

Canadian Cardiovascular Society 2009 Consensus Conference on the management of adults with congenital heart disease: Complex congenital cardiac lesions

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With advances in pediatric cardiology and cardiac surgery, the population of adults with congenital heart disease (CHD) has increased. In the current era, there are more adults with CHD than children. This population has many unique issues and needs. They have distinctive forms of heart failure and their cardiac disease can be associated with pulmonary hypertension, thromboemboli, complex arrhythmias and sudden death. Medical aspects that need to be considered relate to the long-term and multisystemic effects of single ventricle physiology, cyanosis, systemic right ventricles, complex intracardiac baffles and failing subpulmonary right ventricles. Since the 2001 Canadian Cardiovascular Society Consensus Conference report on the management of adults with CHD, there have been significant advances in the field of adult CHD. Therefore, new clinical guidelines have been written by Canadian adult CHD physicians in collaboration with an international panel of experts in the field. Part III of the guidelines includes recommendations for the care of patients with complete transposition of the great arteries, congenitally corrected transposition of the great arteries, Fontan operations and single ventricles, Eisenmenger's syndrome, and cyanotic heart disease. Topics addressed include genetics, clinical outcomes, recommended diagnostic workup, surgical and interventional options, treatment of arrhythmias, assessment of pregnancy risk and follow-up requirements. The complete document consists of four manuscripts, which are published online in the present issue of *The Canadian Journal of Cardiology*. The complete document and references can also be found at www.ccs.ca or www.cachnet.org.

Key Words: Adult congenital heart disease; Complete transposition of the great arteries; Congenital heart disease; Congenitally corrected transposition of the great arteries; Cyanotic heart disease; Eisenmenger's syndrome; Fontan operation; Guidelines; Single ventricle

COMPLETE TRANSPOSITION OF THE GREAT ARTERIES

Part I. Background information

In complete transposition of the great arteries (TGA), there is atrioventricular (AV) concordance and ventriculoarterial discordance (ie, the right atrium [RA] connects to the morphological right ventricle [RV], which gives rise to the aorta, and the left atrium connects to the

La conférence consensuelle 2009 de la Société canadienne de cardiologie sur la prise en charge des adultes ayant une cardiopathie congénitale : Résumé

Étant donné les progrès de la cardiologie pédiatrique et de la chirurgie cardiaque, la population d'adultes ayant une cardiopathie congénitale (CPC) a augmenté. Il y a maintenant plus d'adultes que d'enfants ayant une CPC. Cette population a de nombreux problèmes et besoins uniques. Ces adultes ont des formes particulières d'insuffisance cardiaque, et leur maladie cardiaque peut s'associer à une hypertension pulmonaire, à des thromboembolies, à des arythmies complexes et à une mort subite. Les aspects médicaux à envisager sont liés aux effets multisystémiques et à long terme de la physiologie monoventriculaire, de la cyanose, des ventricules droits systémiques, des cloisons intracardiaques complexes et de l'insuffisance du ventricule droit sous-pulmonaire. Depuis le rapport de la conférence consensuelle 2001 de la Société canadienne de cardiologie sur la prise en charge des adultes ayant une CPC, on constate d'importantes avancées dans la compréhension des issues tardives, de la génétique, de la thérapie médicale et des démarches d'intervention dans le domaine des CPC chez les adultes. Par conséquent, de nouvelles lignes directrices cliniques ont été rédigées par des médecins canadiens s'occupant des CPC chez les adultes, en collaboration avec un groupe d'experts internationaux dans le domaine. Le présent résumé donne un bref aperçu des nouvelles lignes directrices et contient les recommandations d'interventions. Le document complet se compose de quatre manuscrits publiés par voie électronique dans le présent numéro du *Journal canadien de cardiologie*, y compris des rubriques sur la génétique, les issues cliniques, les bilans diagnostiques recommandés, les possibilités chirurgicales et d'intervention, le traitement des arythmies, l'évaluation des risques de la grossesse et de la contraception et les recommandations de suivi. Le document complet et les références figurent également aux adresses www.ccs.ca et www.cachnet.org.

morphological left ventricle [LV], which gives rise to the pulmonary artery [PA]).

Approximately two-thirds of patients have no major associated abnormality ('simple' transposition). Approximately one-third have associated abnormalities ('complex' transposition), the most common being ventricular septal defect (VSD), pulmonary/subpulmonary stenosis, patent ductus arteriosus and coarctation. Variations in the origin and

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course of coronary arteries are present in one-third of patients, and an intramural coronary artery course is present in 3% to 4% (1,2).

Part II. Genetics

In general, there is no clear association with a genetic syndrome. Very rarely, TGA can occur in the context of trisomy 1. There is a 2:1 male preponderance.

Part III. History and management

Unoperated, simple transposition is a lethal condition with 90% mortality in the first year of life (3). Associated lesions have a marked effect on prognosis. Nearly all patients seen as adults will have had intervention.

The most common surgical procedure in patients who are now adult remains the atrial switch operation in the form of a Senning or a Mustard procedure. Blood is redirected at the atrial level using atrial flaps (Senning operation), or a baffle composed of Dacron or pericardium (Mustard operation), achieving physiological correction. The RV continues to support the systemic circulation.

The atrial switch operation has been supplanted by the arterial switch operation (Jatene procedure), with the oldest recipients now having reached adulthood. Blood is redirected at the great artery level by switching the aorta and PAs so that the LV supports the systemic circulation. The coronary arteries are translocated to the neo-aorta (formerly the PA). Tissue resected from the sinuses of the neo-PA is replaced by pericardial patches. The PA is usually translocated anterior to the aorta (Lecompte manoeuvre).

In a small proportion of patients (less than 10%) who have a VSD and pulmonary/subpulmonary stenosis, a Rastelli operation will have been performed. This surgery involves redirecting blood flow at the ventricular level (with the LV outflow tunnelled to the aorta) and a valved conduit from the RV to the PA. The LV supports the systemic circulation.

Part IV. Diagnostic workup in operated patients

All patients with complete transposition should have regular echocardiograms (echos) and/or other cardiac imaging studies interpreted by individuals with expertise in adult congenital cardiac imaging.

Cardiac catheterization and arrhythmia interventions in patients with complete transposition should be performed in centres with expertise in adult congenital heart disease (ACHD).

Class I, level C

Because virtually all adult patients will have had surgery, investigations are directed toward postoperative sequelae and will vary according to the type of operation performed.

All patients should have the following (at a minimum):

- A thorough clinical assessment.
- Electrocardiogram (ECG).
- Chest x-ray.
- Resting oxygen saturation.
- Transthoracic echo-Doppler evaluation by an appropriately trained individual. In patients with an atrial switch operation, assessment should include evaluation of systemic ventricular function, baffle obstruction or baffle leaks, AV valve regurgitation and subpulmonary obstruction. In patients with an arterial switch operation, assessment should include ventricular function, RV outflow obstruction (the most common problem is branch pulmonary stenosis due to the Lecompte manoeuvre), neo-aortic root dilation, valvular regurgitation and coronary ostial status (this may be difficult to assess in an adult). In patients with a Rastelli operation, the assessment should include ventricular function, obstruction of the RV-to-PA conduit, patency of the connection between the LV (posteriorly positioned) and the aortic valve (anteriorly positioned), discrete subaortic stenosis, aortic regurgitation and AV valve regurgitation.

Patients who have had an atrial switch operation may also require the following:

- Echo with contrast injection for detection of baffle leaks. In some patients, transesophageal echo (TEE) may be necessary to assess baffle anatomy and function.
- A Holter monitor in patients with a history suggestive of arrhythmias or syncope.
- Cardiac magnetic resonance imaging (MRI) to evaluate baffle anatomy, and ventricular volumes and function.
- Radionuclide angiography may be an alternative for quantitative assessment of RV function in patients not able to undergo a cardiac MRI.
- Multidetector computed tomography (CT) angiography may be an alternative to MRI for assessment of intra-atrial baffle anatomy, and RV size and function.
- Exercise testing to evaluate functional capacity, including heart rate and blood pressure response, and oxygen saturation to unmask shunting due to baffle leaks and to assess whether arrhythmias may be provoked.
- Heart catheterization, including coronary angiography if there are doubts about additional lesions, if surgical reintervention is planned or if adequate assessment of the hemodynamics is not obtained by noninvasive means.
- Electrophysiological study to assess documented or suspected arrhythmias.

Patients who have had an arterial switch operation also require the following:

- Periodic functional testing for coronary ischemia.
- Selective coronary angiography or other imaging modalities if ischemia is suspected.

These patients may also require the following:

- Holter monitoring, if arrhythmia is suspected.
- Complete heart catheterization if adequate assessment of the hemodynamic status is not obtained by noninvasive means or additional lesions are suspected.
- MRI to assess PA stenosis (subvalvular, pulmonary trunk, branch PA). Multidetector CT angiography is an alternative if MRI is not possible.

Patients who have had a Rastelli operation may also require the following:

- Holter monitoring if arrhythmia is suspected.
- MRI to assess RV size and function, conduit function and PA anatomy. Multidetector CT angiography is an alternative if MRI is not possible.
- Heart catheterization to assess conduit function and severity of conduit failure, and the status of the distal PAs if inadequate information is obtained from noninvasive testing and surgery is contemplated.

Part V. Indications for reintervention

The following situations may warrant reintervention following the atrial switch procedure:

- Significant systemic (tricuspid) AV valve regurgitation without significant ventricular dysfunction.
- Superior vena cava (SVC) or inferior vena cava (IVC) pathway obstruction.
- Pulmonary venous pathway obstruction.
- Baffle leak resulting in a significant left-to-right shunt ($Q_p:Q_s$ of greater than 1.5:1), symptoms, pulmonary hypertension or progressive ventricular enlargement/dysfunction.
- Baffle leak resulting in a significant right-to-left shunt and symptoms.
- Symptomatic bradyarrhythmias or tachyarrhythmias.

Class IIa, level C (4-11)

The following situations may warrant reintervention following the arterial switch procedure:

- Significant PA stenosis (subvalvular, pulmonary trunk or branch PA).
- Coronary arterial obstruction.
- Severe neo-aortic valve regurgitation.
- Severe neo-aortic root dilation.

Class IIa, level C (12-17)

The following situations may warrant reintervention following the Rastelli procedure:

- Significant RV-to-PA conduit obstruction.
- Severe RV-to-PA conduit regurgitation with symptoms, progressive RV enlargement, and the occurrence of atrial or ventricular arrhythmias.
- Severe subaortic obstruction across the LV-to-aorta tunnel (mean gradient of greater than 50 mmHg).
- Significant branch PA stenosis.
- Residual VSD resulting in a Qp:Qs of greater than 1.5:1, pulmonary hypertension or progressive LV enlargement/dysfunction.

Class IIa, level C (18,19)

Part VI. Surgical/interventional/management options

Patients who require reintervention should be treated by ACHD cardiologists and congenital heart surgeons with appropriate experience.

