Management of the Adult Patient With Congenitally Corrected Transposition: Challenges and Uncertainties

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Congenitally corrected transposition (ccTGA) is a rare form of congenital heart disease characterized by atrioventricular and ventriculoarterial discordance. Patients with ccTGA usually have associated congenital cardiovascular conditions; less than 1% have no associated lesions. Generally, ccTGA is identified during infancy or childhood with features of heart failure or cyanosis when there are associated lesions such as ventricular septal defect and/or pulmonic stenosis. Presentation later in life generally occurs when there are either mild or no associated lesions. Presentation during adulthood may be prompted by symptoms or signs of cardiovascular disease or due to abnormal findings on cardiac testing. Management of patients with ccTGA depends on presentation, symptoms, and associated defects. In this review, we will focus on the management of adult patients with ccTGA.

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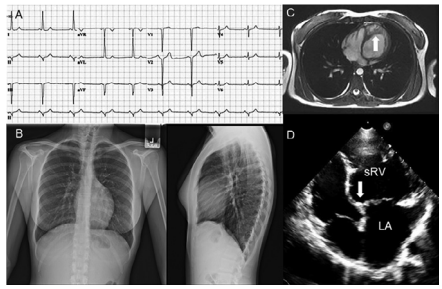

Multimodality findings in congenitally corrected transposition of the great arteries.

Central Message

Systemic ventricular or atrioventricular valve dysfunction and arrhythmias are common in adults with congenitally corrected transposition.

INTRODUCTION

Congenitally corrected transposition (ccTGA) is a rare form of congenital heart disease accounting for less than 1% of congenital cardiac lesions. It is characterized by atrioventricular and ventriculoarterial discordance, that is the morphologic right ventricle and tricuspid valve receive pulmonary venous blood and in turn are connected to the aorta, thus being in the systemic circulation. In contrast, the morphologic mitral valve and left ventricle receive systemic venous blood and are connected to the pulmonary artery. This defect occurs due to abnormal cardiac development during the third gestational week where left looping (L-loop) of the heart tube instead right looping occurs. This leads to abnormal positioning of the ventricles, and abnormal connections among the atrial, ventricular, and arterial segments of the heart. In ccTGA, the aorta is typically anterior and to left of the pulmonary artery. Although it describes the relationship between the great vessels, the term *l-transposition* (l-TGA) is often used interchangeably with ccTGA in contrast to d-TGA, used to describe complete transposition of the great arteries.

Most patients with ccTGA have 1 or more associated congenital cardiac lesions. The most common associated lesions in patients with ccTGA include ventricular septal defect (60–80%), subvalvular or valvular pulmonic stenosis (30–50%), and abnormalities of the systemic atrioventricular valve (up to 90%). An Ebstein-like anomaly of the systemic atrioventricular valve is often reported, but this valve abnormality is usually characterized by excessive apical displacement of the tricuspid valve rather than abnormal adherence of the valve leaflets to the underlying endocardium, one of the hallmarks of classic Ebstein's anomaly. Ultimately most patients with ccTGA develop systemic (morphologic right) ventricular dysfunction and systemic (morphologic tricuspid) valve regurgitation. The conduction system is also abnormal in ccTGA patients with displacement of the atrioventricular node to an anterior/superior position within the right atrium. This predisposes patients to arrhythmias and heart block. Heart block occurs at a rate of approximately 2% per year in patients with ccTGA [1,2]. Mesocardia or dextrocardia also occurs with increased frequency in

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patients with ccTGA and the presence of ccTGA should always be entertained in patients with cardiac malposition in the absence of heterotaxy [3–5].

EARLY PRESENTATION

Most patients with ccTGA present after delivery, although antenatal diagnosis has been reported [6]. Those presenting early in life generally have associated cardiac lesions, including ventricular septal defect and/or pulmonic stenosis. Depending on the predominant lesion, they may present with heart failure (secondary to pulmonary over circulation) and/or cyanosis (due to the pulmonary/subpulmonary obstruction). Many patients with ccTGA and associated defects require early operative intervention; the criteria used to select patients for anatomic vs physiologic repair are reviewed elsewhere.

LATE PRESENTATION

Adults with ccTGA may be identified with abnormal cardiovascular signs or symptoms such as a murmur (typically tricuspid regurgitation), loud second heart sound (due to anterior position of the aortic valve), arrhythmia, heart failure or by abnormal findings on cardiovascular testing such as an abnormal electrocardiogram, chest radiograph, transthoracic echocardiogram, or cross-sectional imaging (Fig. 1). Most patients presenting as young adults have mild or no associated congenital cardiovascular lesions [7]. Occasionally, unoperated adults with ccTGA and associated ventricular septal defect and/or pulmonic stenosis are encountered; this occurs when the lesions are either well balanced and the patients have minimal cyanosis and symptoms early in life, or when there has been limited access to medical care. Rarely, patients with ccTGA are incorrectly diagnosed as left ventricular noncompaction cardiomyopathy, due to prominent trabeculation of the systemic right ventricle (Fig. 1C) and failure to recognize that the right ventricle is the systemic ventricle.

