Long-Term Outcome in Congenitally Corrected Transposition of the Great Arteries
A Multi-Institutional Study

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| OBJECTIVES | The purpose of this study was to determine long-term outcome in adults with congenitally corrected transposition of the great arteries (CCTGA), with particular emphasis on systemic ventricular dysfunction and congestive heart failure (CHF). |
| BACKGROUND | Patients with CCTGA have the anatomical right ventricle as their systemic pumping chamber, with ventricular dysfunction and CHF being relatively common in older adults. |
| METHODS | Retrospective analysis of records of 182 patients from 19 institutions were reviewed to determine current status and possible risk factors for systemic ventricular dysfunction and CHF. Factors considered included age, gender, associated cardiac defects, operative history, heart block, arrhythmias and tricuspid regurgitation (i.e., systemic atrioventricular) regurgitation (TR). |
| RESULTS | Both CHF and systemic ventricular dysfunction were common in groups with or without associated cardiac lesions. By age 45, 67% of patients with associated lesions had CHF, and 25% of patients without associated lesions had this complication. The rates of systemic ventricular dysfunction and CHF were higher with increasing age, the presence of significant associated cardiac lesions, history of arrhythmia, pacemaker implantation, prior surgery of any type, and particularly with tricuspid valvuloplasty or replacement. Aortic regurgitation (a previously unreported problem) was also relatively common in this patient population. |
| CONCLUSIONS | Patients with CCTGA are increasingly subject to CHF with advancing age; this complication is extremely common by the fourth and fifth decades. Tricuspid (systemic atrioventricular) valvular regurgitation is strongly associated with RV (anatomical right ventricle connected to aorta in CCTGA patients; systemic ventricle in CCTGA) dysfunction and CHF; whether it is causative or a secondary complication remains speculative. (J Am Coll Cardiol 2000;36: 255–61) © 2000 by the American College of Cardiology |

In congenitally corrected transposition of the great arteries (CCTGA), dysfunction of the systemic right ventricle occurs with increasing frequency in older patients (1–4). The factors contributing to this problem are poorly understood. Indeed, there are patients with uncomplicated CCTGA whose right ventricles appear to function normally, well into late adulthood (5–12). Surgical intervention for associated lesions has been associated recently with prolonged adult survival. Various potential risk factors for systemic ventricular failure in CCTGA have been implicated, including systemic atrioventricular valvular regurgitation (tricuspid regurgitation [TR]) (3,4,13,14), associated congenital cardiac defects (15,16), complete heart block (17), and surgical intervention, particularly open heart operations (18–20). The rarity of this condition has contributed to limited experience at any single institution, and published reports therefore contain relatively small numbers of patients. Accordingly, the Project Committee of the

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International Society of Adult Congenital Cardiac Disease undertook a multicenter retrospective review to determine the prevalence of congestive heart failure (CHF) and right ventricular dysfunction in CCTGA as a function of age, and the probable risk factors associated with this problem.

METHODS

All members of the International Society for Adult Congenital Cardiac Disease were invited to include patients fulfilling entry criteria in the study by filling out a patient data form and sending it to the coordinating center by October 27, 1997. In centers where an institutional review board required approval for the study, it was obtained. Most institutions reported exemption from this requirement because no patient names or identifying numbers were made known to the data coordinating center at Vanderbilt University Medical Center. The criteria for inclusion or exclusion from the study are shown in Table 1. There were 182 patients from 19 institutions enrolled. The institution physician director and number of patients from each institution are indicated in Table 2. Not all institutions had a robust database to ensure capture of all adult congenital heart disease patient encounters. Each physician director, however, provided a careful search of his own database to ensure as complete a CCTGA population capture as possible. Because CCTGA is such an unusual diagnosis, it is our hypothesis that most patients would be included in this review.

These chart reviews were performed without any patient being identified except by number. The study was in compliance with each institution’s human studies committee.