Class I, level C (20,21)

A. Atrial switch operations:

Systemic RV dysfunction:

- The role of medical therapy in patients with a failing systemic RV has not been established (22-26). Beta-blockers have also been associated with fewer appropriate implantable cardioverter defibrillator (ICD) shocks (27).
- Although electrical dyssynchrony is a common finding in TGA patients with a systemic RV, the selection of appropriate candidates for cardiac resynchronization therapy remains to be determined (28-31). Epicardial leads are often required to pace the systemic RV.
- A conversion procedure to an arterial switch following retraining of the LV with a PA band is experimental, with little data available in adults (9,32,33). The LV of an adult with an arterial switch seems less likely to be successfully retrained than the LV of a pediatric patient. In some patients, PA banding alone may be an effective palliative procedure that improves RV geometry. This intervention can precipitate LV failure and should only be performed at centres with expertise in the procedure (34,35).
- In some patients, heart transplantation should be considered.

Baffle obstruction/leaks:

- Surgery or percutaneous interventions may be necessary for baffle stenosis or leakage in symptomatic patients, or in those requiring a transvenous pacemaker or ICD. If there are no other indications for surgery, percutaneous stenting is the treatment of choice, with surgery being reserved for failures or complete baffle occlusions that cannot be recanalized (4,36). These procedures should be performed in centres with experience in these techniques. The Senning operation is associated with a lower incidence of systemic venous pathway obstruction than the Mustard baffle, but more frequent pulmonary venous obstruction (37). Chronic stenosis of either the SVC or IVC baffle is often tolerated due to adequate collateral circulation through the azygos system. Progressive SVC stenosis is often benign, unlike IVC stenosis, which may be life threatening. Stent insertion may be considered for SVC or IVC stenosis.

Intrinsic tricuspid valve abnormalities:

- Patients with an atrial switch procedure and severe systemic (tricuspid) AV valve regurgitation may benefit from valve replacement if systemic ventricular function is adequate; PA banding to improve tricuspid regurgitation by altering septal geometry might be considered as an alternative for valve replacement.

B. Arterial switch operations:

Coronary artery obstruction:

- In patients with a previous arterial switch procedure, myocardial ischemia can be clinically silent, and noninvasive functional tests to detect coronary artery obstruction have limited sensitivity (38). Significant coronary sequelae are found in 5% to 10% of children undergoing routine coronary angiography (13,38).
- The benefit of intervening in coronary obstructions without previous documentation of reversible ischemia has not yet been elucidated and may not outweigh procedure-related risks. When symptomatic, patients may require coronary artery bypass grafting (preferably with arterial conduits) or percutaneous interventions for myocardial ischemia.

RV outflow tract augmentation:

- Patients who have had an arterial switch operation may require surgical reintervention to augment the RV outflow tract for outflow tract obstruction.

C. Rastelli operation:

Conduit/LV-to-aorta baffle revisions:

- Rastelli conduits are subject to failure over time, with one-half requiring conduit replacement at 10 years and two-thirds requiring replacement at 20 years (39).
- Patients who have had a Rastelli operation may require LV-to-aorta baffle revision because of obstruction.

Part VII. Surgical/interventional outcomes

The survival rate of patients who have had an atrial switch procedure is approximately 75% to 85% at 25 years, with increased likelihood of survival with later year of operation (7,40). Late mortality is generally lower in patients with 'simple' transposition (10% at 25 years) than in those with 'complex' transposition (25% at 25 years) (7). Causes of death include sudden unexpected (presumed arrhythmic) death, heart failure, baffle obstruction, pulmonary vascular disease and reoperation.

Midterm survival data following the arterial switch are beginning to emerge. The mortality rate after the first postoperative year is low (14,16). Neo-aortic root dilation, neo-aortic valve regurgitation, PA stenosis and coronary artery stenosis/occlusion are recognized complications. The association of a VSD, and a discrepancy in the size of the native aorta and PA predispose to neo-aortic root dilation after the switch operation. Supravalvular PA stenosis, especially branch PA stenosis, is the most common late complication (12,14). Neo-aortic root dilation is common and can result in aortic regurgitation (16,17). At this point in time, we have no true long-term follow-up data.

The survival curve of patients with a previous Rastelli operation indicates substantial late mortality. Overall survival is 70% at 15 years. Sudden death, LV dysfunction and reoperation contribute to late mortality (19). Following the Rastelli operation, repeated conduit changes are often necessary.

Part VIII. Arrhythmia

Atrial flutter/intra-atrial re-entry tachycardia occurs in 20% of atrial switch patients by 20 years of age. Progressive sinus node dysfunction and/or junctional rhythm are seen in more than one-half of the patients by that time (8,40,41). Atrial macro-reentrant rhythms in patients with TGA tend to have a slower atrial rate than typical atrial flutter. This may facilitate 1:1 conduction, which, in turn, may result in hemodynamic instability. An aggressive management strategy to prevent rapidly conducting atrial tachyarrhythmias is generally advisable.

Supraventricular arrhythmias may precede or coexist with ventricular arrhythmias (42). Catheter ablation is often considered the treatment of choice, but should be performed by electrophysiologists with knowledge and expertise in congenital heart disease (CHD) (43).

Primary ventricular arrhythmias (ie, monomorphic and polymorphic ventricular tachycardia and ventricular fibrillation) have also been noted, and may relate to decreasing RV function (27). Risk factors for sudden death include symptoms of arrhythmias, documented atrial fibrillation or flutter, systemic ventricular dysfunction and age. Selecting appropriate candidates for primary prevention ICDs remains a major challenge.

When transvenous pacemakers or ICD leads are required, issues regarding vascular access and lead positioning must be overcome (44). Stenting of a baffle stenosis or obstruction may permit transvenous lead implantation (45). Routine venography, CT angiography or MRI before surgical incision is recommended to assess the patency of the systemic venous pathway. When venous access is prohibitive and/or transvenous approaches are contraindicated, epicardial leads should be considered.

Pacemaker insertion for symptomatic bradycardia or antitachycardia pacing for some atrial arrhythmias may be required. Before transvenous lead implantation, the superior baffle must be evaluated for stenosis and/or baffle leaks with appropriate intervention undertaken. (Level B)

Given the association between rapidly conducting atrial arrhythmias and sudden death, an aggressive management strategy that includes catheter ablation is often recommended. (Level C) Ablation and device implantation should be undertaken by an electrophysiologist with appropriate training/experience in the ACHD population. (Level C)
Class I, level B or C as indicated (8,41,42,45-48)

In patients with sustained ventricular tachyarrhythmia and/or resuscitated from sudden cardiac death with no clear identified reversible cause, ICDs are indicated for secondary prevention.
Class I, level B (27)

Patients deemed to be at particularly high risk for sudden cardiac death may benefit from ICDs for primary prevention.
Class IIb, level C

Sustained monomorphic ventricular tachycardia and supraventricular tachycardias may occur late after the Rastelli operation. In these patients, evaluation of hemodynamic alterations, including conduit dysfunction, is recommended.

Midterm outcomes after an arterial switch operation suggest a low incidence of arrhythmias. Ventricular arrhythmias may be related to coronary artery obstruction.

Part IX. Pregnancy and contraception

Pregnancy in women with a normal functional class following an atrial switch operation is usually well tolerated. Arrhythmias and worsening systemic RV function, sometimes irreversible, during or shortly after pregnancy, are reported in approximately 10% to 35% of patients (49-52). In addition to the known lesion-specific risks, general cardiac risk factors for adverse events during pregnancy need to be incorporated into the risk assessment (53,54). There may be a higher incidence of spontaneous miscarriages and obstetric complications than in the general population. Because of the teratogenic effects, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers should be discontinued.

Pregnancy is generally well tolerated in women with a previous Rastelli operation, normal functional class and preserved conduit function. Arrhythmias may increase during pregnancy.

Only a few reports describe pregnancy in women with a previous arterial switch operation. Although data are limited, pregnancy in a woman with good functional class should generally be well tolerated in the absence of significant hemodynamic residue or sequelae.

All women with complete transposition contemplating pregnancy should undergo a comprehensive cardiological evaluation at an ACHD centre and, preferably, have preconception counselling.
Class I, level C (49-52,55)

Part X. Follow-up

All patients should have regular cardiology follow-up by an ACHD cardiologist.
Class I, level C

Endocarditis prophylaxis is not recommended in patients who have had an atrial switch operation or an arterial switch operation, unless there is a history of infective endocarditis, and a residual VSD after patch closure and during the first six months after prosthetic patch or device implantation.
Class III, level B (56)

Endocarditis prophylaxis is required in patients who have had a Rastelli operation with an RV-to-PA conduit.
Class I, level B (56)

CONGENITALLY CORRECTED TGA

Part I. Background

Congenitally corrected TGA (CCTGA) is characterized by a double discordance, with AV and ventriculoarterial discordance. Hence, systemic venous return to the RA enters the morphological LV (through a morphological mitral valve), which then pumps this blood to the PA. The pulmonary venous return from the left atrium enters a morphological RV (through a morphological tricuspid valve), which then ejects the blood into the aorta. This arrangement provides a 'corrected' physiology but with a morphological RV supporting the systemic circulation. Other terms used for this condition are levo-TGA, ventricular inversion and double discordance.

Part II. Prevalence and associated lesions

The prevalence of CCTGA has been estimated at 0.03 per 1000 live births, which accounts for 0.4% of all congenital heart defects (57). The majority of patients have associated congenital cardiac anomalies and only approximately 1% of patients have an isolated CCTGA. Associated cardiac anomalies include VSDs (60% to 80%; majority are perimembranous), pulmonary stenosis (30% to 50%; majority are associated with a VSD) and tricuspid valve (systemic AV valve [SAVV]) anomalies (close to 60%; majority are Ebstein-like malformations). The AV node and His bundle are characteristically displaced.

Part III. History and management in unoperated patients

Patients with isolated CCTGA may go unrecognized until the third or fourth decade of life due to lack of symptoms, and survival into the sixth or seventh decade of life has been reported in such patients (58-61). However, many patients develop symptoms associated with progressive systemic ventricular dysfunction, systemic AV valve regurgitation and complete heart block. Spontaneous complete heart block in these patients occurs at a rate of 2% per year, irrespective of associated anomalies (62,63). There is also an increase in the incidence of atrial arrhythmias in adult survivors.

The majority of patients with CCTGA are born with hemodynamically significant associated cardiac defects that require intervention early in life. If possible, surgical intervention in children is aimed not only at correcting the hemodynamic lesion (eg, VSD), but restoring the LV as the systemic ventricle. In patients with an unrestricted VSD and subpulmonic obstruction, anatomical repair (Ilbawi type: LV tunnel to aorta via VSD, RV-to-PA conduit and atrial switch procedure) is often performed. Surgery for adult patients is predominantly for significant systemic AV valve regurgitation and/or AV block. Pacemaker implantation for AV block is often indicated.