An abnormal systemic tricuspid valve with progressive regurgitation is common in adult patients with ccTGA. As the systemic ventricle and the tricuspid annulus dilate, failure of leaflet coaptation contributes to valve regurgitation. In addition, the tricuspid valve itself is frequently abnormal in ccTGA, predisposing these patients to progressive valve regurgitation, especially in those with the Ebstein-like anomaly of the tricuspid valve. Ventricular dysfunction commonly occurs in conjunction with systemic tricuspid valve regurgitation. In 1 small study, the only significant predictor of death was at least moderately severe systemic tricuspid valve regurgitation, and only the presence of a morphologically abnormal systemic tricuspid valve predicted systemic tricuspid valve regurgitation [8]. Systemic tricuspid valve regurgitation may progress after endocardial pacemaker implantation; this is thought to be due to

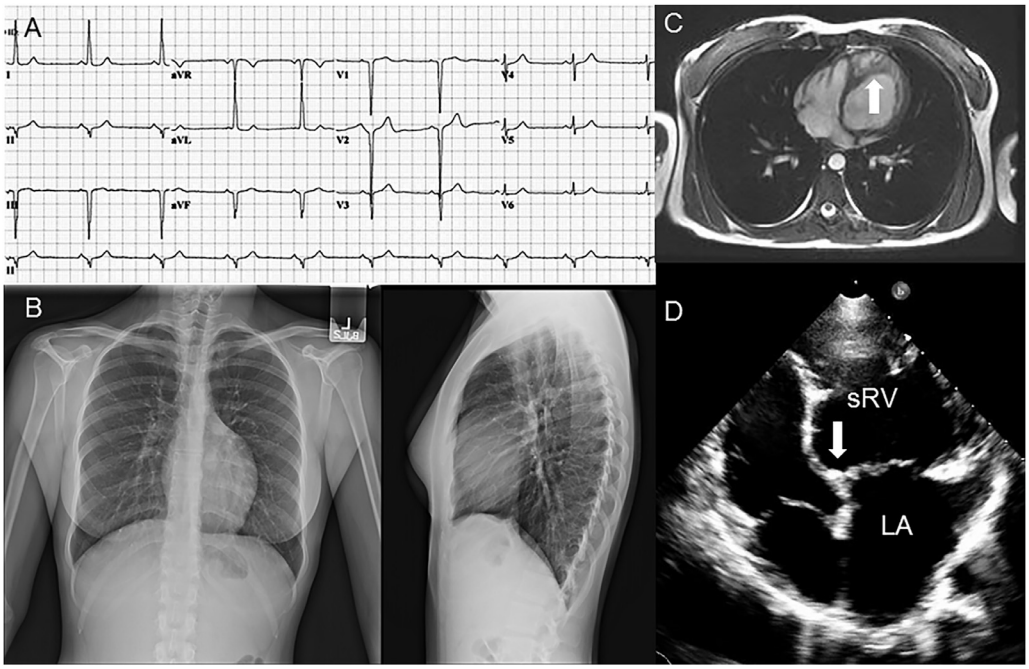

Figure 1 Cardiovascular testing from a patient with congenitally corrected transposition of the great arteries. The electrocardiogram (A) demonstrates Q waves in the inferior leads (II, III, and AVF), as well as V1 and V2 and absence of Q waves in V5 and V6, as typically seen in ccTGA. The chest radiograph (B) demonstrates a narrow vascular pedicle due to the abnormal relationship between the aorta and pulmonary artery. The left heart border has a "humped appearance" commonly seen in patients with ccTGA. The cardiac magnetic resonance imaging study (C) demonstrates prominent ventricular trabeculation (arrow) in the systemic right ventricle. The apical 4-chamber view from the transthoracic echocardiogram (D) demonstrates apical displacement of the systemic tricuspid valve (arrow), trabeculation affecting the systemic right ventricle (sRV), and left atrial (LA) dilatation.

septal shift and further distortion of the systemic tricuspid valve annulus. Intracardiac repair such as relief of subpulmonary/pulmonary obstruction may also exacerbate systemic tricuspid valve regurgitation as a result of septal shift.

