the Fontan circulation.⁷

Rhythm Disturbances

Arrhythmias are common late after CHD surgery. Atrial fibrillation or flutter is common after Fontan palliation, atrial switch procedures, and ASD closure.^{5,8,9} Sinus node dysfunction is common after extensive atrial surgery and may require pacing.⁹ Complete heart block may be induced at surgery; some patients with lesser conduction disturbances may progress to complete heart block over time. Ventricular arrhythmias are of increased concern with longer duration of follow-up, particularly after TOF repair.¹⁰ Long-standing ventricular pressure and/or volume load, such as in aortic or pulmonary valve disease, may lead to a propensity for ventricular ectopy.¹¹ Finally, there are growing concerns about the arrhythmogenic potential of the chronic pressure load on a right ventricle in the systemic circulation, such as in HLHS or atrial repair of D-TGA.¹²

Endocarditis

The risk of endocarditis is reduced by corrective surgery in left-to-right shunt defects, provided that no residual shunt is present. Consequently, SBE prophylaxis is no longer recommended 6 months after complete closure of the defect.¹³ This recommendation was borne out by a population-based study of the risk of endocarditis after CHD surgery.¹⁴ No patient after surgery for secundum ASD, isolated VSD without residual shunt, patent ductus arteriosus, or pulmonic stenosis (PS) was observed to develop endocarditis. However, the risk of endocarditis persists for patients with abnormal valves, prosthetic material, residual shunts, and complex CHD. The highest cumulative incidence of endocarditis was found in patients with valvar AS, 13.3% at 25 years. It is unclear

whether the newer trans-catheter interventions will alter the frequency of late endocarditis because the follow-up is too short.

Exercise Limitations

Exercise capacity after surgical repair of different forms of CHD varies depending on whether a complete repair versus palliation can be achieved, the presence of residual shunt or valvar dysfunction, and the status of the conduction system. In patients with large ASDs, exercise capacity and lung function were abnormal preoperatively but normalized by 10 years postoperatively.¹⁵ Patients with surgically treated AS had normal exercise duration on a treadmill test in follow-up, although many had a blunted blood pressure response.¹⁶ Patients with more complex lesions, including TOF, D-TGA, and lesions managed with surgical reconstruction culminating in the Fontan circulation, have exercise capacities that are diminished to differing degrees.¹⁷⁻¹⁹ Mechanical and chronotropic impairment contribute to the decrease in exercise capacity. Patients typically report less subjective impairment than is indicated by objective testing, reinforcing the notion that the impact on lifestyle from late sequelae is different from the clinician's and patient's perspective.

Neurocognitive Outcomes

Intense interest has been focused on neurocognitive outcomes in patients with CHD, particularly among those with complex lesions undergoing neonatal cardiac surgery. The longest reported follow-up of a prospectively studied cohort of such patients is now 8 years;²⁰ much remains to be learned about how cardiac surgery in the neonate affects long-term outcomes. Among patients who underwent surgery in the neonatal period or early infancy for complex CHD in the late 1980s to early 1990s, mean IQ scores are generally found to be within the normal range but slightly lower than the general population mean.²⁰⁻²⁴ Performance IQ is often more affected than verbal IQ.^{23,24} Abnormalities of visual-spatial and visual-motor integration and executive function are noted. There is a frequent need for remedial educational services.²⁰ The mechanisms of brain injury are multifactorial, are most likely cumulative, and are beyond the scope of this discussion. Several review articles describe in more detail the results of these investigations.²⁵⁻²⁷

Pregnancy in Women with Congenital Heart Disease

Pregnancy imposes a hemodynamic burden that is usually well tolerated by women with normal hearts. As more women with surgically repaired or palliated CHD reach child-bearing age, pregnancy in CHD has become an important issue. Eisenmenger syndrome carries an extremely high risk of maternal mortality (~45%).²⁸ Reports of large series of women with various forms of heart disease indicate a low maternal mortality (~1%) among the self-selected group of women who become pregnant.²⁹ Among patients with CHD, pre-pregnancy functional class, ventricular dysfunction, cyanosis, outflow tract obstruction, mitral stenosis, pulmonary hy-

pertension, and the need for anticoagulation are predictors of maternal morbidity.²⁹⁻³² The miscarriage rate among women with mixed forms of heart disease is elevated above normal³³ and is 39% among those with the Fontan circulation.³⁴ Maternal cyanotic heart disease is associated with a high rate of premature birth (37%) and a mean birth weight of 2,575g.³⁵ Neonatal complications are more common in pregnancies of women with heart disease.³³ In addition, the recurrence risk for CHD in the child is elevated above the population risk and varies with the underlying maternal lesion.^{30,36}

Functional Status and Quality of Life

The late morbidities outlined above, the difficulty obtaining insurance, and the need for life-long medical follow-up, chronic medications, and SBE prophylaxis may collectively affect overall health-related QOL. Some long-term follow-up series have reported New York Heart Association (NYHA) functional class, frequency of medication use, and proportion of patients employed. In the Second Joint Study on the Natural History of Congenital Heart Defects (NHS-2) 92%, 97%, and 94% of the surviving, surgically managed, full participants with AS, PS, and VSD, respectively, were in NYHA class I.³⁷⁻³⁹ Cardiac medications were used by 10.1%, 3.9%, and 4.2%, respectively. Across all defects managed surgically in NHS-2, 72.3% of subjects were employed.⁴⁰

Relatively few studies have used validated instruments to assess QOL.⁴¹ Lane et al⁴² assessed QOL in adults attending an Adult Congenital Heart Disease clinic using the Medical Outcomes Study short form-36 (SF-36) questionnaire. Although the response rate was only 59%, they found that patients with CHD scored lower on the physical functioning and general health perception domains than the general population. Kamphuis et al⁴³ examined health-related QOL and health status in Danish adults with previously operated complex CHD, using the SF-36 and a QOL instrument developed in the Netherlands. The study population was born between 1968 and 1982; 49% of the cohort died before the study in 1999, and 16% were excluded due to language barriers or important learning disabilities. On both instruments, domains evaluating physical or gross motor functioning and vitality had scores lower than the general population. No differences were seen on domains that evaluated fine motor, social, cognitive, and emotional functions. NYHA class correlated significantly with physical or gross motor functioning. Thus, NYHA class may provide a good estimate of physical functioning but does not comprehensively evaluate health-related QOL in CHD.

Late Outcomes for Individual Lesions

Knowledge of late outcomes guides the choice of current surgical management strategy and provides insight into the expected clinical course. This information is useful for counseling patients and their families, whether the counseling is offered to the parents of a newborn in 2005 or to a patient who underwent surgery for CHD in 1975. Similarly, clini-

cians need to be well versed in the late outcomes of past management strategies so that complications in older patients can be anticipated and managed appropriately. In the sections that follow, we discuss the three most common cyanotic lesions: TOF, D-TGA, and HLHS. As a frame of reference, we provide an overview of prevailing management strategies circa 1975, 1985, and 1995, followed by a discussion of the corresponding late outcomes. These discussions illustrate the challenges in predicting true late outcomes for our current patients as management strategies evolve.

Tetralogy of Fallot

TOF has the longest history of surgical treatment of any cyanotic lesion, with a 60-year history of palliation and a 50-year history of repair.⁴⁴ The era of surgical therapy for cyanotic heart disease began in 1945 with Blalock and Taussig's report of palliation of three patients with TOF by systemic to pulmonary artery shunt.⁴⁵ In 1955, Lillehei et al⁴⁶ reported the first intracardiac correction of TOF.