Survival is better in the absence of associated anomalies but remains limited in comparison with the general population. Usual

causes of death are sudden (presumed arrhythmic) and progressive ventricular dysfunction with systemic (tricuspid) AV valve regurgitation (60,61).

Part IV. Diagnostic workup

All patients with CCTGA should have regular echos and/or other cardiac imaging studies interpreted by individuals with expertise in adult congenital cardiac imaging.

Cardiac catheterization and arrhythmia interventions for adults with CCTGA should be performed in centres with expertise in ACHD.

Class I, level C

An adequate diagnostic workup includes the following:

- Documentation of the anatomy described above.
- Assessment of the presence and severity of associated abnormalities that may influence management (VSD, pulmonary/subpulmonic stenosis, systemic [tricuspid] AV valve regurgitation, systemic ventricular function and AV block).

The diagnostic workup should include the following (at a minimum):

- A thorough clinical assessment (history and physical).
- ECG.
- Chest x-ray.
- Transthoracic echo.
- Exercise or cardiopulmonary testing with oximetry.

The diagnostic workup may require the following:

- Holter monitor to assess the presence of arrhythmias (atrial arrhythmias, heart block).
- TEE.
- Cardiac MRI for assessment of ventricular volumes, mass, systolic function and conduit function.
- Multidetector CT is an alternative for assessment if MRI is not feasible.
- Radionuclide angiography to assess systemic RV systolic function.
- Complete heart catheterization to assess the hemodynamics, especially in the operated patient who has a conduit between the LV and PA, or the unoperated patient who is being considered for surgery.
- Coronary angiography in patients at risk of coronary artery disease, or if the patient is older than 40 years of age and surgery is planned.
- Electrophysiological study for documented or suspected arrhythmias.

Part VI. Indications for intervention/reintervention

Unoperated patients with a VSD and significant pulmonary outflow tract obstruction are often cyanotic, and may have had palliation with systemic-to-PA shunts in childhood. In these patients, the presence of significant cyanosis (O₂ saturation of less than 90% on room air) in the absence of severe pulmonary hypertension should prompt consideration for intracardiac repair.

In patients with moderate or greater SAVV regurgitation, replacement of the SAVV may delay the progression of systemic RV dysfunction and should be considered before development of severe systemic RV dysfunction (64).

The following situations may warrant surgical intervention/reintervention:

- Presence of VSD or residual VSD. **(Level C)**
 - Moderate or severe SAVV regurgitation. **(Level B)**
 - Hemodynamically significant pulmonary or subpulmonary obstruction. **(Level B)**
 - Significant stenosis across an LV-to-PA conduit. **(Level C)**
 - Deteriorating systemic (right) ventricular function. **(Level C)**
- Class IIa, level B or C as indicated (18,20,64-68)**

Part V. Medical/interventional options

There are no data available to support the use of standard heart failure medications in patients with CCTGA and significant systemic ventricular dysfunction. However, it is common practice to use standard heart failure medications until data become available. Antiarrhythmic agents and drugs that are known to influence AV node conduction should be used cautiously in patients without pacemakers.

Patients who require intervention or reintervention should be treated by ACHD cardiologists and congenital heart surgeons with appropriate experience.

Class I, level C (20,21)

Repair may involve implantation of a valved conduit from the pulmonary (left) ventricle to the PA and repair of the VSD(s).

A double switch operation (a combination of atrial switch and arterial switch procedures) has been performed in selected pediatric patients with CCTGA, and promising results have been reported with limited medium- and long-term data (69-72). A double switch operation for adult patients with a failing RV is considered to be a very high-risk procedure.

Part VII. Interventional outcomes

Following surgical repair of VSD and/or subpulmonary stenosis, rapidly progressive systemic (tricuspid) AV valve regurgitation is well recognized. Medical therapy is often attempted, but valve replacement is usually required before the RV has deteriorated substantially.

Part VIII. Arrhythmias

The most common problem is complete AV block, which occurs at the level of the AV node or high in the His bundle. It occurs spontaneously at a rate of 2% per year, irrespective of associated anomalies, or it can be caused by an intervention. Complete AV block follows surgical repair of an associated VSD in over 25% of patients (62,66), but is also reported after cardiac catheterization. A stable narrow QRS escape rhythm often accompanies complete AV block.

Tachyarrhythmias can occur, and may be supraventricular or ventricular. Both are associated with RV dysfunction. Atrial fibrillation is common in the aging adult patient and seems to be related to the degree of SAVV regurgitation. In operated patients, atriotomy incisions may form the substrate for macro-reentrant atrial tachyarrhythmias. Accessory pathway-mediated atrial reentrant tachycardias occur relatively often because the prevalence of accessory pathways is increased, most being left-sided and associated with Ebstein's malformation of the left-sided tricuspid valve (73). Atrial reentrant tachyarrhythmias can be managed by ablation – either transcatheter ablation or surgical ablation at the time of tricuspid valve surgery. Tricuspid valve repair or replacement alone does not seem to prevent recurrence of atrial arrhythmias (74).

Pacemakers are indicated in patients with spontaneous or postoperative third-degree and advanced second-degree AV block, or documented periods of asystole (3.0 s or more). **(Level C)**

Ablation and device implantation should be undertaken by an electrophysiologist with appropriate training/experience in the ACHD population. **(Level C)**

Class I, level C

Deterioration in systemic ventricular function has been reported following transvenous ventricular pacing. Ventricular function should be monitored closely after ventricular pacing is initiated.

In the presence of intracardiac shunts, shunt closure should be considered before the application of transvenous pacing due to the increased risk of paradoxical embolization. If shunt closure is not feasible, epicardial leads should be considered.

Class IIa, level B (75,76)

Part VIII. Pregnancy and contraception

In patients with CCTGA, pregnancy may be associated with significant deterioration of systemic ventricular function, associated

SAVV regurgitation (77,78) and, occasionally, complete AV block. Women with significant systemic ventricular dysfunction (ejection fraction of less than 40%) may be at significantly higher risk for maternal and fetal complications (79). In addition to known lesion-specific risk factors, general cardiac risk factors (systemic ventricular dysfunction, history of cardiac adverse events) for adverse events during pregnancy need to be incorporated into the risk assessment (53,54).

Women with CCTGA contemplating pregnancy should have preconception counselling with an expert in ACHD to discuss maternal and fetal risks and complications.
Class I, level C (54,79-81)

Part IX. Follow-up

All patients should have regular cardiology follow-up by an ACHD cardiologist. Particular attention should be paid to the following:

- Ventricular function.
- Systemic (tricuspid) AV valve regurgitation.
- Progressive and/or complete AV block.
- Atrial fibrillation.

Class I, level C

In patients with systemic ventricular dysfunction, AV valve regurgitation must be excluded.

Antibiotic prophylaxis is not recommended in patients with CCTGA unless they are cyanotic, or have a prosthetic valve or conduit, a residual VSD patch leak or a history of infective endocarditis.

Class III, level B (56)

FONTAN OPERATION

Part I. Background information

The Fontan operation and its modifications are palliative procedures for patients with a functionally or anatomically single ventricle, or with a complex malformation considered unsuitable for biventricular repair. There is diversion of all the systemic venous return to the PAs, usually without employing a subpulmonary ventricle. Originally described for patients with tricuspid atresia, it has now been extended to most forms of single-ventricle circulation such as mitral atresia, double-inlet LV, and hypoplastic LV or RV.

The Fontan procedure may be performed as a single or staged procedure. In the current era, a bidirectional cavopulmonary connection (BCPC), also known as bidirectional Glenn anastomosis, which connects the SVC to the PA, is commonly performed as an initial procedure before total cavopulmonary connection (TCPC), whereby the IVC is connected to the PA to complete the Fontan procedure. There have been numerous variations in the surgical approach over the years, leading to a variety of Fontan configurations in adult patients seen in congenital heart clinics. The most common types of Fontan procedure encountered in adults include the atriopulmonary Fontan (direct RA to PA connection with or without a BCPC or classic Glenn anastomosis), the lateral tunnel (SVC to PA and IVC to PA through a tunnel utilizing the lateral wall of the RA), the extracardiac conduit (SVC to PA and IVC to PA through an external conduit), the intra-atrial conduit (SVC to PA and IVC to PA through a conduit within the atria, which is preferred in certain anatomical situations to avoid compression of an extracardiac conduit [eg, dextrocardial]), and RA-RV connection through a conduit or connecting flap to the RV outflow tract. In addition, the Fontan may be fenestrated by a surgically created atrial septal defect (ASD) or connection to the pulmonary venous atrium to permit right-to-left shunting as an escape mechanism in certain hemodynamic situations. Fenestrations are usually closed by transcatheter intervention before adulthood.

Part II. History and management of the operated patient

Patients who have had a Fontan operation are at risk from the following:

- Arrhythmias.
 - Atrial arrhythmias commonly consist of intra-atrial reentrant tachycardia (potentially involving multiple reentry sites), although atrial fibrillation can occur. Both can be associated with profound hemodynamic deterioration and require prompt medical attention. Arrhythmias are particularly troublesome after the atriopulmonary Fontan procedure, and risk increases with increasing duration of follow-up.
 - Sinus node dysfunction and heart block may also occur, and the latter is often associated with hemodynamic deterioration.
- Thromboembolism, both systemic and pulmonary.
 - Factors that increase the tendency to thrombose include the sluggish circulation in the Fontan pathway, intravascular prosthetic material, clotting factor abnormalities and atrial arrhythmias.
 - Thrombus within the Fontan circuit can lead to obstruction of the circulation, pulmonary emboli, or paradoxical embolism via a residual ASD or Fontan fenestration.
 - Systemic emboli may result from thrombus in the ligated PA stump (80), the pulmonary venous atrium or the systemic ventricle.
- Cyanosis.
 - Expected oxygen saturation after the Fontan procedure is above 94% (if there is no fenestration). Worsening cyanosis may occur due to the development of right-to-left shunts of various forms, including systemic venous collateral channels draining to the pulmonary veins or pulmonary venous atrium, pulmonary arteriovenous malformations (AVMs) (especially if a classic Glenn procedure remains as part of the Fontan circuit), residual interatrial communications, fenestrations, leaks in the Fontan conduit or interatrial right-to-left shunting via Thebesian veins. Ventricular dysfunction and pulmonary pathology may also contribute to cyanosis.
- Progressive deterioration of ventricular function with or without AV valve regurgitation.
- Protein-losing enteropathy (PLE).
 - Occurring in up to 10% of postoperative Fontan patients, PLE is associated with ascites, peripheral edema, pleural and pericardial effusions, chronic diarrhea and an elevated stool alpha-1 antitrypsin level.
- Hepatic dysfunction.
 - Sustained elevated right-sided venous pressure produces hepatic congestion that may lead to cardiac cirrhosis and, rarely, hepatic neoplasms.
- Right pulmonary vein compression/obstruction.
 - This usually occurs in the setting of an atriopulmonary connection due to compression of the veins at the site where they enter the left atrium, due to leftward bulging of the interatrial septum.
- Ventricular outflow tract obstruction.
 - When the outflow from the systemic ventricle is via a VSD in the setting of transposed great vessels or double outlet morphology, outflow tract obstruction may result, leading to ventricular hypertrophy and elevated filling pressures, which are poorly tolerated in the Fontan circulation.