LONG-TERM OUTCOME

Patients with ccTGA demonstrate a variable natural history. Thus, the care of these patients needs to be individualized. For example, occasionally, patients survive to advanced age with minimal symptoms, mild right ventricular dysfunction, and mild tricuspid valve incompetence. Those patients can be closely monitored without need for intervention. Since patients may survive to the ninth decade, this suggests that failure of the systemic right ventricle is not inevitable. However, in most patients, failure of the systemic right ventricle, systemic tricuspid valve regurgitation, and arrhythmias or heart block will ensue, leading to symptoms, and impacting survival.

The long-term outcome of ccTGA patients was reported in a multicenter retrospective study including patients from 19 institutions [9]. Patients were divided into those with associated lesions (n = 132), and those with mild or no associated lesions (n = 50). Freedom from heart failure and systemic ventricular dysfunction varied between groups with and without associated lesions. In patients with significant associated defects and prior cardiac surgery, two-thirds of patients had heart failure symptoms by the age of 45 years compared to 25% of patients without associated lesions. Predisposing factors for systemic right ventricular dysfunction included age, associated cardiac lesions, systemic tricuspid valve regurgitation, arrhythmias, pacemaker implantation, and prior surgery, particularly if it involved the systemic tricuspid valve. The role of coronary ischemia is unclear, but is of concern given that the coronary arteries and ventricles are morphologically concordant, so the right coronary artery supplies the entire systemic right ventricle [10].

Despite the long-standing debate among experts, it is still unproven whether systemic ventricular dysfunction causes atrioventricular valve regurgitation or whether atrioventricular valve regurgitation precipitates progressive systemic ventricular dysfunction. Predisposing factors for systemic tricuspid valve regurgitation include age, abnormal tricuspid valve morphology, history of intracardiac surgical procedure, pacemaker placement, ventricular volume overload such as occurs with a ventricular septal defect or surgical shunt, and systematic right ventricular dysfunction. Late referral for intervention adversely impacts survival and increases the need for late transplantation [11].

MANAGEMENT

Follow-Up

All patients with ccTGA require life-long informed cardiovascular follow-up. Regular assessment at our center includes clinical evaluation, cardiovascular imaging, arrhythmia, and exercise assessment. Counseling regarding lifestyle issues such as activity, endocarditis prophylaxis (when indicated), and pregnancy are important.

In our practice, we see adult patients with ccTGA at least annually with comprehensive cardiovascular testing including transthoracic echocardiography evaluation of systemic ventricular function and systemic atrioventricular valve function. Advanced imaging, such as cardiac magnetic resonance imaging and gated computerized tomography, or ventriculography is used to further assess ventricular and valve function in patients with discordant clinical and echocardiographic findings.

Congenital heart rhythm consultation is arranged when tachy- or bradyarrhythmias are identified. The most appropriate timing for referral to an advanced heart failure/heart transplant program is less well delineated, but will require a multispecialty team with expertise in the care of patients with congenital heart disease. In our practice, as systemic right ventricular dysfunction is common, the need for advanced heart failure management is prompted by symptoms and decline in functional capacity.

Medical Therapy

There are limited data to support the use of pharmacotherapy for systemic ventricular dysfunction [12,13]. Afterload reduction with angiotensin converting enzyme inhibitors or angiotensin II receptor blockers appear less successful than when used for a morphologic left ventricle [14], but most experts advise these therapeutic agents for ccTGA patients demonstrating any degree of systemic ventricular dysfunction, unless specific contraindications exist such as pregnancy. Data are lacking to support the use of beta blockers to improve ventricular function in ccTGA, and caution must be used due to the propensity for heart block. In our experience, this concern is more theoretical than real; beta blockers are generally well tolerated in most adults with ccTGA. Decline in systemic ventricular function in patients with ccTGA should prompt a careful search for treatable causes such as arrhythmias and systemic atrioventricular valve regurgitation.

Antiarrhythmic drug therapy selection is similar in ccTGA patients to management in patients with other forms of heart disease; special concerns include proarrhythmia, and negative inotropic or chronotropic potential in this population.

Cardiac Devices

Systemic right ventricular dysfunction in ccTGA increases the risk of sudden death and ventricular tachyarrhythmias; whether defibrillators offer survival benefit remains unclear at this time [15].

Cardiac resynchronization therapy (CRT) is feasible in ccTGA but the anatomy of the coronary sinus may be variable. Thus, a heart rhythm specialist familiar with ccTGA, including the potential caveats, should be involved [16]. Preliminary data suggest CRT may be an effective option in the treatment of patients with systemic right ventricular dysfunction [17]. However, at this time data do not support placement of a CRT

device, or CRT upgrade in those with a pacemaker, in an effort to prevent systemic ventricular dysfunction or systemic atrioventricular valve regurgitation in this patient population.

SURGICAL REPAIR AND INTERVENTION

Most patients presenting early in life with ccTGA and associated defects require operative intervention with options including anatomic vs physiologic repair. The surgical options, most appropriate procedure and the technical aspects of these procedures will be reviewed elsewhere in this edition.