Management of Tetralogy of Fallot Circa 1975 and its Late Follow-up

In 1975, diagnosis was suspected clinically and confirmed by cardiac catheterization; the prevailing philosophy was elective repair in childhood, with palliative shunts and propranolol therapy used for cyanotic neonates and infants. The strategy of primary repair in infancy was reported in 1973,⁴⁷ but typically operations were performed in toddlers or school-age children. One third to one half of patients had a palliative procedure before surgical repair.⁴⁸⁻⁵⁰ Thus, long-standing volume overload and pulmonary artery distortion were not uncommon and influence the long-term outcome in series from that era. A ventriculotomy was almost always used, and transannular patches, when used, were extensive. Temperature management on cardiopulmonary bypass was highly variable.⁵¹⁻⁵⁵ Normothermic or moderately hypothermic aortic cross-clamping or topical cooling of the heart were used in the early 1970's;^{53,54,56} the use of cardioplegia was first reported in 1978.⁵² Operative mortality was 5% to 10%.^{51,53-56}

Late survival of patients who underwent surgical repair of TOF in these early years has been good, especially in contrast to the natural history of TOF, which rarely allowed survival to adulthood. Murphy et al⁴⁸ reported an 86% survival at 32 years among patients operated on between 1955 and 1960 who survived the immediate postoperative period, and Nollert et al⁴⁹ reported an 89% 30-year actuarial survival of patients corrected between 1958 and 1977 who survived the first postoperative year. In both studies, survival was slightly less than expected for the normal population. In the Nollert study, mortality was linear for the first 25 years after operation (0.24% per year) but then increased significantly to 0.94% per year. Similarly, in a population-based study, the risk of sudden death after repair of TOF increased 20 years postoperatively.³ These observations raise the concern that survivors of TOF repair in this early era of cardiac surgery may not begin to experience late morbidity and mortality until several decades postoperatively.

The risk of sudden death after TOF repair has been recognized since the early 1970s. The incidence of sudden death after TOF repair is 1.2% at 10 years postoperatively, 2.2% at 20 years, 4% at 25 years, and 6% at 30 years.³ Ventricular arrhythmias likely account for the majority of cases of sudden death. QRS duration longer than 180 milliseconds, older age at repair, a history of atrial flutter or fibrillation, prior Waterston or Potts shunts, pulmonary regurgitation, residual right ventricular hypertension and/or outflow tract obstruction, left ventricular dysfunction, and perioperative transient AV block have been associated with sudden death.^{10,57-59}

Reoperation has been performed in a minority (7% to 10%) of patients after TOF repair in long-term follow-up series.⁴⁸⁻⁵⁰ Actuarial survival with freedom from reoperation is 88% at 30 years.⁴⁸ The most common reason for reoperation was residual or recurrent VSD; pulmonary valve replacement was rare. However, in a recent series from Toronto, the frequency of late reoperations after repair of TOF is increasing; pulmonary valve replacement accounts for 38% of these.⁶⁰

Semilunar valve function is of concern on the right and left sides of the heart. Pulmonary regurgitation often results from transannular patching or pulmonary valvotomy, whereas the aortic annulus and root may dilate over time, leading to insufficiency. At least moderate pulmonary insufficiency occurred in 54% of patients in a six-center study for whom echocardiography data were available.¹⁰ Mean follow-up after initial repair was 21 years. Pulmonary insufficiency has been associated with sudden death, exercise intolerance, and tachyarrhythmias.^{10,61,62} Pulmonary valve replacement stabilizes right ventricular size and QRS duration and improves symptoms of congestive heart failure; data are conflicting as to whether right ventricular function improves postoperatively.⁶³⁻⁶⁵ Appropriate timing of pulmonary valve replacement is being debated.

Aortic root dilation occurred in 14.8% of a cohort of adults (mean age 31 years) with TOF and was progressive, but aortic valve or root replacement remains rare.^{60,66} Patients with aortic root dilation had a longer shunt-to-repair interval and a higher prevalence of pulmonary atresia and right aortic arch. Given the different surgical strategy from this era, the frequency of and indications for future reoperation in TOF are unlikely to be well predicted by these initial long-term follow-up series.

Exercise capacity of patients operated on in this early era is consistently lower than population norms, although the degree of impairment is variable.^{62,67} In a review of all studies of exercise capacity in TOF (spanning different eras), mean work capacity was 85% of predicted, and VO_2max averaged 81% of predicted.¹⁷ Pulmonary insufficiency has been implicated as a cause of reduced exercise tolerance,⁶⁸ whereas restrictive right ventricular diastolic physiology has a beneficial effect.⁶²

In a description of 43 women with TOF (including eight women with unrepaired TOF) who had 112 pregnancies, miscarriage occurred in 27% of pregnancies, but only 1.2% of completed pregnancies were preterm.⁶⁹ Six of the 35 women with repaired TOF had cardiovascular complications

during the pregnancy, including arrhythmias, LV dysfunction, and progressive RV dilatation.

To our knowledge, no large study of QOL using validated instruments has been performed in adults after TOF repair. Several long-term follow-up series have reported gross measures of functional status and QOL at late follow-up: 90% to 95% of patients report being in NYHA class I or II, 71% to 85% are employed, 17% to 25% take routine medications, and 50% participate in recreational sports.⁴⁸⁻⁵⁰

Bacha et al⁷⁰ reported on long-term survivors who had primary repair of TOF at <24 months of age at Children's Hospital, Boston between 1972 and 1977. Unlike most patients treated in that era, no palliative procedures were performed, so the volume load associated with a shunt was averted and the duration of cyanosis was shortened. There are important differences between this cohort and patients managed currently. Postoperative care was according to the standards of the era, and the VSD was typically closed through a ventriculotomy. Actuarial survival was 86% at 20 years, freedom from reintervention was 79% at 20 years, and one patient underwent a pulmonary valve replacement.

Management of Tetralogy of Fallot Circa 1985 and its Late Follow-up

By 1985, primary repair in infancy was increasingly used at selected large-volume centers.^{51,55} Early neonatal correction with profound hypothermia and circulatory arrest was being proposed. However, the Pediatric Cardiac Care Consortium (PCCC), which had 12 member institutions of variable size across the United States, reported that 35% of patients repaired between 1986 and 1990 had a prior palliative shunt.⁷¹ The percentage of initial shunts at the member institutions ranged from 8% to 70%. The mean age at repair was 2.4 years, and in-hospital mortality was 6.6%. The use of cardioplegia for myocardial protection was well established, and other aspects of intraoperative support management were being actively investigated. Thus, this cohort represents a heterogeneous surgical approach, age at repair, and comorbidities.

There is little late follow-up data that can be linked specifically to patients operated on in this time period. Yetman et al⁷² reported on 74 patients repaired between 1982 and 1992, 22 of whom had been repaired before 18 months of age. There were no demonstrable differences in exercise capacity between those operated on early versus later (peak VO_2 70% v 75% predicted, ventilatory anaerobic threshold 69% v 75% predicted). DeRuijter et al⁷³ examined the effects of pulmonary regurgitation in 171 patients repaired at a mean of 1.9 years of age between 1977 and 2000. Right ventricular dilation was noted in 38% at a mean of 9.6 years of follow-up, and 9% underwent pulmonary valve replacement at a mean of 9.2 years after initial repair.

Management of Tetralogy of Fallot Circa 1995 and its Late Follow-up

As the field moved into the 1990s, preoperative catheterization was replaced by echocardiography, and significant advances were made in postoperative care. The fraction of patients palliated initially with a shunt continued to decline.

