Systemic right ventricle in elderly patients with congenitally corrected transposition of the great arteries: Clinical profile, cardiac biomarkers, and echocardiographic parameters

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ABSTRACT

Objective: The number of patients with congenitally corrected transposition of the great arteries (ccTGA) surviving to old age is increasing. This study therefore sought to characterize "geriatric" systemic right ventricle (sRV) in terms of clinical profile, cardiac biomarkers, and echocardiography-derived function when compared with findings in younger patients.

Methods: A single-center cross-sectional study of adults with ccTGA was performed. Patients underwent clinical assessment; transthoracic echocardiography; and venous blood sampling including N-terminal pro–B-type natriuretic peptide (NTproBNP), galectin-3, and soluble suppression of tumorgenicity 2 (sST2) measurements. In the echocardiographic study, the sRV function was assessed using fractional area change (FAC), tricuspid annular plane systolic excursion (TAPSE), systolic pulsed-wave Doppler velocity (s´), and longitudinal strain (LS).

Results: Ten patients with ccTGA aged 60 years or older and 53 patients younger than 60 years of age were included. There were significantly more individuals with hypertension (40% vs. 5.7%), dyslipidaemia (50% vs. 5.7%), and atrial fibrillation (70% vs. 20.7%) in the older group; similarly, we found higher NTproBNP (2706 pg/mL vs. 784.7 pg/mL; p<0.001), and galectin-3 (10.15 ng/mL vs. 7.24 ng/mL; p=0.007) concentrations in elderly ccTGA individuals, while sST2 content did not vary significantly according to age. Upon echocardiographic assessment, lower sRV FAC (28.6% vs. 36.1%; p=0.028) and LS (−12% vs. −15.5%; p=0.017) values were observed in patients aged 60 years or older. TAPSE and s' did not differ between the age groups.

Conclusion: Careful screening for acquired comorbidities, particularly atrial fibrillation, in elderly ccTGA patients is warranted. Examining selected cardiac biomarkers and echocardiography-derived parameters are useful in the assessment of the aging sRV. *(Anatol J Cardiol 2020; 24: 92-6)*

Keywords: systemic right ventricle, congenitally corrected transposition, aging, cardiac biomarkers, congenital heart disease, echocardiography

Introduction

Coexisting atrioventricular and ventriculoarterial discordance [congenitally corrected transposition of the great arteries (ccTGA)] is a rare defect, accounting for 0.5% to 1% of congenital heart disease (CHD). It creates a unique pathophysiological condition in which the morphologically right ventricle (RV) sustains systemic circulation from birth (1). In this context, the subaortic position of the RV with subsequent substantial increase in afterload leads to its remodeling, including geometric changes of the chamber, muscle hypertrophy, and fibrosis. In these settings, the RV is at increased risk of developing severe dysfunction over time (2, 3). The natural history of ccTGA varies from patient to patient and depends on coexisting malformations and the need for cardiac surgery. In favorable scenarios, isolated ccTGA may go unrecognized for decades. Cases of ccTGA have been discovered in athletes (4) and multiparous women (5), while late clinical presentations and survival to old age have reported (6). Recently, a growing heterogeneous population of elderly adult CHD patients with acquired comorbidities and high mortality rates was published (7), justifying the introduction of the phrasing "geriatric" CHD. This observation is supported by data from our clinic. We have observed a rapid increase in the number of ccTGA patients aged 60 years or older as well (Fig. 1a). This suggests that "geriatric" systemic RV (sRV) is no longer a unique presentation but instead constitutes an emerging problem among adults with complex CHD in specialized centers. Little is known about sRV function in elderly individuals. Therefore, the aim of our study was to characterize "geriatric" sRV in terms of clinical profile, cardiac biomarkers, and echocardiography-derived function when compared with younger (<60 years) ccTGA patients.

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Methods

A cross-sectional study was performed involving adult patients with ccTGA who were evaluated at our CHD out- or inpatient departments between January 2018 and February 2019. The exclusion criteria were: (1) pregnancy, (2) lack of informed consent, and (3) anatomic repair of the anomaly (double switch procedure) or single-ventricle physiology.