Part III. Diagnostic workup in operated patients

All adult Fontan patients should have an echo and/or cardiac imaging interpreted by individuals with expertise in adult congenital cardiac imaging. Cardiac catheterization and arrhythmia interventions of adult Fontan patients should be performed in centres with expertise in ACHD.

Class I, level C

Investigations are directed toward identifying postoperative sequelae. Particular attention should be paid to the following:

- Ventricular function, both systolic and diastolic.
- SAVV regurgitation.
- Obstruction in the Fontan circuit.
- Detection of thrombus within the Fontan circuit.
- Residual shunts.
- Increasing cyanosis.
- Development of atrial tachyarrhythmia or bradycardias.
- Detection of pulmonary AVMs.
- Serum protein and albumin levels as a marker of PLE.
- Hepatic function.

All patients should have the following (at a minimum):

- A thorough clinical assessment.
- Oximetry at rest.
- ECG.
- Serum protein and albumin measurement. If low, increased alpha-1 antitrypsin clearance in the stool confirms the presence of PLE. The diagnosis of PLE should prompt further assessment of Fontan structure, hemodynamics and cardiac rhythm.
- Echo-Doppler examination by an appropriately trained individual to assess systemic ventricular function, AV valve regurgitation, the presence or absence of residual shunts, the presence or absence of obstruction in the Fontan circuit, and spontaneous contrast ('smoke') or thrombus in the Fontan circuit or RA.

The diagnostic workup may require the following:

- Echo with a bubble study to assess right-to-left shunting.
- TEE if there is inadequate visualization of the Fontan circuit or to exclude thrombus in the atrium, particularly before cardioversion.
- MRI to visualize the Fontan circuit when it cannot be assessed reliably by echo, especially in the presence of an extracardiac conduit, and to exclude pulmonary vein compression. Ventricular function may also be quantified by MRI. Multidetector CT may be considered as an alternative when MRI is not possible.
- Radionuclide ventriculography to evaluate ventricular function.
- Cardiopulmonary exercise testing to document functional capacity as a baseline and in follow-up for comparative purposes.
- Biochemical assessment of liver function.
- Complete heart catheterization if adequate assessment of the anatomy, hemodynamics or ventricular function is not obtained by noninvasive means, or before surgical reintervention or transplantation. Even small gradients within the Fontan circuit, such as between the RA and PA, may reflect important obstruction.
- In addition to measuring pressure in all parts of the Fontan circuit and intracardiac chambers, resistance data and cardiac output should be assessed. Angiography may need to be extensive to assess PA anatomy, venovenous collaterals, systemic to PA collaterals, pulmonary AVMs and interatrial shunts.
- Holter monitoring.
- Electrophysiological study to assess documented or sustained arrhythmias.

Part IV. Indications for intervention/reintervention/medical therapy

Fontan patients with a history of atrial thrombus, thromboembolic event, interatrial communication or atrial arrhythmias should be therapeutically anticoagulated with warfarin.

Class I, level C (81,82)

Fontan patients with intracardiac pacemaker or defibrillator leads should be therapeutically anticoagulated with warfarin.

Anticoagulation may be considered in Fontan patients without atrial thrombus or arrhythmias.

Class IIa, level C

When clinical situations or hemodynamics warrant therapy, it may be reasonable to treat ventricular dysfunction in Fontan patients with diuretics, ACE inhibitors and beta-blockers as tolerated.

Class IIb, level C (83-85)

Anticoagulation: Despite the known propensity for thrombosis in Fontan patients, which can occur even late after Fontan palliation (86), the need for routine antithrombotic therapy is controversial due to insufficient data (81). Nevertheless, there is general consensus that it is prudent to anticoagulate patients with a history of thrombus in the atrium or Fontan circuit, and patients with a previous thromboembolic event. Because arrhythmias have been found in a high percentage of Fontan patients with thrombosis (82), anticoagulation is warranted at the onset of atrial tachycardia or atrial fibrillation, and should be continued as long as the patient remains at risk of arrhythmia. Stroke after the Fontan procedure has been reported in patients with residual right-to-left shunts (87,88); therefore, anticoagulation is recommended in the presence of an interatrial communication or Fontan fenestration.

Heart failure therapy: Late after Fontan palliation, the single ventricle may develop progressive dysfunction with or without overt symptoms of heart failure (89). Activation of the neurohormonal systems has been documented in Fontan patients (90), suggesting a potential role for modulation of the renin-angiotensin-aldosterone system with ACE inhibition and beta blockade. Although data on these agents are limited in Fontan patients (83,84,91), in clinical practice, proven effective therapies for left heart failure are often extended to the failing single ventricle.

PLE: Patients with PLE should have any structural or rhythm abnormalities addressed because this may improve hemodynamics and, thereby, PLE symptoms. Medical therapy of PLE is problematic and often only partially effective. Loop diuretics and aldosterone antagonists (85) can be used for fluid retention. Subcutaneous heparin (92-94), prednisone (95,96) and calcium (97) therapy have been tried with variable success. No therapy seems more successful than the others. Nutritional support may include a diet high in proteins and high in medium-chain triglycerides, although compliance is poor and results are disappointing (98).

Reintervention after the Fontan procedure is warranted in the following situations:

- Obstruction to systemic venous return in the Fontan circuit.
- Obstruction of pulmonary venous return.
- Significant (moderately severe or greater) SAVV regurgitation.
- Development of venous collateral channels or pulmonary AVMs resulting in symptomatic cyanosis.
- Residual ASD or fenestration resulting in significant right-to-left shunt.
- Residual shunt secondary to a previous palliative surgical shunt or residual ventricle-to-PA connection causing a hemodynamically significant volume or pressure load.
- Subaortic obstruction with a peak-to-peak gradient of greater than 30 mmHg.
- PLE that is associated with high systemic venous pressures or Fontan abnormality.
- Recurrent or poorly tolerated atrial arrhythmias refractory to medical therapy.

Class I, level C (99-105)

Part V. Interventional/surgical options

Patients who require reintervention should be treated by ACHD cardiologists and congenital heart surgeons with appropriate training/experience.

Class I, level C (20,21)

Heart transplantation should be considered for severe single-ventricle dysfunction leading to symptomatic heart failure despite optimal medical therapy.

Heart transplantation should be considered for refractory PLE symptoms.

Class I, level C (106,107)

The following are possible surgical or intervention strategies:

- Fontan patients with systemic venous obstruction may require conversion of their atriopulmonary or RA-RV Fontan to a TCPC. Obstruction of a TCPC due to thrombus or other obstructing force may require thrombectomy, surgical revision, or percutaneous angioplasty and stenting.
- Pulmonary venous obstruction may require conversion of an atriopulmonary Fontan to a TCPC or revision of repaired anomalous pulmonary venous return.
- Patients with significant SAVV regurgitation should be considered for AV valve repair or replacement.
- Patients with atrial arrhythmias may have an underlying hemodynamic abnormality that warrants surgical or catheter intervention. Recurrent atrial arrhythmias despite medical therapy in patients with atriopulmonary, RA-RV or lateral tunnel connections may benefit from Fontan conversion to an extracardiac conduit with concomitant arrhythmia surgery (108).
- If permanent pacing is required, epicardial pacing should be used to reduce the risk of thromboembolism. If a transvenous approach must be used, long-term anticoagulation should be considered in the presence of intracardiac leads.
- Patients with cyanosis due to venous collateral channels should undergo transcatheter occlusion (99). Pulmonary AVMs can also be addressed percutaneously or, in the case of a classic Glenn shunt, reconstitution of discontinuous PAs by a BCPC may resolve the AVMs.
- Patients with residual shunts of significance should undergo closure via transcatheter occlusion, if possible, or via surgery.
- Subaortic obstruction should be addressed surgically.
- Patients with PLE may be candidates for creation of a fenestration in the atrial septum to lower venous pressures and improve cardiac output at the expense of cyanosis (109,110). If obstruction in the Fontan circuit is the cause of the PLE, successful revision of the Fontan anastomosis may cure the PLE, albeit with increased operative risk (95,111). If no Fontan obstruction is present and PLE remains refractory to medical treatment, heart transplantation may resolve PLE symptoms (106,112).
- Late dysfunction of the single ventricle leading to heart failure should prompt a search for an underlying cause such as AV valve regurgitation, outflow tract obstruction or coronary problem. In the absence of a reversible cause, heart transplantation may need to be considered (107).

Part VI. Interventional/surgical outcomes

The Fontan operation remains a palliative, not a curative, procedure. With advances in surgical technique, early and late survival has continued to improve.

Reported survival rates following Fontan operation in recent series range from 86% to 94% at 10 years (100,113-116), and 82% to 87% at 15 to 20 years (100,101,117). However, if PLE develops, the five-year survival is approximately 50% (95). The most common causes of late death are arrhythmias, heart failure and thromboembolic complications (118).

CHD is a risk factor for adverse outcome after heart transplantation (119), with reported survival rates of 72% to 86% at one year, 68% to 77% at five years and 62% at 10 years (120-122).

Part VII. Arrhythmias

Atrial arrhythmias are common, occurring in approximately 50% of patients, and increase with duration of follow-up (102,123). The most common arrhythmias are macro-reentrant atrial circuits, which may be complex and/or multiple. Patients at greater risk for arrhythmias are those who were operated on at an older age, those with an atriopulmonary connection with resulting dilation and scarring of the RA, as well as those with poor ventricular function, SAVV regurgitation, increased PA pressure or sinus node dysfunction. Compared with the atriopulmonary

connection, the lateral tunnel (113) and, especially, the extracardiac (101,114) TCPCs carry a lower risk of arrhythmias.

Acute management of atrial arrhythmias: Patients not anticoagulated and presenting with atrial tachyarrhythmia should have intravenous heparin started immediately and TEE performed to rule out thrombus. Because tachycardia is poorly tolerated in single-ventricle physiology, prompt attempts should be made to restore sinus rhythm if no thrombus is found and/or if there is hemodynamic compromise. In the presence of chronic thrombus, acute termination of tachycardia should be considered after balancing risks of thromboembolic complications against delayed cardioversion, with potential worsening of hemodynamic status. Intravenous calcium channel blockers or beta-blockers to lower the heart rate (in the hemodynamically stable patient), overdrive pacing or direct current cardioversion may be used. However, cardioversion in this population is not without risk; if possible, a cardiac anesthetist should be in attendance and temporary pacing options available because venous access can be problematic.