The PCCC reported that between 1991 and 1995, 22% of patients had a shunt before definitive repair.⁷¹ The mean age at repair in this consortium decreased to 1.35 years, and mortality declined to 2.3%. Surgical management of neonates with critical CHD expanded, and several large centers adopted primary repair in cyanotic neonates with TOF as their preferred strategy.⁷⁴ The optimal approach in this patient group—shunt followed by later repair or primary repair—continues to be debated in 2005, as illustrated elsewhere in this issue. Finally, the multiple genetic associations with TOF, most importantly the 22q11 deletion syndrome, were increasingly recognized.⁷⁵ Many of these genetic abnormalities have significant implications for long-term outcomes that are hard to separate from the management of the cardiac malformation (eg, neurodevelopmental outcomes).

Hirsch et al⁷⁴ reported on their center's experience with complete repair of TOF in 61 neonates operated on between 1988 and 1999. There was one in-hospital death and four late deaths, with an actuarial survival of 95% at 5 years. Freedom from reoperation was 58% at 5 years. Excellent survival after TOF repair is achievable, even with operation in the neonatal period. However, the frequencies of morbidities well described among patients operated on circa 1975 are undefined for the infant who has undergone routine repair in the recent era.

Summary: Late Outcomes in Tetralogy of Fallot

Adults with TOF face the sequelae of medical and surgical management strategies used during their infancy and childhood. From a clinician's perspective, they enjoy excellent actuarial survival rates, and reintervention has been infrequent. However, there is growing concern about the long-term effects of pulmonary regurgitation and ventricular dysrhythmias, with their attendant influences on functional status, exercise tolerance, and the risk (fear) of sudden death. These late outcomes may or may not be applicable to the current generation of infants with TOF undergoing primary repair. Follow-up studies are needed in more contemporary cohorts to define their truly late outcomes.

Transposition of the Great Arteries

Palliation of D-TGA became possible in 1950 with the development of the Blalock-Hanlon atrial septectomy, which improved intercirculatory mixing.⁷⁶ A physiologic repair using native atrial tissue was first reported by Senning⁷⁷ in 1957, followed by Mustard's⁷⁸ success with an atrial switch using a pericardial baffle in 1963. Atrial switches became widely used in the 1960s and 1970s in a growing population of children stabilized in the neonatal period by a Rashkind transcatheter atrial septostomy.⁷⁹ In 1975, Jatene⁸⁰ reported the first successful arterial switch operation (ASO), ushering in a new era of surgery for D-TGA. Despite an initial difficulty with high operative mortality, the ASO had become the predominant surgical strategy at most institutions by the late 1980s.⁸¹

Management of D-Transposition of the Great Arteries Circa 1975 and its Late Follow-up

Patients born with D-TGA in the 1970s would have typically undergone a cardiac catheterization and a Rashkind balloon

septostomy, followed by a Blalock-Hanlon atrial septectomy (via a thoracotomy) if mixing was still inadequate. An atrial switch was typically performed at 1 to 4 years of age, and the resultant delay in repair was associated with decreased functional status and intelligence testing.⁸² Cardioplegia was not in routine use; operations were performed with hypothermic cardiopulmonary bypass or deep hypothermic circulatory arrest.⁹ Early mortality in this era ranged from 0.9% to 16.5%.^{9,83}

The long-term survival of these patients has been good, although not as favorable as reported for TOF. Actuarial survival at 25 years (including early mortality) is 74% to 77%,^{9,84} with 67% survival at 30 years.⁸³ In one study, the instantaneous risk of late death seems to increase after about 10 years postoperatively.⁹ The most problematic long-term cardiovascular issues have been (1) loss of sinus rhythm, (2) atrial tachyarrhythmias, (3) baffle obstruction or leak, (4) decline in systemic right ventricular function, and (5) sudden death. Among operative survivors, 40% to 63% are still in sinus rhythm 20 to 25 years postoperatively,^{9,84} with 5.5% to 22% requiring pacemaker placement, depending on the length of follow-up.^{83,85} Atrial flutter is the most common atrial tachyarrhythmia, occurring in 24% of survivors by 20 years.⁹ Reintervention for baffle leak or obstruction is reported in 5% to 31% of patients.^{9,84} Concern that the right ventricle may not be able to sustain systemic work for decades in some patients seems to be borne out as this patient group is observed over time. Serial echocardiographic assessment of right ventricular function has been performed at approximately 14 and 25 years after surgery. Ventricular function in all patients was classified as normal (68%) or mildly impaired (32%) at the first study. Only 4 of 47 (8%) had stable ventricular function at follow-up, with 38% classified as moderately impaired and 23% as severely impaired.⁸⁴ Relatively few heart transplants are reported in long-term follow-up series, but myocardial failure accounted for 21 of 77 late deaths in one series.⁹ A population-based study reported a cumulative incidence of sudden death in TGA of 4.9 per 1,000 patient-years.³ These deaths are presumed to be arrhythmic and were associated with exercise in 81% of cases.¹² In the ASO era, coronary anomalies associated with D-TGA are increasingly recognized; the role that these anomalies might play in sudden death after atrial repairs has, to our knowledge, not been investigated.

Despite the above cardiovascular concerns, a convenience sample of long-term survivors without learning disabilities reported a favorable perceived health, functional status, and QOL.⁸⁶ Distribution of NYHA class has been variable among long-term follow-up series, ranging from 92% class I and 8% class II at a mean of 17 years of follow-up⁸³ to 24% class I, 53% class II, and 23% class III at a median follow-up of 25 years.⁸⁴ A review of 27 exercise studies in this population notes that almost all the patients studied considered that they were leading normal lives.¹⁸ However, work performance was impaired, with most parameters about 75% of predicted values. As in TOF, patient-perceived limitations are less than objectively measured parameters might predict.

Pregnancy and childbirth are generally well tolerated in

women after atrial switch operations, but in a minority functional class and/or right ventricular function may deteriorate and in some cases may not recover after delivery.⁸⁷

Although the follow-up studies of D-TGA after atrial repair are important to the adult congenital heart disease community, they are of less relevance to the patient born in the current era with D-TGA.

Management of D-Transposition of the Great Arteries Circa 1985 and its Late Follow-up

The transition from the atrial repair to the ASO spanned the decade of the 1980s. By 1985, patients with D-TGA with VSD were managed chiefly by ASO. Those with intact ventricular septum were still being managed by either technique.⁸⁸ By the end of the decade, nearly all were undergoing ASO. Thus, as in TOF, the current teenagers with D-TGA represent a heterogeneous group. Of most interest to this discussion of late outcomes is the follow-up of the early cohort of patients repaired by ASO.

Long-term survival after ASO has been excellent and may prove better than long-term survival after atrial switch. The Congenital Heart Surgeon's Society's multi-institution study enrolled 829 neonates from 24 institutions between 1985 and 1989 who were managed surgically according to the choice of the treating physician.⁸⁹ This cohort provided a unique opportunity to study patients treated concurrently with different surgical techniques, although assignment to surgical treatment was not random, so baseline difference between the groups could exist. Operative mortality at the time was 14.9% for ASO, 14.2% for the Senning procedure, and 3.6% for the Mustard procedure; 17-year survival estimates were 81%, 74%, and 94%, respectively. The hazard function for instantaneous death, although higher in the early phase for ASO, has a higher constant phase risk of death for the atrial repair group. If prior trends continue, a crossover of the mortality curves was expected to occur shortly after 17 years. Given that early phase mortality has been substantially reduced for ASO, long-term survival will likely be superior to that after atrial switch procedures. Two other long-term follow-up series that include patients from the early ASO era report 15-year survival of 86% to 88%.^{90,91}

Other long-term outcomes of interest in patients after ASO include the need for reoperation, coronary patency, neo-aortic valve competency, left ventricular function, rhythm disturbances, and functional status (including neurodevelopmental outcome). In one series, freedom from reoperation in survivors of the perioperative period was 82% at 15 years;⁹¹ in another series that included operative and transcatheter interventions, freedom from reoperation was slightly less than 60% at 15 years.⁹² Pulmonary stenosis was the most common reason for reintervention, accounting for 30% to 75% of procedures.⁹⁰⁻⁹² To our knowledge, no study has determined the true frequency of late coronary obstruction after ASO. In the two most frequently cited series, only 43% to 64% of survivors of the perioperative period underwent coronary angiography, and in these series, follow-up was short.^{93,94} Given these limitations, these studies found that 3.4% to 14.6% of patients repaired with usual coronary

transfer techniques had significant obstruction. Significant coronary stenosis or occlusion can be present in otherwise asymptomatic patients.⁹³ Although the long-term implications of neonatal coronary surgery in adulthood are unknown, the impact of adult cardiovascular disease (eg, hypertension, coronary artery disease, diabetes) will almost certainly be of greater significance in these patients than in those with normal hearts.