Patients were classified into two groups. Group I included 132 patients with significant associated lesions. This group included patients with any of the following lesions: large ventricular septal defect (VSD), moderate or severe pulmonary stenosis (PS), pulmonary atresia, moderate or severe TR and Ebstein-like anomaly of the tricuspid valve. Group II consisted of 50 patients with minor or no significant lesions (see Table 3). The VSD size was estimated clinically and by echocardiography.

Pulmonary stenosis was classified as mild if catheterization or Doppler estimates indicated a peak systolic gradient of <35 mm Hg. Estimation of TR was by Doppler study in most patients, with the following guidelines for investigators: mild, no RV (anatomical right ventricle connected to aorta in CCTGA patients; systemic ventricle in CCTGA) enlargement, TR jet <5 cm²; moderate, RV enlargement,
TR jet 5 to 8 cm²; severe, RV enlargement, TR jet 8 cm² + pulmonary vein reversal in systole. Angiographic estimates of TR were used by a few investigators with these guidelines: mild, normal RV size, contrast fills 10% to 25% of left atrium (LA), clears in 1 to 2 beats; moderate, definite RV enlargement, contrast fills 25% of LA, fails to clear in 2 beats; severe, marked RV enlargement, contrast fills most of LA (± pulmonary veins), fails to clear in 3 beats.

In addition, investigators provided the following information for each patient: operative history, occurrence of heart block/pacemaker insertion, occurrence of significant arrhythmia requiring treatment, estimate of mitral and aortic regurgitation, latest chest film with cardiothoracic ratio for cardiomegaly estimate, and right and left ventricular function assessment (echocardiograph, angiogram, magnetic resonance imaging, or radionuclide angiography estimate as normal, or mild, moderate or severely decreased). In addition, evidence for clinical systemic ventricular dysfunction (congestive heart failure, CHF) and date of onset of CHF were provided. Data supporting the diagnosis of CHF were cardiomegaly, pulmonary congestion, edema, hepatomegaly, gallop rhythm, fatigue and digoxin/diuretic/afterload reduction therapy. Finally, current functional classifications using the Warnes-Somerville ability index and the Toronto classification were provided.

**Warnes-Somerville Ability Index**

Grade 1: Normal life; full-time work or school; can manage pregnancy.

Grade 2: Able to do part-time work; life modified by symptoms.

Grade 3: Unable to work; noticeable limitation of activities.

Grade 4: Extreme limitation; dependent; almost housebound.

**Toronto Congenital Heart Disease Functional Class**

Class 1: Asymptomatic.

Class 2: Symptoms are present but do not interfere with normal activities.

Class 3: Symptoms interfere with some but not most activities.

Class 4: Symptoms interfere with most if not all activities.

**Statistical methods.** Demographic and clinical variables were summarized using mean ± SD and proportions within groups I (CCTGA with significant associated lesions) and II (CCTGA with minor or no associated lesions). Differences between groups were assessed by Pearson’s chi-square, the Fisher exact test, and the two-sided, two-sample t test. The association of selected variables with clinical CHF, RV dysfunction, and LV (anatomical left ventricle connected to pulmonary artery in CCTGA patients) dysfunction was assessed by calculating odds ratio (OR) estimates and 95% confidence intervals. These estimates were combined over both groups using the Mantel-Haenszel method in the absence of statistically significant differences between groups. Survival curves were generated using Kaplan-Meier estimates, and differences in survival between groups were assessed by the log-rank test. The statistical software packages S-PLUS and SAS were used. A p value <0.05 was considered statistically significant.

**RESULTS**

Table 4 shows statistical analysis and t-test analysis for pertinent variables for the two groups. Patient ages were not different between the two groups and averaged 32 ± 13 years (range 18 to 75 years) for the entire group of 182 patients.

**Clinical CHF.** Clinical CHF was common and significantly more common in patients with associated lesions, 51% versus 34%. Figure 1 shows that the probability of freedom from CHF is clearly greater for group II versus group I when this variable is assessed versus advancing age. By age 45 years, 67% of patients in group I have CHF,
whereas 25% of patients in group II, those patients with only minor or no associated lesions, have this complication.

**Systemic ventricular dysfunction and tricuspid regurgitation.** Right (systemic) ventricular dysfunction was common in both groups, 70% and 55%, as was TR, 82% and 84%. Neither of these conditions were significantly different between groups (see Table 4).