Chronic management of atrial arrhythmias: Arrhythmias tend to become recurrent and prevention is a challenge. Long-term anticoagulation should be given to all patients with atrial arrhythmias (including paroxysmal). The following options for management need to be tailored to the individual patient's situation:

- Periodic cardioversion is reasonable in patients with infrequent atrial arrhythmias that are reliably recognized, hemodynamically well tolerated and promptly treated. Beta-blockers, calcium channel blockers or digoxin may be used chronically to prevent high ventricular rates during tachycardia.
- Antiarrhythmic medications may be used for patients with recurrent atrial arrhythmias, although these tend to lose efficacy over time. Pacemaker implantation may be used to treat bradycardia or as an antitachycardia pacing device.
- Catheter ablation may be attempted, with acute success rates that are reasonable (70% to 85%), although they are lower than for other forms of CHD. New-onset arrhythmias and recurrences limit long-term success (30% to 50% by six to 12 months) (46,47). Ablation is particularly appropriate in patients without underlying hemodynamic abnormalities or those who are not surgical candidates.
- Reoperation for conversion to an extracardiac Fontan with concomitant atrial cryoablation (for intra-atrial reentry tachycardia) may provide long-term arrhythmia control. Although not routinely performed (because of increased cross-clamp times), a left-sided Cox maze III procedure may be added in patients with atrial fibrillation.

When arrhythmias are present, an underlying hemodynamic cause should always be sought. In particular, obstruction of the Fontan circuit, thrombus formation or ventricular dysfunction need to be excluded by comprehensive imaging. Patients with arrhythmias should be referred for consultation with an electrophysiologist with expertise in CHD. Electrophysiological studies in Fontan patients should be performed in centres with expertise in CHD.
Class I, level C (46,47,102)

Patients with serious refractory atrial arrhythmias may be considered for Fontan conversion to a total cavopulmonary connection with concomitant atrial maze procedure.
Class IIa, level C (102,124-127)

Sinus node dysfunction and complete heart block increase in prevalence over time (128), and may require pacemaker insertion. Endovascular ventricular pacing through the coronary sinus may be possible in selected cases. Epicardial pacing is often the preferred approach when ventricular pacing is required.

Part VIII. Pregnancy and contraception

Women with previous Fontan surgery considering pregnancy should have a comprehensive consultation with an ACHD

cardiologist, ideally before pregnancy occurs.

Class I, level C (49,129,130)

Pregnancy carries additional risks to the mother because of the increased hemodynamic burden of the single ventricle and atrium. There is an increased risk of the following:

- Systemic venous congestion and ascites.
- Deterioration in ventricular function.
- Worsening SAVV regurgitation.
- Atrial arrhythmias.
- Thromboemboli.
- Paradoxical emboli if the Fontan is fenestrated.
- Spontaneous abortion, intrauterine growth restriction and preterm birth.

Successful pregnancies in Fontan patients have been described (129,130); however, careful patient selection, and meticulous cardiac and obstetric supervision by a multidisciplinary team with commitment to this population is advised.

Part IX. Follow-up

All patients who have had a Fontan operation should be followed yearly by an ACHD cardiologist.

Class I, level C

Endocarditis prophylaxis is not recommended in patients with Fontan operations unless they have a recent redo Fontan (within the past six months), cyanosis, prosthetic material in the extracardiac conduit or a prosthetic heart valve, residual patch leaks, or previous endocarditis.

Class III, level B (56)

SINGLE VENTRICLE

Part I. Background information

Patients with single ventricles commonly have a 'functionally single' ventricle with one well-formed ventricle accompanied by a second rudimentary ventricle, and rarely have an 'anatomically single' ventricle of indeterminate ventricular morphology. The atrial situs can be solitus, inversus or ambiguous. The AV valves guarding the inlet of the univentricular heart can consist of either two separate valves (double-inlet LV, double-inlet RV), one patent valve and one atretic valve (tricuspid atresia, mitral atresia, hypoplastic left heart) or consist of a common type (unbalanced AV septal defect). The well-developed ventricular chamber can be of the LV type with an anterosuperior rudimentary RV or, less commonly, of an RV type with a posterior rudimentary LV. The ventriculoarterial connections can be concordant or discordant, or can arise from the same ventricle (double outlet). The great arteries can be patent, stenotic or atretic.

Part II. History and management of unoperated patients

The prognosis of all patients with unoperated univentricular hearts is poor, with a median survival of 14 years (death rate of 4.8% per year). The majority are symptomatic with cyanosis and exercise intolerance (131).

Rarely, patients with a 'well-balanced' circulation (eg, enough pulmonary blood flow to avoid severe hypoxemia, and some degree of pulmonic stenosis to avoid excessive pulmonary blood flow) may achieve unoperated late survival with good ventricular function, reasonable exercise capacity and minimal symptoms (132). The majority of patients surviving to adulthood will have had the Fontan procedure (see previous section) or have undergone a palliative systemic to pulmonary shunt (Blalock-Taussig, classic Glenn anastomosis, BCPC or central shunt).

Single-ventricle patients (unoperated or palliated) are at risk from the following:

- Cyanosis and impaired functional capacity.
- Congestive heart failure.

- Arrhythmias and sudden death.
- Complete AV block.
- Thromboembolic events and stroke.
- Bacterial endocarditis.

Part III. Diagnostic workup

All single-ventricle patients should have regular echos and/or cardiac MRIs interpreted by individuals with expertise in adult congenital cardiac imaging.

When necessary, cardiac catheterization of adult single-ventricle patients should be performed in centres with expertise in ACHD.

Class I, level C

An initial diagnostic workup should include the following:

- Assessment of the anatomy and document the situs of the atria, status of the inlet AV valves (number, patency, and presence or absence of straddling), morphology of the main ventricular chamber as well as position and patency of the great arteries.
- Documentation of the etiology of cyanosis (decreased pulmonary blood flow, arteriovenous mixing or pulmonary hypertension), assess the function of any shunts and evaluate pulmonary resistance.
- Identification of other factors affecting the clinical condition of the patient (see complications and clinical sequelae of cyanotic heart disease).

The diagnostic workup should include the following (at a minimum):

- A thorough clinical assessment.
- Oximetry at rest and, perhaps, with exertion (if the saturation at rest is more than 90%).
- ECG.
- Complete blood count, ferritin, clotting profile, renal function and uric acid (see section on cyanotic heart disease).
- Echo-Doppler evaluation by an appropriately trained individual.

The diagnostic workup may require the following:

- TEE to visualize the anatomy in terms of atrial situs, AV connections, ventricular type and great artery connections as well as patency.
- MRI to visualize the anatomy, assess ventricular size, function and hypertrophy, quantify regurgitant fraction and evaluate associated lesions. Multidetector CT can be used as an alternative imaging modality if MRI is not possible.
- Radionuclide angiography to evaluate ventricular function.
- Cardiopulmonary testing to document functional capacity, the degree and basis for exertional limitation, and exercise desaturation.
- Cardiac catheterization if surgical intervention is considered or before transplantation to determine PA anatomy and PA pressures/resistances if these have not been adequately defined by other investigations.

Part IV. Indications for intervention or surgery

Unoperated adult patients with single-ventricle physiology often have well-balanced circulation. In patients with increasing symptoms of exercise intolerance or progressive cyanosis, treatment decisions have to be individualized after thorough assessment of cardiopulmonary anatomy and function. Interdisciplinary consultations with cardiologists, cardiac surgeons and transplant physicians with experience in ACHD are important for decision making.

Indications for intervention in the adult patient with single-ventricle physiology may include deteriorating functional status or saturation, dilated (volume-overloaded) systemic ventricle, and paradoxical embolism.

Part V. Interventional/surgical options

Patients with single-ventricle physiology who require intervention or surgery should be treated by ACHD cardiologists and congenital heart surgeons with appropriate training and experience.

Class I, level C (20,21)

The following are possible surgical strategies for univentricular hearts. The choice of strategy needs to be tailored to the patient's symptoms, anatomy and hemodynamics.

Systemic to pulmonary shunt: Rarely performed as the sole intervention any more, Blalock-Taussig or central shunts (from ascending aorta to main/right PA) can increase pulmonary blood flow and improve cyanosis if a BCPC is contraindicated due to high pulmonary pressure.

BCPC (also referred to as bidirectional Glenn): Usually performed in infancy as a staged procedure before the Fontan operation, it can be performed in adults as 'definitive palliation' when patients are too high risk for Fontan surgery. It provides a controlled source of pulmonary blood flow to alleviate cyanosis while volume unloading the systemic ventricle (133).

BCPC plus additional pulmonary blood flow: An additional source of pulmonary blood flow via the PA through a PA band or native pulmonary stenosis, or through a Blalock-Taussig shunt, is sometimes added in conjunction with a BCPC to increase oxygen saturation and cardiac output. Potential drawbacks are higher systemic venous pressure and an increased volume load on the systemic ventricle (134).

One-ventricle repair: When the rudimentary subpulmonary ventricle is less than 30% its normal volume, the Fontan procedure will allow systemic venous return to enter directly into the pulmonary circulation, bypassing the pulmonic ventricle (see Fontan section). Successful Fontan operation in adulthood requires careful patient selection. Ideal candidates have low PA pressure (mean PA pressure of lower than 15 mmHg), and preserved ventricular and AV valve function.

One-and-a-half-ventricle repair: When the rudimentary subpulmonary ventricle is between 30% and 80% of its normal volume, the IVC blood flow can be permitted to return to the pulmonary circulation via the pulmonic ventricle, and a BCPC diverts the SVC blood directly to the PAs (135). The heart is usually surgically septated to eliminate shunting.

Two-ventricle repair: In some instances, when the subpulmonary ventricle is more than 80% its normal volume, a biventricular repair or ventricular septation may be feasible. Straddling of the AV valves and TGA may complicate or preclude this type of repair.

Transplantation: Heart transplantation for ventricular failure or heart and lung transplantation for ventricular failure with pulmonary hypertension should be considered when the patient is symptomatic and further palliation/repair is not possible.

Part VI. Interventional/surgical outcomes

Aortopulmonary shunt: Survival is 50% at 20 years of follow-up (136). Systemic ventricular dilation and heart failure, as well as arrhythmias (mainly atrial macro-reentrant tachycardia/fibrillation) occur more commonly than with a BCPC (136).

BCPC: Survival is 50% at 20 years of follow-up (136). Progressive cyanosis may be due to development of pulmonary AVMs or a greater contribution of IVC blood flow compared with SVC blood flow with somatic growth. Tachyarrhythmias, both atrial and ventricular, can occur (136).

BCPC plus additional pulmonary blood flow: No long-term studies of this approach in adults are available. Increased volume loading on the systemic ventricle by the additional pulmonary blood flow is potentially a concern (134), although clinically, it appears to be well tolerated (137-139). For single-ventricle patients who are too high risk for Fontan completion, this may provide reasonable palliation with acceptable midterm outcomes (140).

