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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Original Investigation

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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 tumorigenicity 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 in-patient 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 an MS5 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
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 un-dergoing active follow-up. Further, this trend does not only apply to patients with isolated ccTGA but also to individuals with complex heart defects. In a large series of adults with CHD, Tutar et al. (7) reported assessing 10 individuals with ccTGA 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).

An analysis of data from all patients with ccTGA revealed a significant correlation between sRV FAC and NTproBNP values (r=-0.038; 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 to patients with isolated ccTGA but also to individuals with complex heart defects. In a large series of adults with CHD, Tutarel et al. (7) reported assessing 10 individuals with ccTGA who were 60 years of age or older. Similar to 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.
circulating sST2 rises in response to cardiac mechanical stress previously reported in adult CHD patients (18). As the concentration of sST2 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 RV’s, 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.
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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References

1. Brida M, Diller GP, Gatoumis MA. Systemic Right Ventricle in Adults With Congenital Heart Disease: Anatomic and Phenotypic Spectrum and Current Approach to Management. Circulation 2018; 137: 508-18.
2. Filippov AA, Del Nido PJ, Vasilyev NV. Management of Systemic Right Ventricular Failure in Patients With Congenitally Corrected Transposition of the Great Arteries. Circulation 2016; 134: 1293-302.
3. Kutty S, Danford DA, Diller GP, Tutarel O. Contemporary management and outcomes in congenitally corrected transposition of the great arteries. Heart 2018; 104: 1148-55.
4. Kowalik E, Braksator W, Hoffman P. Congenitally corrected transposition of the great arteries and participation in competitive sport. Kardiol Pol 2010; 68: 1174-5.
5. Binu MG, Nair MR, Vinodini C. A case of cyanotic L-transposition with complete heart block in an adult female who had three in-hospital normal deliveries. J Cardiovasc Dis Res 2011; 2: 247-50.
6. Piacci A, Lovato L, Bonvicini M. Congenitally corrected transposition of the great arteries in an 83-year-old asymptomatic patient: description and literature review. BMJ Case Rep 2014; 2014: bcr2014204228.
7. Tutarel O, Kemny A, Alonso-Gonzalez R, Jabbour R, Li W, Uebing A, et al. Congenital heart disease beyond the age of 60: emergence of a new population with high resource utilization, high morbidity, and high mortality. Eur Heart J 2014; 35: 725-32.
8. Rudski LG, Lai WW, Afifalo J, Hua L, Handschumacher MD, Chandrakaran K, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr 2010; 23: 685-713.
9. Baruteau AE, Abrams DJ, Ho SY, Thambo JB, McLeod CJ, Shah MJ. Cardiac Conduction System in Congenitally Corrected Transposition of the Great Arteries and Its Clinical Relevance. J Am Heart Assoc 2017; 6: e007759.
10. Laredo M, Waldmann V, Khairy P Nattel S. Age as a Critical Determinant of Atrial Fibrillation: A Two-sided Relationship. Can J Cardiol 2018; 34: 1396-406.
11. Hu WS, Lin CL. Risk of Atrial Fibrillation in Patients with Congenital Heart Disease: Results of a Propensity Score-Matched, Nationwide Cohort Study. J Atheroscler Thromb 2019; 26: 670-7.
12. Bauer UMM, Körten MA, Diller GP, Helm P, Baumgartner H, Ewert P, et al. Cardiovascular risk factors in adults with congenital heart defects - Recognised but not treated? An analysis of the German National Register for Congenital Heart Defects. Int J Cardiol 2019; 277: 79-84.
13. Kowalik E, Klisiewicz A, Rybicka J, Biernacka EK, Hoffman P. High sensitivity cardiac troponin T and systemic right ventricular function in adults with congenitally corrected transposition of the great arteries. Int J Cardiol 2017; 241: 168-72.
14. Kowalik E, Klisiewicz A, Kowalski M, Rybicka J, Baranowski R, Biernacka EK, et al. High-Sensitive Cardiac Troponin T and Systemic Right Ventricular Area Predict Outcomes in Adults With Congenitally Corrected Transposition. Can J Cardiol 2018; 34: 1129-36.
15. Geenen LW, van Grooтел RWJ, Aкnen K, Baggen VJM, Menting ME, Eindhoven JA, et al. Exploring the Prognostic Value of Novel Markers in Adults With a Systemic Right Ventricle. J Am Heart Assoc 2019; 8: e013745.
16. Osmančík P, Louchkova A. Biomarkers of apoptosis, inflammation, and cardiac extracellular matrix remodelling in the prognosis of heart failure. Kardiol Pol 2017; 75: 295-305.
17. Baggen VJM, van den Bosch AE, Eindhoven JA, Menting ME, Witsenburg M, Cuypers JAAE, et al. Prognostic value of galectin-3 in adults with congenital heart disease. Heart 2018; 104: 394-400.
18. Geenen LW, Baggen VJM, van den Bosch AE, Eindhoven JA, Cuypers JAAE, Witsenburg M, et al. Prognostic value of soluble ST2 in adults with congenital heart disease. Heart 2019; 105: 999-1006.
19. Januzzi JL Jr. ST2 as a cardiovascular risk biomarker: from the bench to the bedside. J Cardiovasc Transl Res 2013; 6: 493-500.
20. Graham TP Jr, Bernard YD, Mellen BG, Celermajer D, Baumgartner H, Cetta F, et al. Long-term outcome in congenitally corrected transposition of the great arteries: a multi-institutional study. J Am Coll Cardiol 2010; 56: 255-61.
21. Yingchoncharoen T, Agarwal S, Popovic ZB, Marwick TH. Normal ranges of left ventricular strain: a meta-analysis. J Am Soc Echocardiogr 2013; 26: 185-91.
22. Alcidi GM, Esposito R, Evola V, Santoro C, Lembo M, Sorrentino R, et al. Normal reference values of multilayer longitudinal strain according to age decades in a healthy population: A single-centre experience. Eur Heart J Cardiovasc Imaging 2018; 19: 1390-6.
23. Pettersen E, Helle-Valle T, Edvardsen T, Lindberg H, Smith HJ, Smevik B, et al. Contraction pattern of the systemic right ventricle shift from longitudinal to circumferential shortening and absent global ventricular torsion. J Am Coll Cardiol 2007; 49: 2450-6.