Neo-aortic insufficiency of moderate to severe degree has been uncommon to date (1% to 7%); in contrast, trivial to mild neo-aortic insufficiency is common (29% to 34%) at a mean follow-up of approximately 8 years.⁹⁵⁻⁹⁷ Neo-aortic root dilation is common and may have significant implications in adulthood as afterload increases. In a recent report from Boston, freedom from aortic root dilation (Z score ≥ 3) was only 51% at 10 years, and patients operated on more recently seem to be dilating earlier.⁹⁷ However, dilation does not seem to be progressive once a Z score ≥ 3 is reached. Thus, the functional fate of the neo-aortic root is unclear and may prove to be the most significant long-term issue in early adulthood. In contrast to the atrial level repairs, systemic ventricular function is normal in 97% to 99% of patients,⁹⁰⁻⁹² and significant arrhythmias are rare.⁹² Freedom from permanent pacemaker implantation at 15 years after ASO is 98%, in contrast to 89% after an atrial repair.⁸⁹ Functional status is excellent, with physical and psychosocial health status similar to the general population at 8 years of age⁹⁸ and with 97% of patients in NYHA class I.⁹² Exercise capacity in early childhood is normal.⁹⁹

Neurodevelopmental outcome has been extensively studied in the Boston Circulatory Arrest Trial, which enrolled neonates with D-TGA between 1988 and 1992. Eight-year follow-up demonstrated mean full-scale IQ 97.1, mean performance IQ 94.9, and mean verbal IQ 99.8.²⁰ All of these results fall within the normal range, but full-scale IQ and performance IQ are statistically lower than the population norm of 100. Deficits were noted in other outcomes, including academic achievement, fine motor function, visual-spatial skills, working memory, hypothesis generating and testing, sustained attention, and higher-order language skills.

Management of D-Transposition of the Great Arteries Circa 1995 and its Late Follow-up

By the mid 1990s, the ASO had essentially completely replaced the atrial level switch, except in rare complicated anatomic or clinical situations. The first decade of routine use of the ASO was marked by a decline in the operative mortality rates in several large series^{100,101} and increasing success with complex coronary patterns. Dibardino et al¹⁰² reported an overall 1.6% early mortality at their center since 1995; no patient was denied ASO on the basis of a coronary anomaly. Actuarial analysis of this series shows 96% survival and 90% freedom from reoperation at 7 years. In contrast, a publication from the PCCC using slightly older data (1992 to 1996) reported an overall hospital mortality of 15.1% with marked variation in mortality by center, ranging from 0% to 50%.¹⁰³ This study reminds us that publication bias favors good results, and although most results of the ASO in the literature

are outstanding, a subset of patients may not be enjoying such outcomes. Finally, prenatal diagnosis became increasingly common in the 1990s and has been embraced by clinicians as a mechanism to improve outcomes; however, a beneficial effect on long-term outcome has yet to be demonstrated.¹⁰⁴

Summary

The medium- and long-term outcomes for D-TGA are reassuring, although older patients after atrial repair are at risk for arrhythmia, ventricular failure, and sudden death. Although these sequelae are not likely to affect younger children with ASO to the same degree, new and emerging difficulties, such as coronary disease or aortic root dilation, may become the "Achilles heel" of the new approach. The transition of surgical management from the atrial to the arterial repair and its emerging sequelae reminds us of two important facts: (1) Innovation based on past results is necessary to improve overall outcomes, and (2) naïveté that the heart is "corrected" cannot replace systematic, comprehensive follow-up.

Hypoplastic Left Heart Syndrome

Hypoplastic left heart syndrome (HLHS) was the last common type of complex CHD to become amenable to surgical therapy. It was not until 1983 that Norwood et al¹⁰⁵ reported successful palliation of a patient with HLHS to the Fontan circulation. Thus, the longest follow-up for any patient with HLHS is just over 20 years, although additional predictions can be extrapolated from data on late outcomes of the Fontan palliation for other forms of CHD.

Management of Hypoplastic Left Heart Syndrome Circa 1985 and its Late Follow-up

The mid-1980s was early in the evolution of surgical palliation for HLHS, which was available at relatively few centers. Nonintervention ("compassionate care") was the standard at most hospitals. Mortality was high with surgery, with long-term survival of only ~30% for children treated in the mid-1980s at two high-volume institutions.^{106,107} The prevailing surgical strategy was to place a shunt large enough to last approximately 2 years and then to convert from the Stage I Norwood directly to a Fontan (unfenestrated). Restriction at the atrial septum, arch obstruction, and pulmonary artery distortion were common surgical sequelae, and the myocardial effects of long-term volume overload (until the Fontan operation) are now being recognized.

Aside from mortality, limited long-term follow-up data are available on the survivors of the early era of palliation for HLHS, likely because of the rarity of long-term survival. Cohen et al¹⁰⁸ reported on the fate of the neo-aortic root in 53 patients with HLHS born before 1995. At a median duration of follow-up of 9.2 years, 98% had a neo-aortic annulus Z score >2, a similar finding to the pattern of neo-aortic root dilation after ASO. Some degree of neo-aortic insufficiency was present in 61%, but was greater than mild in only 6%. Mahle et al²² reported on 143 school-aged survivors of staged palliation for HLHS born before 1992. There were three late deaths, and two patients underwent heart transplantation.

Parents of 83% of the remaining patients returned a questionnaire. At a mean age of 9 years, health by parental report was excellent in 45%, good in 40%, fair in 12%, and poor in 9%. Nineteen percent had been held back in school, and 34% required special instruction. Standardized testing was performed on a convenience sample of 28 patients who resided locally. Median values for full-scale IQ, verbal IQ, and performance IQ were 86, 90, and 83, respectively. Mental retardation (IQ <70) was noted in 18% of subjects. Rogers et al¹⁰⁹ reported a 64% incidence of mental retardation among 11 preschool-aged survivors of surgery for HLHS. Joshi et al¹¹⁰ reported the results of exercise testing in seven early Fontan survivors with HLHS. Mean $\dot{V}O_2$ was 25.9 mL/kg/min, with the normal range specified as 35.6 to 61.3. These results were comparable to those of subjects with Fontan palliation for other forms of single ventricle physiology.