One-ventricle repair: Operative mortality of the Fontan procedure in adults has been reported to be approximately 10% (141,142). Survival after Fontan operation in adulthood is 76% to 89% at five years, 72% to 75% at 10 years, and 67% to 68% at 15 years (141,142). See the

Fontan operation section for a description of outcomes and complications.

One-and-a-half-ventricle repair: Operative mortality in a cohort of patients with a variety of congenital heart lesions was 10%, and survival at seven years was 82% (143). Complications, such as PLE seen after Fontan procedure, and pulmonary AVMs seen after BCPC, do not appear to occur with one-and-a-half-ventricle repair (143,144), although arrhythmias do manifest (143).

Two-ventricle repair: A complex biventricular repair (needing valved conduit or complex intraventricular tunnel) may not be preferable in the short or intermediate term to a simple one- or one-and-a-half-ventricle repair (145).

Transplantation: CHD is a risk factor for adverse outcome after heart transplantation (146,147). Survival after transplant for palliated single ventricle has been reported to be comparable with survival after transplant for Fontan patients, with a one-year survival of 72% and a five-year survival of 68% (146,147). The survival outcome of heart and lung transplant is lower, with a one-year survival of 64% and a five-year survival below 50% (148).

Part VII. Arrhythmias

Atrial arrhythmias are a common complication of palliated single-ventricle physiology. Patients with an aortopulmonary shunt will develop significantly more atrial fibrillation or flutter at 10 years of follow-up than patients palliated with a cavopulmonary shunt (35% versus 15%) (136). Supraventricular arrhythmias also occur after one-and-a-half-ventricle repair, affecting approximately 15% of patients at seven years of follow-up (143). Progressive ventricular dysfunction has been linked to the development of atrial arrhythmias (136,143). In a pediatric cohort of single-ventricle patients, a BCPC conveyed a lower risk of arrhythmias than did the Fontan procedure over the intermediate term (149).

Ventricular arrhythmias can occur late after shunt palliation and are associated with sudden death.

Part VIII. Pregnancy and contraception

Women with unoperated or palliated single-ventricle physiology who are considering pregnancy should have a comprehensive consultation with an ACHD cardiologist, ideally before pregnancy occurs.

Class I, level C (49,150)

Pregnancy can be tolerated in women with single-ventricle physiology with good functional class, good ventricular function, no pulmonary hypertension and an oxygen saturation of greater than 85%. However, for cyanotic patients, there is approximately a 30% incidence of maternal cardiovascular complications, and an increased chance of prematurity and low birth weight infants (150).

The risk of paradoxical emboli is high in unoperated or palliated single-ventricle patients, and meticulous attention should be paid to avoid deep vein thrombosis.

Part X. Follow-up

All patients with single-ventricle physiology should be followed at least yearly by an ACHD cardiologist.

Class I, level C

Annual clinic visits to follow functional status and oxygen saturation are recommended, as well as yearly echos to assess systemic ventricular function, semilunar valve stenosis and AV valve regurgitation. Complete blood count, ferritin, clotting profile, renal function and uric acid should also be assessed yearly.

The majority of patients with single-ventricle physiology have a significant degree of cyanosis; as such, they are in a high-risk category for development of infective endocarditis. Endocarditis prophylaxis is recommended.

Class I, level B (56)

TABLE 1
Complications of Eisenmenger's syndrome

| |
|---|
| Congestive heart failure |
| Secondary erythrocytosis |
| Bleeding disorders |
| Sudden death |
| Arrhythmias (atrial fibrillation/flutter) |
| Paradoxical emboli |
| Pulmonary arterial aneurysm/calcification |
| Angina pectoris |
| Thrombosis in the proximal pulmonary arteries |
| Syncope |
| Progressive valvular stenosis/regurgitation |
| Infective endocarditis |
| Hyperuricemia/gouty arthritis |
| Brain abscess |
| Stroke/transient ischemic attack |
| Gallstones |
| Renal dysfunction |
| Intrapulmonary hemorrhage, usually manifested with hemoptysis |

EISENMENGER'S SYNDROME

Part I. Background information

Eisenmenger's syndrome, a term first used by Paul Wood in 1958, is defined as pulmonary vascular obstructive disease that develops as a consequence of a large pre-existing communication between the systemic and pulmonary circulation, and subsequent left-to-right shunt, such that PA pressures and pulmonary vascular resistance approach systemic levels and the flow becomes bidirectional or right to left (151). The high pulmonary vascular resistance is usually established in infancy (by two years of age, except in ASD), and can sometimes be present from birth in patients with a nonrestrictive communication at the ventricular or arterial level. Eisenmenger's syndrome is the most advanced form and extreme end of the wide spectrum of PA hypertension (PAH) associated with CHD.

Part II. Prevalence

Advances in both diagnostic and therapeutic measures have reduced the overall prevalence of Eisenmenger's syndrome since Wood's landmark publication (151-153).

Part III. Natural history and complications

Patients with defects that allow free communication between the pulmonary and systemic circuits at the aortic or ventricular levels may experience congestive heart failure in infancy; but otherwise, they usually have a fairly healthy childhood, then gradually become progressively cyanotic with each succeeding decade. Exercise intolerance (dyspnea and fatigue) is proportional to the degree of hypoxemia or cyanosis. In the absence of complications, these patients report a good functional capacity and only mild limitations in their daily activities up to their third decade of life. Thereafter, they usually experience a slowly progressive decline in their physical abilities. Patients with Eisenmenger's syndrome have the worst exercise capacity among adults with CHD, and objective measurement of exercise capacity usually reveals more severe impairment than subjective report.

In patients with medium or large ASDs, Eisenmenger's physiology usually appears later in life, often associated with pregnancy, recurrent thromboembolism or in the setting of other causes of PAH. It is not yet clear whether such additional factors, perhaps in combination with undefined genetic mutations, are required in ASD patients to develop this physiology, because it is uncommon even in large ASDs.

Most patients with Eisenmenger's syndrome survive to adulthood (154-157). In one large study, the median survival was 53 years (155).

Complications from Eisenmenger's syndrome tend to occur from the third decade onward. Congestive heart failure usually occurs after 40 years of age (154,156). Complications are listed in Table 1. Additional details can be found in the section on cyanotic heart disease.

Part IV. Diagnostic workup

When necessary, cardiac catheterization of patients with Eisenmenger's syndrome should be performed in centres with expertise in ACHD.

Class I, level C

An adequate diagnostic workup should include the following:

- Documentation of the presence of one or more communications between the systemic and pulmonary circuits at the great artery, ventricular or atrial level.
- Documentation of the existence of severe pulmonary hypertension with significant right-to-left shunting (saturation of less than 90% at rest).
- Identification of other factors affecting the clinical condition of the patient (see complications and manifestations).

The diagnostic workup should include the following (at a minimum):

- A thorough clinical assessment, including examination of the toes, looking for differential cyanosis.
- ECG (for assessment of rhythm and RV hypertrophy).
- Chest x-ray.
- Echo-Doppler evaluation by an appropriately trained individual.
- Oximetry at rest and, occasionally, with exertion (if the saturation at rest is more than 90%). Saturation measurement must be obtained after the patient has been at rest in the supine or sitting position for at least 5 min.
- Blood work (complete blood count, serum ferritin, transferrin, transferrin saturation; folic acid and vitamin B₁₂ in the presence of iron deficiency, and normal or elevated mean corpuscular volume; creatinine and uric acid; clotting profile as needed).
- Exercise testing: 6 min walk test or cardiopulmonary study.

The diagnostic workup may require the following:

- MRI to visualize the defect(s) between the pulmonary and systemic circuits, or to better define their location(s) and size(s), to evaluate the size of the proximal PAs, and to screen for mural or obstructive thrombi.
- TEE (rarely indicated) to visualize defects between the pulmonary and systemic circuits or to better define its/their location(s) and size(s). Caution should be exercised with sedation because of the risk of depressed systemic vascular resistance with consequent increase in right-to-left shunting.
- Spiral/high-resolution CT scan of the chest in patients with hemoptysis to evaluate the possibility of major pulmonary hemorrhage, especially in the setting of a chest x-ray showing pulmonary infiltrate(s).
- Cardiac catheterization to determine PA pressures and vascular resistances if these have not been adequately defined by other investigations and to rule out potentially reversible pulmonary vascular disease. Vasoreactivity testing is controversial (158).
- Open-lung biopsy should be considered only when the reversibility of the pulmonary hypertension is uncertain from the hemodynamic data. It is potentially hazardous and should be done only at centres with substantial relevant experience in CHD and interpretation of the specimens by the pathologist. Circulating endothelial cells were identified as a valuable tool to define irreversibility of PAH associated with CHD (159).

Part V. Indications for interventions/reinterventions/medical therapy

An important management principle in patients with Eisenmenger's syndrome is to avoid any factors that may destabilize the delicately

balanced physiology. The main interventions are directed toward preventing complications (eg, influenza and pneumococcal vaccination to reduce the morbidity of respiratory infections) or to restore the physiological balance (eg, iron replacement for iron deficiency; antiarrhythmic management of atrial arrhythmias; salt restriction and diuretics for right-sided heart failure, etc).

The following carry increased risk in patients with Eisenmenger's syndrome:

- Pregnancy.
- Noncardiac surgery.
- Cardiac surgery.
- General anesthesia.
- Dehydration.
- Hemorrhage.
- Certain drugs (eg, vasodilators, diuretics, some oral contraceptive pills, danazol, nonsteroidal anti-inflammatory drugs).
- Agents that impair renal function worsen platelet function/coagulation abnormalities.
- Anemia, most commonly due to iron deficiency secondary to inappropriate phlebotomies.
- Cardiac catheterization.
- Intravenous lines (because of the risk of paradoxical air embolism and infection).
- Acute high altitude exposure (greater than 2500 m above sea level).
- Strenuous exercise.
- Exposure to heat.
- Pulmonary infections.

Class III, level C (160-168)

Patients with Eisenmenger's syndrome should generally be given the following advice:

- Ask to be referred to an ACHD cardiologist who understands and has experience in management of the Eisenmenger's syndrome (Canadian centres and physicians are listed on www.cachnet.org).
- Ask to be referred to a gynecologist with expertise in high-risk pregnancy to get contraceptive counselling. Pregnancy is very high risk. Preconception counselling should be sought.
- Take medication only after consultation with your physician and your ACHD cardiologist.
- Avoid dehydration.
- Avoid smoking or recreational drug use.
- Tell your ACHD cardiologist if you need noncardiac surgery or have suffered serious illness or injury.
- Avoid excessive physical activity.
- Avoid prolonged exposure to heat (sauna or hot tub).
- Decrease the risk of infectious disease (annual flu shot and pneumococcal vaccine every five years).
- Practice excellent oral hygiene and arrange regular dental visits (every six months).
- Use endocarditis prophylaxis.
- Promptly secure treatment for upper respiratory tract infections from your family physician.
- Avoid needless acute high-altitude exposure, especially when combined with significant physical activity.
- Flying on commercial airline flights is safe in stable patients.