Each eligible patient underwent meticulous clinical assessment, peripheral venous blood sampling, and standard transthoracic echocardiography on the same day. The presence of concomitant lesions, a history of interventions, pharmacological treatment, self-reported functional capacity, and the incidence rates of established cardiovascular risk factors and acquired heart disease were analyzed. Data obtained from ccTGA patients aged 60 years or older were compared to those collected from ccTGA patients younger than 60 years of age.

Blood samples were collected via peripheral venipuncture and processed to plasma within 30 minutes of collection. Plasma N-terminal pro–B-type natriuretic peptide (NTproBNP) was measured in fresh samples on a Cobas e601 analyzer using the Elecys proBNP II immunoassay (Roche Holding AG, Basel, Switzerland). The remaining plasma was aliquoted and stored at −20°C until further analysis. The concentrations of galectin-3 (Gal-3) and soluble suppression of tumorgenicity 2 (sST2) were determined using the Quantikine sandwich enzyme-linked immunosorbent assay kits (R&D Systems, Minneapolis, MN, USA).

Transthoracic echocardiographic examinations were performed by cardiologists experienced in studying CHD and certified in echocardiography. These physicians used for echocardiographic examinations commercially available equipment (Vivid E95; GE Healthcare, Chicago, IL, USA) with am M5S matrix probe. The RV end-diastolic diameter was measured in the apical four-chamber view at the level of the basal segments. From the same view, the RV end-diastolic area and end-systolic area were measured and the RV fractional area change (FAC) was calculated (8). The tricuspid annular plane systolic excursion (TAPSE) was acquired by the M-mode method at the lateral tricuspid annulus. Pulsed-wave tissue Doppler with a sample volume placed at the lateral corner of the tricuspid annulus was adopted to assess its systolic velocity (RV s′). The speckle-tracking method was used to analyze sRV myocardial deformation. The longitudinal strain (LS) was measured in the apical four-chamber view and defined as the mean of the sRV free wall and interventricular septum segment strains.

The study was approved by the relevant Institutional Medical Ethics Committee and patients provided written informed consent.

Statistical analysis

Unless stated otherwise, continuous variables were presented as means±standard deviations and categorical variables were expressed as numbers and proportions. The normal distribution of variables was checked using the Shapiro–Wilk test.

Comparisons of differences between groups were performed using the Mann–Whitney U test or Fisher's exact test in the case of categorical variables. Pearson's correlation was used to indicate the strength of a relationship between and with echocardiographic parameters and cardiac biomarkers taken into account. A two-sided p-value of less than 0.05 was considered to be statistically significant. All data were analyzed using the R version 3.2.4 software package (R Foundation for Statistical Computing, Vienna, Austria).

Results

We identified 10 patients with sRV who were 60 years of age or older who visited our outpatient clinic during the study period. This population constituted 16% of all adults (n=63) with ccTGA under active follow-up at our institution (Fig. 1b). The study groups of patients older and younger 60 years of age, respectively, did not differ significantly in terms of gender, associated lesions, history of surgery, or permanent pacemaker (PPM) or
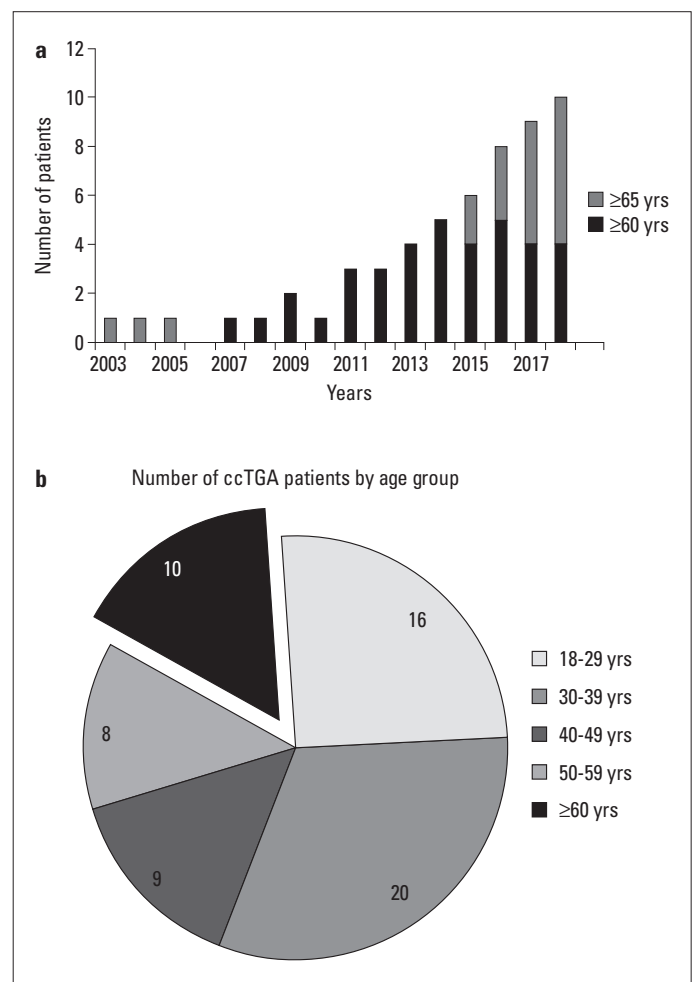