Management of Hypoplastic Left Heart Syndrome Circa 1995 and its Late Follow-up

By 1995, surgical palliation of HLHS was more widely accepted and performed, although by no means was it considered the standard of care. Chang et al,¹¹¹ using national hospital discharge data for 1993 through 1997, reported that 48% of neonates with a diagnosis of HLHS died in the hospital without surgery or were discharged home without surgery. The management of an additional 23% was undefined due to transfer to another institution. For neonates in 1995 who underwent surgical treatment, several surgical innovations in the previous decade had decreased the early mortality of HLHS, including superior cavopulmonary connection as "second stage" operation¹⁰⁵ and fenestration of the baffle at Fontan completion.¹¹²⁻¹¹⁴ Survival at many institutions improved to approximately 65% to 70% at 5 years of age.^{106,114}

Unplanned reintervention after Stage I Norwood reconstruction most commonly occurs early in infancy, typically for recurrent coarctation, which occurs in up to 20% of patients.^{115,116} Restriction at the atrial septum recurred in 4% of patients who underwent Stage I reconstruction between 1984 and 2000.¹¹⁷ Additional series evaluating neurodevelopmental outcome, with somewhat overlapping surgical eras to those cited previously, have been performed. Kern et al¹¹⁸ studied 14 patients over 3 years of age with HLHS who had undergone operations for HLHS between 1990 and 1996. Median full-scale, verbal, and performance IQ were 88, 91, and 83, respectively. Goldberg et al¹¹⁹ reported on 26 patients with HLHS whose initial surgical palliation was performed between 1989 and 1994. This group had a mean full-scale IQ of 94 and verbal and performance scores of 99 and 90, respectively, which were not different from the general population.

Speculation on Late Outcomes of Hypoplastic Left Heart Syndrome

Little long-term follow-up data beyond mortality are available for patients who have undergone staged reconstruction for HLHS. Further conclusions must be extrapolated from data on the Fontan palliation in other lesions. The most comparable cohort reported underwent lateral tunnel Fontan between 1987 and 1991 at a single institution with a mean of

10.2 years of follow-up.¹²⁰ Of the 220 patients, 26 (12%) had HLHS. Median age at Fontan completion was 3.9 years, and fenestration was used in 63%. Freedom from new atrial tachyarrhythmias was 91% at 10 years, and 6% of patients underwent pacemaker placement in the follow-up period. Two patients developed hemiplegia 3 and 14 months after Fontan operation. Physician-assigned NYHA class distribution was class I, 41%; class II, 53%; and class III, 6%.

The National Heart, Lung and Blood Institute-sponsored Pediatric Heart Network (PHN) performed a multi-center cross-sectional study of 544 children with a Fontan circulation aged 6 to 18 years, recently reported in abstract form.¹²¹⁻¹²⁴ The median age at Fontan was 2.9 years. At the study evaluation, 32% of patients were not in sinus rhythm. Other medical morbidities included ventricular dysfunction (13%), thrombosis (6%), stroke (3%), and protein-losing enteropathy (PLE) (4%). PLE has been reported in other series to occur in 2.6% to 13.4% of patients after the Fontan operation and is associated with a 59% 5-year survival.¹²⁵⁻¹²⁷ The PHN study administered a generic QOL instrument, the Child Health Questionnaire. Physical and psychosocial summary scores were below normal.

Exercise capacity in the Fontan circulation is diminished due to abnormal stroke volume and chronotropic impairment, with maximal VO_2 ranging from 43% to 64% of normal.¹⁹ The PHN study reported a peak VO_2 of 65% predicted; higher peak VO_2 was correlated with younger age at testing and younger age at first volume unloading surgery (superior cavopulmonary anastomosis or Fontan completion).¹²⁴ Mahle et al¹²⁸ reported good maximal VO_2 (76% of predicted) in 46 children after lateral tunnel Fontan, 41% of whom had HLHS. Mean age at volume unloading surgery was 2.7 years. Earlier age at volume unloading was associated with improved aerobic capacity. These data provide hope that current management strategies will result in improved long-term outcomes.

The management of HLHS continues to evolve. Relative to the treatment of lesions such as TOF and D-TGA, the evolutionary process is much more active. Examples include the modification of Stage I reconstruction using a right ventricle to pulmonary artery conduit,¹²⁹ the choice between a lateral tunnel and extracardiac Fontan, modifications of cardiopulmonary bypass during Stage I surgery (eg, continuous cerebral perfusion), and proposed interventional catheter techniques to replace one or more stages of the Fontan. These innovations promise that assessing long-term outcomes in HLHS will continue to be a moving target for the foreseeable future and requires that systematic long-term studies follow any new approach.

Summary

The future for children and young adults born with CHD remains both optimistic and uncertain. What clinicians consider the most important “outcomes” (eg, mortality and re-intervention) may be different from the outcomes considered important to our patients (eg, QOL), their parents (eg, early functional limitations and recurrence risks), and society (eg,

cost of long-term sequelae). Truly “late” results await decades and decades of follow-up, when our management strategies will have changed significantly. Although they have improved upon the natural history of most lesions, surgical (and now transcatheter) interventions have created an “unnatural history” that requires ongoing, life-long, systematic follow-up.

References

1. Boneva RS, Botto LD, Moore CA, et al: Mortality associated with congenital heart defects in the United States: Trends and racial disparities, 1979-1997. *Circulation* 103:2376-2381, 2001
2. Morris CD, Menashe VD: 25-year mortality after surgical repair of congenital heart defect in childhood: A population-based cohort study. *JAMA* 266:3447-3452, 1991
3. Silka MJ, Hardy BG, Menashe VD, et al: A population-based prospective evaluation of risk of sudden cardiac death after operation for common congenital heart defects. *J Am Coll Cardiol* 32:245-251, 1998
4. Mavroudis C, Deal BJ, Backer CL: The beneficial effects of total cavopulmonary conversion and arrhythmia surgery for the failed Fontan. *Semin Thorac Cardiovasc Surg* 5:12-24, 2002
5. Murphy JG, Gersh BJ, McGoon MD, et al: Long-term outcome after surgical repair of isolated atrial septal defect: Follow-up at 27 to 32 years. *N Engl J Med* 323:1645-1650, 1990
6. Roos-Hesselink JW, Meijboom FJ, Spitaels SE, et al: Outcome of patients after surgical closure of ventricular septal defect at young age: Longitudinal follow-up of 22-34 years. *Eur Heart J* 25:1057-1062, 2004
7. Piran S, Veldtman G, Siu S, et al: Heart failure and ventricular dysfunction in patients with single or systemic right ventricles. *Circulation* 105:1189-1194, 2002
8. Burkhart HM, Dearani JA, Mair DD, et al: The modified Fontan procedure: Early and late results in 132 adult patients. *J Thorac Cardiovasc Surg* 125:1252-1259, 2003
9. Gelatt M, Hamilton RM, McCrindle BW, et al: Arrhythmia and mortality after the Mustard procedure: A 30-year single-center experience. *J Am Coll Cardiol* 29:194-201, 1997
10. Gatzoulis MA, Balaji S, Webb SA, et al: Risk factors for arrhythmia and sudden cardiac death late after repair of tetralogy of Fallot: A multicentre study. *Lancet* 356:975-981, 2000
11. Wolfe RR, Driscoll DJ, Gersony WM, et al: Arrhythmias in patients with valvar aortic stenosis, valvar pulmonary stenosis, and ventricular septal defect: Results of 24-hour ECG monitoring. *Circulation* 87:189-1101, 1993
12. Kammeraad JA, van Deurzen CH, Sreeram N, et al: Predictors of sudden cardiac death after Mustard or Senning repair for transposition of the great arteries. *J Am Coll Cardiol* 44:1095-1102, 2004
13. Dajani AS, Taubert KA, Wilson W, et al: Prevention of bacterial endocarditis: Recommendations by the American Heart Association. *Circulation* 96:358-366, 1997
14. Morris CD, Reller MD, Menashe VD: Thirty-year incidence of infective endocarditis after surgery for congenital heart defect. *JAMA* 279:599-603, 1998
15. Helber U, Baumann R, Seboldt H, et al: Atrial septal defect in adults: cardiopulmonary exercise capacity before and 4 months and 10 years after defect closure. *J Am Coll Cardiol* 29:1345-1350, 1997
16. Mitchell BM, Strasburger JF, Hubbard JE, et al: Serial exercise performance in children with surgically corrected congenital aortic stenosis. *Pediatr Cardiol* 24:319-324, 2003
17. Wessel HU, Paul MH: Exercise studies in tetralogy of Fallot: A review. *Pediatr Cardiol* 20:39-47, 1999
18. Paul MH, Wessel HU: Exercise studies in patients with transposition of the great arteries after atrial repair operations (Mustard/Senning): A review. *Pediatr Cardiol* 20:49-55, 1999
19. Driscoll DJ, Durongpisitkul K: Exercise testing after the Fontan operation. *Pediatr Cardiol* 20:57-59, 1999