Class I, level C (56,160,165,169,170)

Hypovolemia should be avoided. Any cause of hypovolemia may lead to hypotension and hypoxemia, but may cause hyperviscosity symptoms. Volume expansion should be provided immediately.

Supplemental oxygen at home may reduce episodes of dyspnea and improve well-being, although its routine use is not recommended because long-term nocturnal oxygen therapy does not improve symptoms or outcomes in adults with Eisenmenger's syndrome. Psychological dependence may develop and oxygen therapy may predispose patients to epistaxis because of its drying effect.

Eisenmenger's patients should have a hemoglobin and hematocrit level inversely proportional to their saturation level. Excessive phlebotomy or blood loss may result in suboptimal hemoglobin.

Anticoagulation: The beneficial effect and safety of routine anticoagulation in Eisenmenger's patients remains controversial. Long-term anticoagulation of Eisenmenger's patients would be attractive because of the high frequency of thrombus formation in the enlarged PAs (171-173). However, this approach is questioned and may cause harm because of the pre-existing bleeding tendencies (161).

Specific therapies for PAH: Recent advances in PAH therapy have opened new therapeutic horizons beyond preventive measures and risk reduction strategies. Treatments are available targeting three distinct physiological mechanisms: the endothelin pathway, the nitric oxide pathway and the prostacyclin pathway (174).

- Endothelin antagonists
 - Endothelin antagonists target a potent pathway involved in the pathobiology of PAH (174). Bosentan is a dual endothelin (endothelin receptor type A and endothelin receptor type B) antagonist that is effective in the short-term therapy of different forms of PAH including patients with Eisenmenger's syndrome (175-178). A prospective, double-blind, randomized multicentre study confirmed the safety profile of bosentan in Eisenmenger's syndrome patients without an adverse impact on oxygen saturation, and a positive effect on 6 min walk distance, and pulmonary and systemic hemodynamics (179). Longer follow-up of this cohort has been reported (180,181).
- Phosphodiesterase-5 inhibitors
 - Sildenafil has been tested predominantly in patients with idiopathic and other forms of PAH. CHD patients with a shunt or Eisenmenger's syndrome have remained a minority of the studied patients, and no blinded, randomized, placebo-controlled study is available (182-184). As a consequence, at the present time, sildenafil should be prescribed only in selected patients refractory to other therapies specific for PAH.
- Prostacyclin
 - Prostacyclin analogues have been used predominantly in idiopathic and other forms of PAH therapy not associated with CHD, but have also been shown to have a favourable effect in CHD associated with a shunt or Eisenmenger's syndrome (185,186). There are drawbacks to intravenous prostacyclin analogues, such as continuous intravenous application with the risk of infection and/or paradoxical embolization, and risk of rebound pulmonary hypertension if the intravenous application is discontinued. There are only preliminary data available for oral and inhaled prostanoids. Combined therapies may be indicated in selected patients.

Pulmonary vasodilator therapy may help to improve quality of life in patients with Eisenmenger's syndrome.

Class IIa, level B (179-181)

Noncardiac surgery should be performed only when unavoidable because of its high associated mortality (154,167). An experienced cardiac anesthetist with an understanding of Eisenmenger's physiology should administer anesthesia. Eisenmenger's patients are particularly vulnerable to alterations in hemodynamics induced by anesthesia or surgery, such as a minor decrease in systemic vascular resistance that can increase right-to-left shunting and possibly potentiate cardiovascular collapse. Local or regional anesthesia should be used whenever possible. Avoidance of prolonged fasting and, especially, dehydration, the use of antibiotic prophylaxis when appropriate and careful intraoperative monitoring are recommended (167). The choice of general versus epidural-spinal anesthesia should be made after considering the patient's unique physiology and in consultation with a cardiac anesthetist. Additional risks of surgery include excessive bleeding, postoperative arrhythmias and deep venous thrombosis with paradoxical emboli. An 'air filter' or 'bubble trap' should be used on intravenous lines when possible, and meticulous attention should be paid to eliminating air bubbles from all intravenous

lines. Early ambulation is recommended. Postoperative care in an intensive care unit setting is optimal (164,168).

Hemoptysis, in general, is an external manifestation of an intrapulmonary hemorrhage; this should result in an urgent hemoglobin measurement, chest x-ray and, often, CT scanning to look for the extent of intrapulmonary hemorrhage or secondary cause. A treatable cause should be excluded, although hemoptysis is most commonly due to bleeding bronchial vessels or pulmonary infarction. Acetylsalicylic acid, nonsteroidal anti-inflammatory agents and oral anticoagulants must be immediately discontinued. Administration of platelets and/or fresh frozen plasma, factor VIII, vitamin K, cryoprecipitate, desmopressin, etc, should be considered if bleeding persists (154,161,162).

Part VI. Surgical/interventional options

Phlebotomy with fluid replacement and iron supplementation should be performed only in patients who are symptomatic from secondary erythrocytosis. Prevention of iron deficiency is important.

Class I, level C (156,161,163,166,187)

Transplantation: When patients are severely incapacitated from severe hypoxemia or congestive heart failure, the main intervention available is lung transplant with concomitant repair of the cardiac defect or heart-lung transplantation. The decision to proceed to this therapy is fraught with difficulty because of the unpredictability of the time course of the disease and the risk of sudden death. There are formidable technical considerations including complexity of the underlying anatomy, previous sternotomies and thoracotomies, major aortopulmonary or pleuropulmonary collaterals, and risk of bleeding. Previous operative procedures seem to have a negative impact on survival after transplantation, and the existence of extensive pleuropulmonary collateral vessels is considered a contraindication for heart-lung transplantation (188).

Part VII. Arrhythmias

Patients with Eisenmenger's syndrome are at risk for sudden cardiac death, the etiology of which remains poorly defined (155,156,172,189). Arrhythmias (supraventricular or ventricular) are generally poorly tolerated. The presence of atrial flutter/fibrillation will increase the risk of paradoxical embolization and stroke. The choice of antiarrhythmic drugs is complicated by the presence of ventricular dysfunction and lung disease. In addition, amiodarone is associated with increased risk for thyroid dysfunction, particularly hyperthyroidism, in patients with cyanosis (190). There have been no drug trials in this patient population to determine possible proarrhythmic effects.

The use of implantable defibrillators for symptomatic malignant ventricular arrhythmia has not been studied in this patient population.

Sinus rhythm should be restored promptly and maintained whenever possible. **(Level C)**

Transvenous pacing leads are not recommended and must be avoided in the presence of intracardiac shunts due to the risk of paradoxical embolization. **(Level B)**

Symptomatic arrhythmias should be treated with individualized antiarrhythmic therapy. **(Level C)**

Insertion of an implantable defibrillator is a high-risk endeavour. It may be considered in patients with syncope and documented concurrent ventricular arrhythmia. Epicardial approaches should be used. **(Level C)**

Patients with atrial fibrillation/flutter should receive warfarin therapy with judicious monitoring of international normalized ratio levels (sodium citrate adjusted to hematocrit). **(Level C)**

Class I, level B or C as indicated (76,191)

Part VIII. Pregnancy and contraception

If pregnancy is continued, maternal mortality approaches 50% with each pregnancy and fetal loss occurs at similar rates. Maternal mortality continues to be increased in the first three to four weeks after delivery (53,164,192,193).

Contraception is extremely important. Sterilization (by means of laparoscopy) is generally preferred (but is not without risks), and should be conducted with skilled anesthetic and intensive care support after full consultation with the patient. Mini laparotomy or intratubal stents may be safe options. Combined oral contraceptive pills are best avoided because of the associated thrombosis risk. Progesterone-only depot injections and subdermal insertion of etonogestrel may be safe options.

Pregnancy in women with Eisenmenger's syndrome is not advised because of the high maternal and fetal mortality.

Class III, level B (191-193)

If pregnancy is continued despite advice to the contrary, or the patient presents late, management should be referred to groups with combined expertise in ACHD cardiology, high-risk obstetrics and pulmonary hypertension to attempt to optimize outcomes.

Class I, level C

Part IX. Follow-up

All Eisenmenger's patients should be cared for by an ACHD cardiologist in collaboration with a PAH specialist as needed. They may also benefit from the involvement of other specialists within such an ACHD centre (nursing, respirology, psychology/psychiatry, hematology, gynecology, anesthesia, intensive care and social work).

Annual clinical visits with comprehensive, systematic assessment and laboratory evaluation for potential complications are recommended. Imaging tests should be performed every two to three years in a stable patient.

Class I, level C

Endocarditis prophylaxis is recommended for all patients with Eisenmenger's syndrome.

Class I, level B (56)

CYANOTIC HEART DISEASE

Part I. Background information

Cyanosis is a bluish discoloration of the skin and mucous membranes resulting from an increased amount of reduced hemoglobin. Central cyanosis in patients with CHD occurs when persistent venous-arterial mixing occurs secondary to a right-to-left shunt, resulting in chronic hypoxemia. In the presence of hypoxemia, adaptive mechanisms increase oxygen delivery. These include an increase in oxygen content, a rightward shift in the oxyhemoglobin dissociation curve and an increase in cardiac output. Oxygen delivery is enhanced at the cost of a higher hematocrit as erythropoietin production is stimulated.

Cyanosis is observed in unoperated and palliated patients with cyanotic lesions. Cyanotic lesions are summarized in Table 2.

Part II. History and management of unoperated patients

Adult survival into the seventh decade, although rare, has been documented in cyanotic patients (171,194). Survival is determined by two sets of factors: the underlying cardiac condition, and its repercussion on the heart and pulmonary circulation; and the medical complications of cyanosis. Cyanotic heart disease, a multisystem disease involving hematological, neurological, renal and rheumatic complications, develops in response to chronic hypoxemia and associated erythrocytosis (159).

Hematological complications of chronic hypoxemia include secondary erythrocytosis due to erythropoietin stimulus, iron deficiency and bleeding diathesis (160,187).

Secondary erythrocytosis can result in hyperviscosity symptoms including headaches, faintness, dizziness, fatigue, altered mentation, visual disturbances, paresthesias, tinnitus and myalgias (160,187).

Hemostatic abnormalities may occur in cyanotic patients with erythrocytosis in up to 20% of patients. Bleeding tendency can be mild and superficial, leading to easy bruising, skin petechiae and mucosal bleeding, or can be moderate or life-threatening with epistaxis, hemoptysis or postoperative bleeding (161,163,187,191). Eisenmenger's syndrome patients are also at risk for thrombus formation, invoking a therapeutic dilemma (171-173).