Figure 2 shows the probability of freedom from moderate or severe RV (systemic ventricular) dysfunction as a function of age. There is a clear continuing increase in systemic ventricular dysfunction with increasing age; by age 45 years, 56% of patients with associated lesions and 32% of patients without significant associated lesions have this complication. Although group I patients did have a higher incidence of RV dysfunction than group II patients at any age, the probability curves were not statistically different ($p = 0.08$).

The incidence of pacemaker therapy, significant arrhythmia requiring treatment, and open heart surgery were all significantly greater in group I patients than group II patients (see Table 4).

**Pulmonary ventricular dysfunction and AR.** Pulmonary (anatomical left ventricular) dysfunction was present in 25% of patients in group I and only 7% in group II. Left ventricular dysfunction also showed an increase in incidence with increasing age (Fig. 3). By age 45 years, 20% of patients in group I and 5% in group II had LV dysfunction. Again, although LV dysfunction as a function of age was more common in group I than group II patients, the difference in probability curves was not significant ($p = 0.11$).

Finally, aortic regurgitation (AR) was a relatively common finding in patient groups I and II, 36% and 25%, but not significantly different between groups (Table 4).

**Risk factors for CHF: Ventricular dysfunction.** In an attempt to determine potential correlates for all patients, clinical CHF, RV dysfunction, and LV dysfunction, OR estimates were calculated for possible risk factors (Table 5). For clinical CHF, the strongest risk factors were tricuspid valve surgery, TR, significant arrhythmia, history of any open heart surgery, and pacemaker therapy. For RV dysfunction, these same risk factors are significant. In addition, male gender appears to be a risk factor of borderline significance.

For LV dysfunction, there were no clearly significant risk factors as assessed by this method of OR estimates.

**Functional classification.** Despite the relatively high frequency of objective CHF and/or ventricular dysfunction, Figures 4 and 5 show estimates of the functional classification in which most patients consider themselves, with none or minimal symptoms when assessed in this manner.

**DISCUSSION**

**Systemic ventricular dysfunction and CHF.** The present study is the largest multicenter attempt to review the clinical
course of patients with a rare form of congenital heart disease—congenitally corrected transposition of the great arteries. These data clearly indicate the increasing incidence of systemic ventricular dysfunction and clinical CHF with increasing age in patients with CCTGA. In patients’ most productive middle years, symptomatic CHF is extremely common. In patients with significant associated defects and prior open heart surgery, two thirds of patients have CHF by age 45. This complication also is common in middle-aged adults with CCTGA and no associated significant lesions; by the fifth decade more than one-third developed this symptom. This is the largest cohort reported with this condition, and it clearly indicates the potentially tenuous nature of the compensated systemic right ventricle.

TR. Although it appears that systemic atrioventricular valve (tricuspid) regurgitation plays a role in the determination of RV dysfunction and clinical CHF with increasing age in patients with CCTGA. In patients’ most productive middle years, symptomatic CHF is extremely common. In patients with significant associated defects and prior open heart surgery, two thirds of patients have CHF by age 45. This complication also is common in middle-aged adults with CCTGA and no associated significant lesions; by the fifth decade more than one-third developed this symptom. This is the largest cohort reported with this condition, and it clearly indicates the potentially tenuous nature of the compensated systemic right ventricle.

TR. Although it appears that systemic ativoventricular valve (tricuspid) regurgitation plays a role in the determination of RV dysfunction and CHF, it is extremely difficult to estimate whether this abnormality plays a primary or a secondary role. Prieto and associates (14) in a cohort of 40 patients with CCTGA found TR to be a major risk factor for systemic ventricular dysfunction during a follow-up of 7 to 36 years (mean 20 years). These investigators considered the valvular abnormality to precede or precipitate CHF in most of their patients.