20. Bellinger DC, Wypij D, duDuplessis AJ, et al: Neurodevelopmental status at eight years in children with dextro-transposition of the great arteries: The Boston Circulatory Arrest Trial. *J Thorac Cardiovasc Surg* 126:1385-1396, 2003
21. Wernovsky G, Stiles KM, Gauvreau K, et al: Cognitive development after the Fontan operation. *Circulation* 102:883-889, 2000
22. Mahle WT, Clancy RR, Moss EM, et al: Neurodevelopmental outcome and lifestyle assessment in school-aged and adolescent children with hypoplastic left heart syndrome. *Pediatrics* 105:1082-1089, 2000
23. Gaynor JW, Gerdes M, Zackai EH, et al: Apolipoprotein E genotype and neurodevelopmental sequelae of infant cardiac surgery. *J Thorac Cardiovasc Surg* 126:1736-1745, 2003
24. Bellinger DC, Wypij D, Kuban KC, et al: Developmental and neurological status of children at 4 years of age after heart surgery with hypothermic circulatory arrest or low-flow cardiopulmonary bypass. *Circulation* 100:526-532, 1999
25. Mahle WT, Wernovsky G: Long-term developmental outcome of children with complex congenital heart disease. *Clin Perinatol* 28:235-247, 2001
26. Majnemer A, Limperopoulos C: Developmental progress of children with congenital heart defects requiring open heart surgery. *Semin Pediatr Neurol* 6:12-19, 1999
27. Shillingford AJ, Wernovsky G: Academic performance and behavioral difficulties after neonatal and infant heart surgery. *Pediatr Clin North Am* 51:1625-1639, 2004
28. Vongpatanasin W, Brickner ME, Hillis LD, et al: The Eisenmenger syndrome in adults. *Ann Intern Med* 128:745-755, 1998
29. Siu SC, Sermer M, Colman JM, et al: Prospective multicenter study of pregnancy outcomes in women with heart disease. *Circulation* 104:515-521, 2001
30. Deanfield J, Thaulow E, Warnes C, et al: Management of grown up congenital heart disease. *Eur Heart J* 24:1035-1084, 2003
31. Foster E, Graham TP Jr, Driscoll DJ, et al: Task force 2: Special health care needs of adults with congenital heart disease. *J Am Coll Cardiol* 37:1176-1183, 2001
32. Child JS: Fallot's tetralogy and pregnancy: Prognostication and prophesy. *J Am Coll Cardiol* 44:181-183, 2004
33. Siu SC, Colman JM, Sorensen S, et al: Adverse neonatal and cardiac outcomes are more common in pregnant women with cardiac disease. *Circulation* 105:2179-2184, 2002
34. Canobbio MM, Mair DD, van der Velde M, et al: Pregnancy outcomes after the Fontan repair. *J Am Coll Cardiol* 28:763-767, 1996
35. Presbitero P, Somerville J, Stone S, et al: Pregnancy in cyanotic congenital heart disease: Outcome of mother and fetus. *Circulation* 89:2673-2676, 1994
36. Burn J, Brennan P, Little J, et al: Recurrence risks in offspring of adults with major heart defects: Results from first cohort of British collaborative study. *Lancet* 351:311-316, 1998
37. Keane JF, Driscoll DJ, Gersony WM, et al: Second natural history study of congenital heart defects: Results of treatment of patients with aortic valvar stenosis. *Circulation* 87:116-127, 1993
38. Hayes CJ, Gersony WM, Driscoll DJ, et al: Second natural history study of congenital heart defects: Results of treatment of patients with pulmonary valvar stenosis. *Circulation* 87:128-137, 1993
39. Kidd L, Driscoll DJ, Gersony WM, et al: Second natural history study of congenital heart defects: Results of treatment of patients with ventricular septal defects. *Circulation* 87:138-151, 1993
40. Gersony WM, Hayes CJ, Driscoll DJ, et al: Second natural history study of congenital heart defects: Quality of life of patients with aortic stenosis, pulmonary stenosis, or ventricular septal defect. *Circulation* 87:152-165, 1993
41. Moons P, Van Deyk K, Budts W, et al: Caliber of quality-of-life assessments in congenital heart disease: A plea for more conceptual and methodologic rigor. *Arch Pediatr Adolesc Med* 158:1062-1069, 2004
42. Lane DA, Lip GY, Millane TA: Quality of life in adults with congenital heart disease. *Heart* 88:71-75, 2002
43. Kamphuis M, Ottenkamp J, Vliegen HW, et al: Health related quality of life and health status in adult survivors with previously operated complex congenital heart disease. *Heart* 87:356-362, 2002
44. Neill CA, Clark EB: Tetralogy of Fallot: The first 300 years. *Texas Heart Inst J* 21:272-279, 1994
45. Blalock A, Taussig HB: The surgical treatment of malformations of the heart in which there is pulmonary stenosis or pulmonary atresia. *JAMA* 128:189-202, 1945
46. Lillehei CW, Cohen M, Warden HE, et al: Direct vision intracardiac surgical correction of the tetralogy of Fallot, pentalogy of Fallot, and pulmonary atresia defects: Report of the first ten cases. *Ann Surg* 142:418-445, 1955
47. Barratt-Boyes BG, Neutze JM: Primary repair of tetralogy of Fallot in infancy using profound hypothermia with circulatory arrest and limited cardiopulmonary bypass: A comparison with conventional two stage management. *Ann Surg* 178:406-411, 1973
48. Murphy JG, Gersh BJ, Mair DD, et al: Long-term outcome in patients undergoing surgical repair of tetralogy of Fallot. *N Engl J Med* 329:593-599, 1993
49. Nollert G, Fischlein T, Bouterwek S, et al: 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* 30:1374-1383, 1997
50. Norgaard MA, Lauridsen P, Helvind M, et al: Twenty-to-thirty-seven-year follow-up after repair for Tetralogy of Fallot. *Eur J Cardiothorac Surg* 16:125-130, 1999
51. Kirklin JW, Blackstone EH, Pacifico AD, et al: Routine primary repair vs two-stage repair of tetralogy of Fallot. *Circulation* 60:373-386, 1979
52. Conti VR, Bertranou EG, Blackstone EH, et al: Cold cardioplegia versus hypothermia for myocardial protection: Randomized clinical study. *J Thorac Cardiovasc Surg* 76:577-589, 1978
53. Arciniegas E, Farooki ZQ, Hakimi M, et al: Early and late results of total correction of tetralogy of Fallot. *J Thorac Cardiovasc Surg* 80:770-778, 1980
54. Zhao HX, Miller DC, Reitz BA, et al: Surgical repair of tetralogy of Fallot: Long-term follow-up with particular emphasis on late death and reoperation. *J Thorac Cardiovasc Surg* 89:204-220, 1985
55. Castaneda AR, Freed MD, Williams RG, et al: Repair of tetralogy of Fallot in infancy: Early and late results. *J Thorac Cardiovasc Surg* 74:372-381, 1977
56. Chiariello L, Meyer J, Wukasz DC, et al: Intracardiac repair of tetralogy of Fallot: Five-year review of 403 patients. *J Thorac Cardiovasc Surg* 70:529-535, 1975
57. Hokanson JS, Moller JH: Significance of early transient complete heart block as a predictor of sudden death late after operative correction of tetralogy of Fallot. *Am J Cardiol* 87:1271-1277, 2001
58. Garson A Jr, McNamara DG: Postoperative tetralogy of Fallot. *Cardiovasc Clin* 11:407-429, 1981
59. Ghai A, Silversides C, Harris L, et al: Left ventricular dysfunction is a risk factor for sudden cardiac death in adults late after repair of tetralogy of Fallot. *J Am Coll Cardiol* 40:1675-1680, 2002
60. Oechslin EN, Harrison DA, Harris L, et al: Reoperation in adults with repair of tetralogy of Fallot: Indications and outcomes. *J Thorac Cardiovasc Surg* 118:245-251, 1999
61. Harrison DA, Harris L, Siu SC, et al: Sustained ventricular tachycardia in adult patients late after repair of tetralogy of Fallot. *J Am Coll Cardiol* 30:1368-1373, 1997
62. Gatzoulis MA, Clark AL, Cullen S, et al: Right ventricular diastolic function 15 to 35 years after repair of tetralogy of Fallot: Restrictive physiology predicts superior exercise performance. *Circulation* 91:1775-1781, 1995
63. Cesnjevar R, Harig F, Raber A, et al: Late pulmonary valve replacement after correction of Fallot's tetralogy. *Thorac Cardiovasc Surg* 52:23-28, 2004
64. Yemets IM, Williams WG, Webb GD, et al: Pulmonary valve replacement late after repair of tetralogy of Fallot. *Ann Thorac Surg* 64:526-530, 1997
65. Therrien J, Siu SC, McLaughlin PR, et al: Pulmonary valve replacement in adults late after repair of tetralogy of Fallot: Are we operating too late? *J Am Coll Cardiol* 36:1670-1675, 2000
66. Niwa K, Siu SC, Webb GD, et al: Progressive aortic root dilatation in