Iron deficiency is a common finding in cyanotic adult patients, occurring because of inappropriate phlebotomies or excessive bleeding. Although normochromic erythrocytosis is not usually symptomatic at hematocrit levels of lower than 65%, iron deficiency may manifest with symptoms similar to hyperviscosity at hematocrits well below 65% (194).

Systemic endothelial dysfunction is common and is demonstrated by striking impairment of endothelium-dependent vasodilation. This may be a contributor to other complications (thrombotic diathesis, ischemic complication, etc).

Neurological complications include cerebrovascular accidents (stroke/transient ischemic attack) and cerebral hemorrhage. Hemorrhage can occur secondary to hemostatic defects and can be seen following the use of anticoagulant therapy. Hematocrit per se is not a risk factor for ischemic stroke (195); microcytosis was identified as a strong independent predictor for cerebrovascular accident (196). Patients with right-to-left shunts may be at risk for paradoxical cerebral emboli (76). Brain abscess should be suspected in any cyanotic patient with a new or different headache, or any neurological symptoms.

Renal dysfunction can manifest as proteinuria, hyperuricemia or renal failure, and is an independent predictor of mortality. Hyperuricemia is common. Urate nephropathy and uric acid nephrolithiasis are rare. Gouty arthritis is seen more often.

Rheumatological complications include gout and hypertrophic osteoarthropathy, which is thought to be responsible for the arthralgias and bone pain, affecting up to one-third of patients.

Gallstones composed of calcium bilirubinate and consequent cholecystitis occur with increased frequency.

Part III. Diagnostic workup

An initial diagnostic workup should include the following:

- Establishment of the cause of cyanosis and the source of right-to-left shunting.
- Documentation of the anatomy of underlying cardiac anomaly and palliative intervention when applicable.
- Documentation of the hemodynamic consequences of the lesion.
- Documentation of the presence or absence and degree of pulmonary hypertension.
- Determination of whether the patient may benefit or is eligible for intervention.
- Documentation of the presence or absence of the medical complications of cyanosis and determine whether medical therapy is needed.

The diagnostic workup should include the following:

- In addition to a full cardiac history, a history documenting the presence or absence of symptoms of hyperviscosity, a functional inquiry pertinent to bleeding diathesis, neurological complications, renal dysfunction, gallstones and arthritis should be obtained. The functional capacity and its change over time should be documented.
- An oxygen saturation level at rest in all patients and with exercise if resting saturation is greater than 90%.
- 12-lead ECG.
- Chest x-ray.
- Baseline complete blood count, ferritin, transferrin and transferrin saturation; folic acid and vitamin B₁₂ in the presence of iron deficiency and normal or elevated mean corpuscular volume;

TABLE 2
Cyanotic lesions

- | |
|---|
| I. Eisenmenger's physiology |
| <ul style="list-style-type: none"> • Isolated, nonrestrictive communications without obstruction across the pulmonary outflow tract: <ul style="list-style-type: none"> ◦ VSD ◦ ASD ◦ Patent ductus arteriosus ◦ Aortopulmonary window • Complex lesions without obstruction across the pulmonary outflow tract: <ul style="list-style-type: none"> ◦ Complete atrioventricular canal ◦ Complete TGA with nonrestrictive VSD ◦ Truncus arteriosus ◦ Univentricular heart ◦ Tricuspid atresia with TGA and nonrestrictive VSD ◦ Ebstein's anomaly with an ASD |
| II. Congenital heart defects without Eisenmenger's physiology |
| <ul style="list-style-type: none"> • Congenital heart defects with obstruction across the pulmonary outflow tract (subvalvular, valvular and supra-valvular) <ul style="list-style-type: none"> ◦ VSD with pulmonary stenosis ◦ Tetralogy of Fallot ◦ Discordant atrioventricular and ventriculoarterial connections (congenitally corrected TGA) with VSD and pulmonary stenosis ◦ Tricuspid atresia with ASD, VSD and restrictive VSD/pulmonary stenosis ◦ Complete atrioventricular septal defect with pulmonary stenosis ◦ Others • Congenital heart defect without obstruction across the pulmonary outflow tract: <ul style="list-style-type: none"> ◦ Ebstein's anomaly with a secundum ASD |

ASD Atrial septal defect; TGA Transposition of the great arteries; VSD Ventricular septal defect

- clotting profile, renal function and uric acid.
- Echo-Doppler evaluation by an appropriately trained individual.
- Cardiac catheterization with a pulmonary vascular study and coronary angiography in patients older than 40 years of age when surgical intervention is considered.
- MRI for unrestricted anatomical visualization, with cine imaging and velocity mapping for investigation of shunt lesions.

Part IV. Indications for intervention/reintervention/medical therapy

Secondary erythrocytosis may cause hyperviscosity symptoms (160,187). Symptoms will be relieved by phlebotomy to an appropriate hematocrit level. In the iron-replete state, hyperviscosity symptoms may occur, typically when hematocrit levels are in excess of 65%. Dehydration and iron deficiency should be excluded or corrected before phlebotomy.

Cyanotic patients having surgery may undergo prophylactic phlebotomy to reduce the hematocrit to less than 65%. When specific factor deficiencies are documented, fresh frozen plasma can be used as a substitute for volume replacement during prophylactic preoperative phlebotomy.
Class IIa, level C

Hemostatic abnormalities: The management of bleeding diathesis is determined by the clinical circumstance, the severity and the hemostatic parameters. Because of the risk of bleeding events from acetylsalicylic acid, some experts strongly believe that heparin, warfarin and acetylsalicylic acid should be avoided unless indicated for persistent

atrial fibrillation, the presence of a mechanical prosthetic valve, deep vein thrombosis or pulmonary embolus.

Nonsteroidal anti-inflammatory agents should be avoided to prevent bleeding events. Platelet transfusions, fresh frozen plasma, vitamin K, cryoprecipitate and desmopressin can be used to treat severe bleeding. If iron deficiency anemia is confirmed, iron replacement should be prescribed.

Class I, level C (160)

For moderate to severe symptoms of hyperviscosity, phlebotomy can be performed. Dehydration and iron deficiency should be excluded or corrected before phlebotomy. A brain abscess must be considered as a cause of headache.

Hydration should be prescribed before procedures involving contrast media to avoid renal dysfunction. Symptomatic hyperuricemia and gouty arthritis can be treated as necessary with colchicine, probenecid or sulfinpyrazone; and with allopurinol for prophylaxis.

Class I, level C (161,163)

The goal of interventions is to either prolong life or improve symptoms. There is controversy regarding whether a cyanotic adult survivor who is stable, but eligible for complete physiological repair, should be considered for surgery to improve or prolong life. Outcome varies widely, and depends on the lesion and the surgical expertise and support. Symptomatic patients may manifest worsening cyanosis and ensuing medical complications, or decreasing functional capacity with or without the occurrence of symptomatic arrhythmias.

Patients with symptoms of worsening cyanosis, decreasing functional capacity or symptomatic arrhythmias should be considered for intervention. Eligible cyanotic patients should be considered for complete physiological repair in conjunction with congenital heart surgeons. Advanced pulmonary vascular obstructive disease with a resistance, which is fixed, in combination with the absence of left-to-right shunting, render a patient ineligible for cardiac repair. These patients may be candidates for palliative procedures or transplantation.

Class I, level C

Part V. Interventional/surgical options

Percutaneous closure of intracardiac shunts. A variety of devices can be used to close ASDs, patent ductus arteriosus and, occasionally, VSDs (see previous sections).

Palliative surgical interventions performed in patients with cyanotic lesions are defined as operations that increase or decrease pulmonary blood flow while allowing mixed circulation and cyanosis to persist. Palliative surgical shunts are aimed at increasing pulmonary blood flow.

Physiological repair is a term that can be applied to procedures that result in total or near-total anatomical and physiological separation of the pulmonary and systemic circulations in complex cyanotic lesions, resulting in relief of cyanosis. These are described throughout the present document with reference to specific lesions.

Transplantation of the heart and one or both lungs with surgical shunt closure and heart-lung transplantation has been performed in cyanotic patients with or without palliation who are no longer candidates for other forms of intervention. Pulmonary vascular obstructive disease precludes isolated heart transplantation, but an increasing number of patients with previous palliation and ventricular failure are successfully undergoing cardiac transplantation. Technical difficulties relate to previous thoracotomies and bleeding tendency in addition to intracardiac and pulmonary anatomical distortion from previous intervention.

Part VI. Interventional outcomes

Palliative surgical interventions: Systemic arterial-to-PA shunts result in improved saturation levels, with high levels of pulmonary blood flow. The long-term complications of these shunts may include pulmonary hypertension, PA stenosis and volume overload of the systemic ventricle, often making further surgical intervention more difficult or impossible. This is particularly true of large central shunts, the Potts shunt and the Waterston anastomosis. Blalock-Taussig shunts result in more controlled pulmonary flow but may stenose over time and can distort the PA anatomy. PA banding can lead to distortion of the PA, complicating later repair.

Transplantation: The results of cardiac transplantation in properly selected patients with CHD, with and without previous palliative surgery, have improved in recent years. Lung transplantation (single or double) with intracardiac repair can be effective in reducing pulmonary hypertension.

Part VII. Pregnancy and contraception

Pregnancy in cyanotic CHD, excluding Eisenmenger's reaction, can result in maternal cardiovascular complications and prematurity (49,53,54,150). Pregnant women with an oxygen saturation of greater than 85% fare better than women with an oxygen saturation of less than 85%.

Combined oral contraceptive pills are best avoided because of the associated thrombosis risk. Progesterone-only depot injections and subdermal insertion of etonogestrel may be safe options.

Pregnancy in women with Eisenmenger's syndrome is not advised because of the high maternal and fetal mortality.

Class III, level B (53,192,193)

If pregnancy is continued despite advice to the contrary, or the patient presents late, management should be referred to groups with combined expertise in ACHD cardiology, high-risk obstetrics and pulmonary hypertension to attempt to optimize outcomes.

Class I, level C

Part VIII. Follow-up

All patients with cyanotic CHD should be cared for by an ACHD cardiologist. They may also benefit from the involvement of other specialists within such an ACHD centre (nursing, respiratory, psychology/psychiatry, hematology, gynecology, anesthesia, intensive care and social work).

Annual clinical visits with comprehensive, systematic assessment and laboratory evaluation for potential complications are recommended.

Imaging tests should be performed every two to three years in a stable patient.

Class I, level C

Particular attention should be paid to the following:

- Symptoms of hyperviscosity.
- Systemic complications of cyanosis.
- A change in exercise tolerance.
- A change in saturation level.
- Occurrence of arrhythmias.
- Cardiovascular risk modification and surveillance for acquired cardiovascular diseases.
- Prompt therapy for infections.
- Endocarditis prophylaxis.
- Perioperative assessment for noncardiac surgery.

Endocarditis prophylaxis is recommended for all patients with cyanotic heart disease.

Class I, level B (56)

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