Figure 1. Prevalence of ccTGA patients aged 60 years or older seen in the last 15 years (a) and the current age structure of adults with ccTGA at our center (b)

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Table 1. Clinical characteristics, laboratory testing, and echocardiographic parameters of the study groups

	Patients ≥60 years (n=10)	Patients <60 years (n=53)	P-value
Clinical characteristics			
Age (years)	64.1±3.7	35.5±10.8	**<0.001**
Male (n, %)	5 (50)	31 (58.5)	0.621
Complex ccTGA (n, %)	3 (30)	23 (44.4)	0.401
NYHA class > II (n, %)	3 (30)	6 (11.3)	0.145
Prior surgery (n, %)	2 (20)	21 (39.6)	0.241
PPM/CRT in situ (n, %)	3 (30)	23 (44.4)	0.401
Acquired comorbidities			
Hypertension (n, %)	4 (40)	3 (5.7)	**0.001**
Diabetes (n, %)	2 (20)	2 (3.8)	0.056
Dyslipidemia (n, %)	5 (50)	3 (5.7)	**<0.001**
AF (n, %)	7 (70)	11 (20.7)	**0.001**
Stroke/TIA (n, %)	1 (10)	1 (1.9)	0.184
Medications			
Diuretics (n, %)	8 (80)	13 (24.5)	**<0.001**
BBs (n, %)	8 (80)	22 (41.5)	**0.026**
ACEIs/ARBs (n, %)	7 (70)	22 (41.5)	0.099
Laboratory testing			
NTproBNP (pg/mL)	2706±3279	784.7±1635	**<0.001**
Gal-3 (ng/mL)	10.15±3.78	7.24±2.79	**0.007**
sST2 (ng/mL)	23.95±8.42	21.41±10.44	0.198
Echocardiographic parameters			
RV EDD (mm)	54.6±8.8	52.6±6.7	0.624
RV ED area (cm²)	27.8±8.5	29.9±8.5	0.479
RV ES area (cm²)	20.3±8.3	19.4±7.8	0.811
RV FAC (%)	28.6±9.4	36.1±9.0	**0.028**
TAPSE (mm)	12.7±5.3	15.7±3.4	0.102
RVs' (cm/s)	7.4±3.4	8.6±2.2	0.099
RV LS (%)	-12.0±3.8	-15.5±4.4	**0.017**
LA area (cm²)	38.3±10.2	29.2±9.9	**0.013**
Significant TR (n, %)	1 (12.5)	3 (6.8)	0.508

ACEI - angiotensin-converting enzyme inhibitor, ARB - angiotensin receptor blocker, AF - atrial fibrillation, BB - beta-blocker, CRT - cardiac resynchronization therapy, ED - end-diastolic, EDD - end-diastolic diameter, ES - end-systolic, FAC - fractional area change, NYHA - New York Heart Association, LA - left atrial, LS - longitudinal strain, PPM - permanent pacemaker, RV - right ventricle, TAPSE -tricuspid annular plane systolic motion, TIA - transient ischemic attack, TR - tricuspid regurgitation

cardiac resynchronization therapy (CRT) device implantation. It is noteworthy that the implantation of PPM/CRT devices, found in 42% of the study population, was the main contraindication for the detailed assessment of sRV using magnetic resonance imaging. The trend of a higher number of elderly patients presenting with New York Heart Association functional class of greater than II was observed. Also, there were more individuals with hyper-tension, dyslipidemia, and atrial fibrillation in the older group. Elderly patients were similarly more likely to be prescribed beta-blockers and diuretics. None of the patients included in this study had angina symptoms or previous acute coronary syndrome or revascularization of the coronary arteries. Clinical characteristics of the study group are given in Table 1.