- adults late after repair of tetralogy of Fallot. *Circulation* 106:1374-1378, 2002
67. Fredriksen PM, Therrien J, Veldtman G, et al: Aerobic capacity in adults with tetralogy of Fallot. *Cardiol Young* 12:554-559, 2002
 68. Carvalho JS, Shinebourne EA, Busst C, et al: Exercise capacity after complete repair of tetralogy of Fallot: Deleterious effects of residual pulmonary regurgitation. *Br Heart J* 67:470-473, 1992
 69. Veldtman GR, Connolly HM, Grogan M, et al: Outcomes of pregnancy in women with tetralogy of Fallot. *J Am Coll Cardiol* 44:174-180, 2004
 70. Bacha EA, Scheule AM, Zurakowski D, et al: Long-term results after early primary repair of tetralogy of Fallot. *J Thorac Cardiovasc Surg* 122:154-161, 2001
 71. Mulder TJ, Pyles LA, Stolfi A, et al: A multicenter analysis of the choice of initial surgical procedure in tetralogy of Fallot. *Pediatr Cardiol* 23:580-586, 2002
 72. Yetman AT, Lee KJ, Hamilton R, et al: Exercise capacity after repair of Tetralogy of Fallot in infancy. *Am J Cardiol* 87:1021-1023, 2001
 73. de Ruijter FT, Weenink I, Hitchcock FJ, et al: Right ventricular dysfunction and pulmonary valve replacement after correction of tetralogy of Fallot. *Ann Thorac Surg* 73:1794-1800, 2002
 74. Hirsch JC, Mosca RS, Bove EL: Complete repair of tetralogy of Fallot in the neonate: Results in the modern era. *Ann Surg* 232:508-514, 2000
 75. Goldmuntz E, Clark BJ, Mitchell LE, et al: Frequency of 22q11 deletions in patients with conotruncal defects. *J Am Coll Cardiol* 32:492-498, 1998
 76. Blalock A, Hanlon CR: The surgical treatment of complete transposition of the aorta and the pulmonary artery. *Surg Gynecol Obstet* 90:1-15, 1950
 77. Senning A: Surgical correction of transposition of the great vessels. *Surgery* 45:966-980, 1959
 78. Mustard WT: Successful two-stage correction of transposition of the great vessels. *Surgery* 55:469-472, 1964
 79. Rashkind WJ, Miller WW: Transposition of the great arteries: Results of palliation by balloon atrioseptostomy in thirty-one infants. *Circulation* 38:453-462, 1968
 80. Jatene AD, Fontes VF, Paulista PP, et al: Anatomic correction of transposition of the great vessels. *J Thorac Cardiovasc Surg* 72:364-370, 1976
 81. Norwood WI, Dobell AR, Freed MD, et al: Intermediate results of the arterial switch repair: A 20-institution study. *J Thorac Cardiovasc Surg* 96:854-863, 1988
 82. Newburger JW, Silbert AR, Buckley LP, et al: Cognitive function and age at repair of transposition of the great arteries in children. *N Engl J Med* 310:1495-1499, 1984
 83. Moons P, Gewillig M, Sluysmans T, et al: Long term outcome up to 30 years after the Mustard or Senning operation: A nationwide multicentre study in Belgium. *Heart* 90:307-313, 2004
 84. Roos-Hesselink JW, Meijboom FJ, Spitaels SE, et al: Decline in ventricular function and clinical condition after Mustard repair for transposition of the great arteries (a prospective study of 22-29 years). *Eur Heart J* 25:1264-1270, 2004
 85. Puley G, Siu S, Connelly M, et al: Arrhythmia and survival in patients >18 years of age after the mustard procedure for complete transposition of the great arteries. *Am J Cardiol* 83:1080-1084, 1999
 86. Moons P, De Bleser L, Budts W, et al: Health status, functional abilities, and quality of life after the Mustard or Senning operation. *Ann Thorac Surg* 77:1359-1365, 2004
 87. Guedes A, Mercier LA, Leduc L, et al: Impact of pregnancy on the systemic right ventricle after a Mustard operation for transposition of the great arteries. *J Am Coll Cardiol* 44:433-437, 2004
 88. Castaneda AR, Trusler GA, Paul MH, et al: The early results of treatment of simple transposition in the current era. *J Thorac Cardiovasc Surg* 95:14-28, 1988
 89. Williams WG, McCrindle BW, Ashburn DA, et al: Outcomes of 829 neonates with complete transposition of the great arteries 12-17 years after repair. *Eur J Cardiothorac Surg* 24:1-9, 2003
 90. Haas F, Wottke M, Poppert H, et al: Long-term survival and functional follow-up in patients after the arterial switch operation. *Ann Thorac Surg* 68:1692-1697, 1999
 91. Losay J, Touchot A, Serraf A, et al: Late outcome after arterial switch operation for transposition of the great arteries. *Circulation* 104:1121-1126, 2001
 92. Hutter PA, Krebs DL, Mantel SF, et al: Twenty-five years' experience with the arterial switch operation. *J Thorac Cardiovasc Surg* 124:790-797, 2002
 93. Tanel RE, Wernovsky G, Landzberg MJ, et al: Coronary artery abnormalities detected at cardiac catheterization following the arterial switch operation for transposition of the great arteries. *Am J Cardiol* 76:153-157, 1995
 94. Bonhoeffer P, Bonnet D, Piechaud JF, et al: Coronary artery obstruction after the arterial switch operation for transposition of the great arteries in newborns. *J Am Coll Cardiol* 29:202-206, 1997
 95. Hutter PA, Thomeer BJ, Jansen P, et al: Fate of the aortic root after arterial switch operation. *Eur J Cardiothorac Surg* 20:82-88, 2001
 96. Formigari R, Toscano A, Giardini A, et al: Prevalence and predictors of neo-aortic regurgitation after arterial switch operation for transposition of the great arteries. *J Thorac Cardiovasc Surg* 126:1753-1759, 2003
 97. Schwartz ML, Gauvreau K, del Nido P, et al: Long-term predictors of aortic root dilation and aortic regurgitation after arterial switch operation. *Circulation* 110:III128-III132, 2004
 98. Dunbar-Masterson C, Wypij D, Bellinger DC, et al: General health status of children with D-transposition of the great arteries after the arterial switch operation. *Circulation* 104:1138-1142, 2001
 99. Mahle WT, McBride MG, Paridon SM: Exercise performance after the arterial switch operation for D-transposition of the great arteries. *Am J Cardiol* 87:753-758, 2001
 100. Prifti E, Crucean A, Bonacchi M, et al: Early and long term outcome of the arterial switch operation for transposition of the great arteries: predictors and functional evaluation. *Eur J Cardiothorac Surg* 22:864-873, 2002
 101. Brown JW, Park HJ, Turrentine MW: Arterial switch operation: factors impacting survival in the current era. *Ann Thorac Surg* 71:1978-1984, 2001
 102. Dibardino DJ, Allison AE, Vaughn WK, et al: Current expectations for newborns undergoing the arterial switch operation. *Ann Surg* 239:588-596, 2004
 103. Scott WA, Fixel DE: Effect of center volume on outcome of ventricular septal defect closure and arterial switch operation. *Am J Cardiol* 88:1259-1263, 2001
 104. Bartlett JM, Wypij D, Bellinger DC, et al: Effect of prenatal diagnosis on outcomes in D-transposition of the great arteries. *Pediatrics* 113:e335-e340, 2004
 105. Norwood WI, Lang P, Hansen DD: Physiologic repair of aortic atresia-hypoplastic left heart syndrome. *N Engl J Med* 308:23-26, 1983
 106. Mahle WT, Spray TL, Wernovsky G, et al: Survival after reconstructive surgery for hypoplastic left heart syndrome: A 15-year experience from a single institution. *Circulation* 102:III136-III141, 2000
 107. Forbess JM, Cook N, Serraf A, et al: An institutional experience with second- and third-stage palliative procedures for hypoplastic left heart syndrome: The impact of the bidirectional cavopulmonary shunt. *J Am Coll Cardiol* 29:665-670, 1997
 108. Cohen MS, Marino BS, McElhinney DB, et al: Neo-aortic root dilation and valve regurgitation up to 21 years after staged reconstruction for hypoplastic left heart syndrome. *J Am Coll Cardiol* 42:533-540, 2003
 109. Rogers BT, Msall ME, Buck GM, et al: Neurodevelopmental outcome of infants with hypoplastic left heart syndrome. *J Pediatr* 126:496-498, 1995
 110. Joshi VM, Carey A, Simpson P, et al: Exercise performance following repair of hypoplastic left heart syndrome: A comparison with other types of Fontan patients. *Pediatr Cardiol* 18:357-360, 1997
 111. Chang RK, Chen AY, Klitzner TS: Clinical management of infants with hypoplastic left heart syndrome in the United States, 1988-1997. *Pediatrics* 110:292-298, 2002
 112. Gaynor JW, Bridges ND, Cohen MI, et al: Predictors of outcome after the Fontan operation: Is hypoplastic left heart syndrome still a risk factor? *J Thorac Cardiovasc Surg* 123:237-245, 2002