Anatomic repair is not performed in our adult ccTGA practice due to the inability to adequately "train" the left ventricle to support a systemic circulation in the majority of adults [18]. In addition, the medium term complications of such complex repairs are significant. Systemic atrioventricular valve replacement is the most common operation performed and is recommended for patients with: (1) severe systemic atrioventricular valve regurgitation with low or mildly increased nonsystemic ventricular pressure, (2) symptoms related to systemic atrioventricular valve regurgitation, (3) more than moderate systemic atrioventricular valve regurgitation in the setting of systemic ventricular dysfunction (EF < 40%), and (4) more than moderate systemic atrioventricular valve regurgitation at the time of intracardiac repair of other lesions [19]. Unfortunately most patients are referred when severe ventricular dysfunction has developed with severe atrioventricular valve regurgitation at which time systemic atrioventricular valve replacement has a higher surgical risk, and unsurprisingly, will not result in improved ventricular function.

Our approach has evolved somewhat over the last 2 decades recognizing that if systemic ventricular function declines in an adult ccTGA patient, the most common explanation is systemic tricuspid regurgitation, thus, detailed clinical evaluation with imaging and ventriculography is conducted to carefully evaluate the degree of regurgitation. Valve replacement when the ejection fraction is preserved (at least >40%) is more likely to stabilize ventricular function, and can be accomplished with a low mortality [20]. This suggests that the added volume load due to valve regurgitation on the vulnerable systemic right ventricle is more often the cause of ventricular dysfunction than an inherent myocardial abnormality. Isolated deterioration in systemic ventricular function without tricuspid regurgitation is less common.

One series reviewed the impact of systemic right ventricular function on late outcome after systemic atrioventricular valve replacement; risk factors for late mortality or transplantation included atrial fibrillation, systemic right ventricular ejection fraction <40%, and nonsystemic ventricular systolic pressure >50 mm Hg [20,21]. We do not recommend systemic atrioventricular valve repair in this patient population, due to reduced durability [22]. The choice of valve prosthesis should be individualized, but a mechanical prosthesis is often preferable to try and avoid another surgical procedure, particularly when ventricular function is already impaired.

Indications for surgical or percutaneous intervention to relieve severe isolated valvular or subvalvular pulmonary obstruction in the adult with ccTGA are not well delineated. In fact, relief of this obstruction may be detrimental to systemic atrioventricular valve function and systemic ventricular function. Pulmonary artery banding has been found to improve systemic atrioventricular valve regurgitation in select ccTGA patients; the role of this is not established in adult ccTGA patients as a palliative procedure.

Ventricular assist device placement and cardiac transplantation should be considered in patients with persistent heart failure refractory to standard medical and surgical management.

PERSISTENT UNCERTAINTIES AND FUTURE DIRECTIONS

The natural history of patients with ccTGA is highly variable with some patients having preserved ventricular and valve function for decades. We do not know how to predict which patients will do well for decades or indeed how to best preserve stability of ventricular and valve function. The complex interplay between the systemic ventricle and systemic atrioventricular valve in this disorder requires further delineation. Better tools to help us risk stratify patients and provide early intervention are needed; cardiac biomarkers, advanced imaging, and/or hemodynamic assessment may provide insights into differentiating the ccTGA patients who will do well for decades without any intervention from those who will not.

Guideline-directed medical therapy has been demonstrated to improve symptoms and survival in patients with systemic left ventricular dysfunction. The impact and optimal medical management strategies to preserve systemic right ventricular function in ccTGA requires further assessment and better delineation — thus far, medical therapies to improve systemic ventricular function and exercise capacity have proved elusive.

Tachy- and bradyarrhythmias are common in ccTGA patients, and therapy for arrhythmias often is associated with progressive clinical decline. Thus, better understanding of how to best manage patients with arrhythmias, including device therapy, is critically needed. In general, for those with atrial tachyarrhythmias, prompt restoration of sinus rhythm is preferable.

Native left ventricular outflow tract obstruction caused by pulmonary valve or subpulmonary stenosis, and pulmonary artery band cause increased nonsystemic ventricular pressure which may have a favorable impact on septal and ventricular morphology and in turn may maintain or improve systemic ventricular and systemic atrioventricular valve function. Placement of noninvasive adjustable pulmonary artery bands may provide an opportunity to increase the interval between recognition of systemic ventricular or valve dysfunction and need for operative intervention.

CONCLUSIONS

ccTGA is a complex and rare form of congenital heart disease. The natural history is highly variable and depends largely on associated cardiac lesions. Current management of adults depends on presentation, symptoms, and associated defects.

There are opportunities to identify improved care options with medical therapy, device, and surgical options.

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