We recorded significantly higher NTproBNP and Gal-3 concentrations among those study participants who were 60 years of age or older as compared with the younger individuals, whereas sST2 concentrations were not significantly different between the study subgroups (Table 1).

During echocardiographic assessment, we observed less FAC and LS among the elderly ccTGA patients. Systemic RV dimensions as well as nongeometric parameters reflecting RV longitudinal systolic function (i.e., TAPSE and RVs') did not differ significantly between the age groups. Meanwhile, although the incidence rate of significant tricuspid regurgitation was similar between the subgroups, the left atrial area was found to be significantly larger in older patients (Table 1).

An analysis of data from all patients with ccTGA revealed a significant correlation between sRV FAC and NTproBNP values ($r=-038$; $p=0.002$) and a significant relationship between sRV LS and NTproBNP ($r=0.61$; $p<0.001$) and Gal-3 ($r=0.31$; $p=0.014$) concentrations. Concentrations of sST2 did not correlate with echocardiography-derived parameters of sRV function.

Discussion

To our knowledge, our study is the first to investigate the concept of "geriatric" sRV in terms of clinical profile, cardiac biomarkers, and echocardiography-derived function. We observed higher incidence rates of hypertension, dyslipidemia, and atrial fibrillation in ccTGA patients who were aged 60 years or older when compared with those younger than 60 years of age. Also, higher values of cardiac biomarkers (NTproBNP and Gal-3) and worse parameters of sRV function (FAC and myocardial deformation) were noted in the older age group.

The number of individuals with sRV surviving to old age is increasing. While from 2003 to 2010, only one or two individuals aged 60 years or older with sRV were regularly seen at our clinic, in 2018, 10 patients with sRV older than 60 years of age were undergoing active follow-up. Further, this trend does not only apply only to patients with isolated ccTGA but also to individuals with complex heart defects. In a large series of adults with CHD, Tut-arel et al. (7) reported assessing 10 individuals with ccTGA who were 60 years of age or older. Similar to in our study, from the years 2000 to 2012, these authors observed a six- to seven-fold increase in the number of patients presenting with CHD. However, the detailed characteristics of the study group were not specified in this retrospective investigation (7).

Conduction abnormalities are common in conjunction with ccTGA and the risk of complete heart block increases with age

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(9). Interestingly, in our study, the percentage of patients who required PPM implantation due to complete heart block was not significantly higher among elderly individuals. Probably, the risk curve of PPM implantation reaches a plateau before 60 years of age.

Our study suggests the existence of an enormous arrhythmic burden of AF in the aged ccTGA population, which is reported for the first time in our study. It is difficult to elucidate the existence of this phenomenon only by the exponential relationship between age and AF (10) and by the generally higher AF incidence among CHD patients than non-CHD individuals (11). One may speculate that it reflects the presence of diastolic dysfunction of the sRV in older patients. Although this was not specifically evaluated in our study, advanced diastolic dysfunction is highly suggested by the significantly enlarged left atrial area seen in the elderly population despite no differences found in tricuspid regurgitation severity between the age groups.

As ccTGA patients continue to age, acquired comorbidities are becoming more frequent. In our study, the incidence rates of established cardiovascular risk factors were significantly higher among older ccTGA patients and were higher than those previously reported in a heterogeneous group of adults with CHD (12). In the study by Tutarel et al. (7), coronary artery disease emerged as a significant predictor of mortality in patients with CHD older than the age of 60 years. Although none of our patients had coronary artery disease, we believe that awareness of this acquired heart disease in ccTGA patients is of great importance, as only one (right) coronary artery supplies the sRV and its significant narrowing or closure might be devastating in this population.