113. Bridges ND, Mayer JE Jr., Lock JE, et al: Effect of baffle fenestration on outcome of the modified Fontan operation. *Circulation* 86:1762-1769, 1992
114. Bove EL: Current status of staged reconstruction for hypoplastic left heart syndrome. *Pediatr Cardiol* 19:308-315, 1998
115. Chessa M, Dindar A, Vettukattil JJ, et al: Balloon angioplasty in infants with aortic obstruction after the modified stage I Norwood procedure. *Am Heart J* 140:227-231, 2000
116. Tworetzky W, McElhinney DB, Burch GH, et al: Balloon arterioplasty of recurrent coarctation after the modified Norwood procedure in infants. *Cath Cardiovasc Int* 50:54-58, 2000
117. Mahle WT, Rychik J, Gaynor JW, et al: Restrictive interatrial communication after reconstructive surgery for hypoplastic left heart syndrome. *Am J Cardiol* 88:1454-1457, 2001
118. Kern JH, Hinton VJ, Nereo NE, et al: Early developmental outcome after the Norwood procedure for hypoplastic left heart syndrome. *Pediatrics* 102:1148-1152, 1998
119. Goldberg CS, Schwartz EM, Brunberg JA, et al: Neurodevelopmental outcome of patients after the Fontan operation: A comparison between children with hypoplastic left heart syndrome and other functional single ventricle lesions. *J Pediatr* 137:646-652, 2000
120. Stamm C, Friehs I, Mayer JE, et al: Long-term results of the lateral tunnel Fontan operation. *J Thoracic Cardiovasc Surg* 121:28-41, 2001
121. Clark BJ III, Sleeper LA, Anderson PA, et al: The Fontan cross-sectional study: Testing for correlations among health-related quality of life, maximal exercise performance, and ventricular mass-to-volume ratio [abstract]. *Circulation* 110:III441, 2004
122. McCrindle BW, Williams RV, Mitchell PD, et al: The relationship of medical and patient characteristics to health-related quality of life in adolescents after the Fontan procedure [abstract]. *Circulation* 110:III441, 2004
123. Blaufox AD, Sleeper LA, Bradley DJ, et al: Association of functional status and heart rate and rhythm at rest and in response to exercise in 508 Fontan patients 6-18 years of age [abstract]. *Circulation* 110:III442, 2004
124. Paridon SM, Mitchell PD, Blaufox AD, et al: A cross-sectional study of exercise performance during the first two decades of life following the Fontan procedure [abstract]. *Circulation* 110:III386, 2004
125. Gentles TL, Gauvreau K, Mayer JE, et al: Functional outcome after the Fontan operation: Factors influencing late morbidity. *J Thoracic Cardiovasc Surg* 114:392-403, 1997
126. Feldt RH, Driscoll DJ, Offord KP, et al: Protein-losing enteropathy after the Fontan operation. *J Thoracic Cardiovasc Surg* 112:672-680, 1996
127. Mertens L, Hagler DJ, Sauer U, et al: Protein-losing enteropathy after the Fontan operation: An international multicenter study. *J Thoracic Cardiovasc Surg* 115:1063-1073, 1998
128. Mahle WT, Wernovsky G, Bridges ND, et al: Impact of early ventricular unloading on exercise performance in preadolescents with single ventricle Fontan physiology. *J Am Coll Cardiol* 34:1637-1643, 1999
129. Sano S, Ishino K, Kawada M, et al: Right ventricle-pulmonary artery shunt in first-stage palliation of hypoplastic left heart syndrome. *J Thoracic Cardiovasc Surg* 126:504-509, 2003