Do these patients develop TR because of systemic ventricular dysfunction, or do they have TR, which hastens the development of systemic ventricular dysfunction? It is probable that each scenario can play a role in individual patients. In addition, it is clear that open heart surgery (particularly tricuspid valve surgery) is associated with an increased risk of RV dysfunction and CHF—possibly related to an increase in afterload and/or difficulty in myocardial protection during surgery. Acar and associates (21) recently reported serial echocardiographic data in 82 patients with CCTGA, which indicated the marked dependence of TR on RV loading conditions. Lundstrom and colleagues (18) suggested that CCTGA patients with symptomatic CHF and TR should have tricuspid valve replacement prior to significant RV dilation. We concur that early tricuspid valve replacement may be useful for selected individuals with RV dilation in an attempt to preserve ventricular function.

Systemic ventricular dysfunction: Associated variables. It is also probable that with the occurrence of symptomatic heart block and ventricular pacing (which can result in discordant ventricular contraction), systemic ventricular dysfunction worsens.

The factors associated with preserved systemic ventricular function in some elderly patients are poorly understood. Recently, Hornung and associates (22) showed myocardial perfusion defects in five unoperated patients with CCTGA studied by myocardial perfusion scanning. There was evidence for reversible myocardial ischemia in four patients and fixed defects indicating infarction in five. One interpretation of these findings is that intermittent episodes of myocardial ischemia occur in these patients at times of high oxygen consumption (stress, exercise, hypertension). There could be inadequate coronary flow to a markedly hypertrophied systemic right ventricle supplied by a right coronary artery system with limited ability to provide adequate perfusion during the extremes of metabolic demands. Patients who continue with good systolic function may have right coronary artery systems that are more well developed and

![Figure 4](image-url) Warnes-Somerville functional classification for both patient groups.

![Figure 5](image-url) Toronto functional classification for both patient groups.
provide adequate myocardial perfusion at times of high oxygen demand.

AR. The presence of AR in 25% to 36% of patients was an unexpected finding that has not been reported previously. In patients with large right to left intracardiac shunts due to VSD and pulmonary outflow obstruction, the aorta would be expected to dilate, a finding that could lead to this complication. In the majority of patients, however, right-to-left shunting was not present, and thus could not account for aortic dilation or AR. Unfortunately, we do not have data quantifying aortic root size in any of our patients, and bicuspid aortic valve was not reported in any of our 182 patients. Thus, the cause(s) of AR in CCTGA remains undefined.

Left ventricular dysfunction. The finding of LV dysfunction in a number of patients limits the option of doing the so-called double switch operation (23–29) or makes this an option best entertained at a relatively young age before LV dysfunction becomes a problem. Because this procedure is most frequently applied in patients with a large VSD, it may need to be considered as a first surgical option before the potential detrimental effects of open heart surgery contribute to clinical CHF.

Study limitations. This study was limited by its retrospective analyses. In addition, patients with CCTGA associated with ventricular dysfunction and CHF may be more likely to be referred to regional centers and thus included in a center’s database. This could theoretically lead to an overestimation of these complications. Because CCTGA is such a rare condition, however, it is likely that most patients with this condition will eventually get referred to a regional center for adult congenital heart disease and be included in a database. Finally, part of the data reported depend on defining the function of the morphologic, subaortic right ventricle. Current information indicates that the ejection fraction values of both the subpulmonary and the subaortic normal right ventricle are nearly the same or only slightly less than the normal left ventricle (30–32).

Conclusions. In conclusion, systemic ventricular dysfunction and clinical CHF are extremely common in middle-aged adults with CCTGA. Although some patients with this congenital abnormality continue to do extremely well beyond age 60, this circumstance is the exception rather than the rule. Aggressive medical treatment with afterload reduction would appear indicated for these patients with ventricular enlargement and early symptoms. The benefits of the prophylactic use of vasodilators is unproven, but deserves study in an attempt to delay or prevent systemic ventricular dysfunction.

In addition, earlier surgical management of these patients before ventricular dysfunction becomes prominent should be incorporated into management in an attempt to improve long-term outcome. Patients with favorable anatomy, depressed RV function, and normal LV function should be considered for the double-switch operation by centers with experience and expertise in this procedure. Multi-institutional collaborative studies will be needed to clarify the merit of each of these management strategies.

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