The application of biomarkers in estimating sRV function and the long-term prognosis has been the subject of several studies to date (13–15). Systemic ventricle overload increase due to age and alongside primary underlying pathophysiology is probably responsible for significantly elevated NTproBNP levels in the patients aged 60 years or older included in our study. As NTproBNP is a prognostic factor for adverse cardiac outcomes in patients with sRV (15) and correlated with echocardiography-derived sRV function parameters in our study, its application in elderly ccTGA patients for serial evaluation among individual subjects seems to be fully justified.

Age-associated changes in ccTGA patients may be also related to myocardial fibrosis and systolic and diastolic dysfunction. Gal-3, a circulating protein released by macrophages and involved in inflammatory processes and tissue fibrosis (16), was related to higher age and worse sRV function in our study. These observations are consistent with the findings by Baggen et al. (17) in adult CHD patients. It is noteworthy that Gal-3 turned out to be a marker of adverse outcome in adult sRVs (15). In contrast, we found no association between age and sST2 concentration in individuals with ccTGA. Our findings are similar to those previously reported in adult CHD patients (18). As the concentration of circulating sST2 rises in response to cardiac mechanical stress (19), it suggests that the mechanical stretching of cardiomyocytes in the sRV does not increase with age. Echocardiography-derived sRV parameters, i.e., end-diastolic diameter and end-diastolic and end-systolic areas, also not being age-related seem to confirm this assumption.

As the morphological RV is not designed to sustain systemic circulation, the long-lasting pressure overload leads to the remodeling of myocardial muscle, followed by ventricular dysfunction and overt heart failure in a vast majority of patients over time (2). In a large multicenter study, Graham et al. (20) observed a continuing increase in systemic RV dysfunction (of a moderate or severe degree) with increasing age. In our study, elderly individuals had decreased sRV longitudinal deformation and FAC relative to younger patients. Other indices describing RV longitudinal systolic function, i.e., TAPSE and RVs', did not differ significantly in our study. Both parameters are more influenced by cardiac motion and by the tethering of neighboring segments and may not reflect subtle changes in the aging myocardium.

Deterioration of global LS with increasing age in the normal left ventricle (LV) was previously reported (21, 22). Notwithstanding, the increase in LV circumferential strain, which facilitates the maintenance of ejection fraction of the normal LV with age, was observed in the abovementioned studies. The predominant circumferential over longitudinal sRV contraction is the adaptation developed when faced with increased afterload since birth (23). However, the reduction in FAC in elderly ccTGA patients suggests that the aging sRV does not develop such an effective compensatory mechanism. Probably, the circumferential myocardial shortening of the sRV reaches the maximum level early in life and no further increase can be generated with advancing age.

Study limitations

Although this study analyzed a relatively large cohort of patients with sRV, its small population of elderly patients is a limitation. Furthermore, the assessment of RV function was limited to the echocardiographic analysis because of contraindications for magnetic resonance imaging (the gold-standard method) in a large proportion of the study cohort. Furthermore, we did not assess the RV diastolic function in the face of the high AF incidence in our population and the lack of a clear definition of diastolic dysfunction for systemic RV. As we performed a cross-sectional study, we could not conclude on the determinants of longer (>60 years of age) survival in ccTGA patients. Finally, our results cannot be extrapolated to other individuals with systemic RV, e.g., patients with dextro-transposition of the great arteries following Senning/Mustard procedures. The distinct clinical course of dextro-transposition of the great arteries (i.e., desaturation present from birth, necessity of cardiac surgery in infancy) and the altered hemodynamic profile due to the redirection of venous returns may influence unique age-related changes of sRV in this population.

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Conclusion

Summarizing, the number of individuals with sRV caused by ccTGA surviving to old age is increasing. The conduct of active screening for acquired comorbidities, particularly atrial fibrillation, in the aging ccTGA population is recommended. The application of cardiac biomarkers in elderly ccTGA patients for clinical evaluation might be considered. The standard echocardiographic assessment of systolic sRV function in the elderly should include FAC measurements and myocardial deformation analysis. Finally, a large multicenter study in elderly patients with sRV as well as studies focusing on sRV diastolic function are warranted.

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