ALMA MATER STUDIORUM UNIVERSITÀ DI BOLOGNA

DOTTORATO DI RICERCA IN SCIENZE CARDIO – NEFRO - TORACICHE

XXXIII CICLO

Settore Concorsuale: 06/E1 Chirurgia cardio-toraco-vascolare

Settore Scientifico Disciplinare: MED/23 Chirurgia cardiaca

LONG TERM FOLLOW-UP OF SYSTEMIC RIGHT VENTRICLE

TESI DI DOTTORATO

Presentata da: Dott.ssa Cristina Ciucă

Coordinatore dottorato:
Chiar.mo Prof.
Gaetano Domenico Gargiulo

Supervisore:
Chiar.mo Prof.
Gaetano Domenico Gargiulo

Esame finale anno 2021

"Everyone knew it was impossible, until a fool who didn't know came along and did it."
Albert Einstein

ABSTRACT

Purpose: to assess the long-term follow-up in patients with systemic right ventricle.

Methods: Seventy-three patients with systemic right ventricle (SRV) evaluated in the outpatient clinic between January 2014 and September 2020 were enrolled in this study. Thirty-four patients had a transposition of the great arteries treated either with Mustard or Senning procedure and 39 patients had a congenitally corrected transposition of the great arteries (ccTGA).

Results: Mean age at the first evaluation was 29.6 ± 14.2 years, 47.9% were female. NYHA class at the visit was as follows: I in 53 % of cases, II in 33 % of cases, III 11% of cases and IV in 3% of cases. The first echocardiographic evaluation testifies end diastolic/systolic area 20.1 ± 5.3 cm2/m2 respectively 12.9 ± 4.4cm2/m2 significantly more dilated was the SRV of ASO patients. Overall, systolic function was normal or slightly impaired. A quarter of patients had significant tricuspid regurgitation (sTR). Cardiac MRI (CMR) confirmed the dilatation of the SRV end diastolic RV volume = 117 ± 40ml/m2 a RV ejection fraction = 49 ± 12%. Late gadolinium enhancement (LGE) was presented 42.3% of cases. CPET showed a reduced exercise capacity.

Survival free from adverse events was 98.6% at one year and 95.8% at 5-year follow-up without difference between the two groups. The most common adverse event during follow-up the presence of arrhythmia requiring hospitalisation (27.1%) followed by signs of heart failure requiring hospitalisation (12.3%). The presence of LGE at CMR together with lower exercise capacity, higher NYHA class and more dilated and/or hypokinetic RV predicted a poorer outcome.

Conclusions: Long term follow-up of patients with systemic right ventricle is characterized by a high incidence of clinical events, prevalently arrhythmias and heart failure which cause most of the unscheduled hospitalisations.

KEYWORDS

Systemic right ventricle, arrhythmias, heart failure, congenital heart disease, adults with congenital heart disease, Mustard operation, Senning operation, atrial switch intervention, congenitally corrected transposition of the great arteries, quality of life, longitudinal right ventricular function, fibrosis, quality of life, pregnancy.

BACKGROUND

The prevalence of congenital heart diseases (CHD) with a morphological right ventricle sustaining the systemic circulation is almost 12%. [1] Two conditions are mostly associated with the presence of a systemic right ventricle (SRV) and a biventricular circulation: the transposition of the great arteries with previous atrial switch repair and the congenitally corrected transposition of the great arteries.

Atrial switch operation (ASO)

Transposition of the great arteries (TGA) is a frequent cyanotic CHD, with an incidence ranging from 20.1 to 30.5 over 100000 live births, with a strong male preponderance, characterised by atrioventricular concordance and ventriculoarterial discordance. Left untreated is often lethal within the first months of life especially in absence of an atrial septal defect. A drastic survival improvement was achieved after the introduction in 1957 of the atrial switch operation (ASO) by Ake Senning [2] subsequently modified by William Mustard in the 1963. [3]). In the Senning repair the atrial baffle is created in situ using tissue from the right atrial wall and interatrial septum, while in the Mustard operation most of the atrial septum is removed and the baffles are made from pericardial tissue or synthetic material.

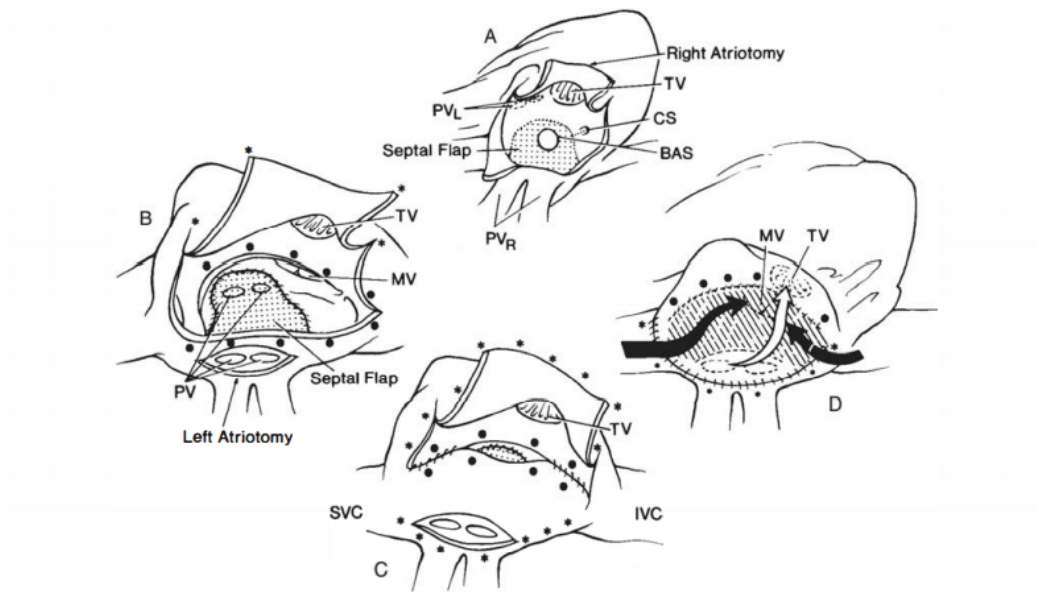


Figure 1: *Adapted from Moss and Adams Heart Disease in infants, children and adolescents ninth edition ASO: Senning technique: A: A right atriotomy parallel to the caval veins extended into the atrial appendage. Exposure of the atrial septum and its incision anteriorly, superiorly, and inferiorly to form a septal flap which remains fixed posteriorly between the caval entrances. B: The systemic venous chamber and conduit to the mitral valve is formed posteriorly by the repositioned septal flap (shaded area), and the conduit then is completed anteriorly by suturing the posterior right atrial free wall flap (z z z) anteriorly to the anterior septal limbus (z z z) as in (C). A left atriotomy is made as long as possible in the internal atrial groove (exposing the orifices of the right pulmonary veins). C,D: The pulmonary venous chamber and pathway to the tricuspid valve are completed with the suturing of the anterior right free wall atrial flap (asterisk) over the right pulmonary veins to the anterior lip of the left atriotomy (asterisk). D: Black arrows indicate systemic venous caval flow through the newly created atrial tissue conduit and systemic venous chamber (cross-hatched area) toward the mitral valve. White arrow indicates pulmonary venous flow path in pulmonary venous atrium passing behind, rightward, and anterior to the systemic venous chamber toward the tricuspid valve (TV). IVC and SVC, inferior and superior vena cavae; MV, mitral valve; PV, PVL, and PVR pulmonary veins, left and right.*

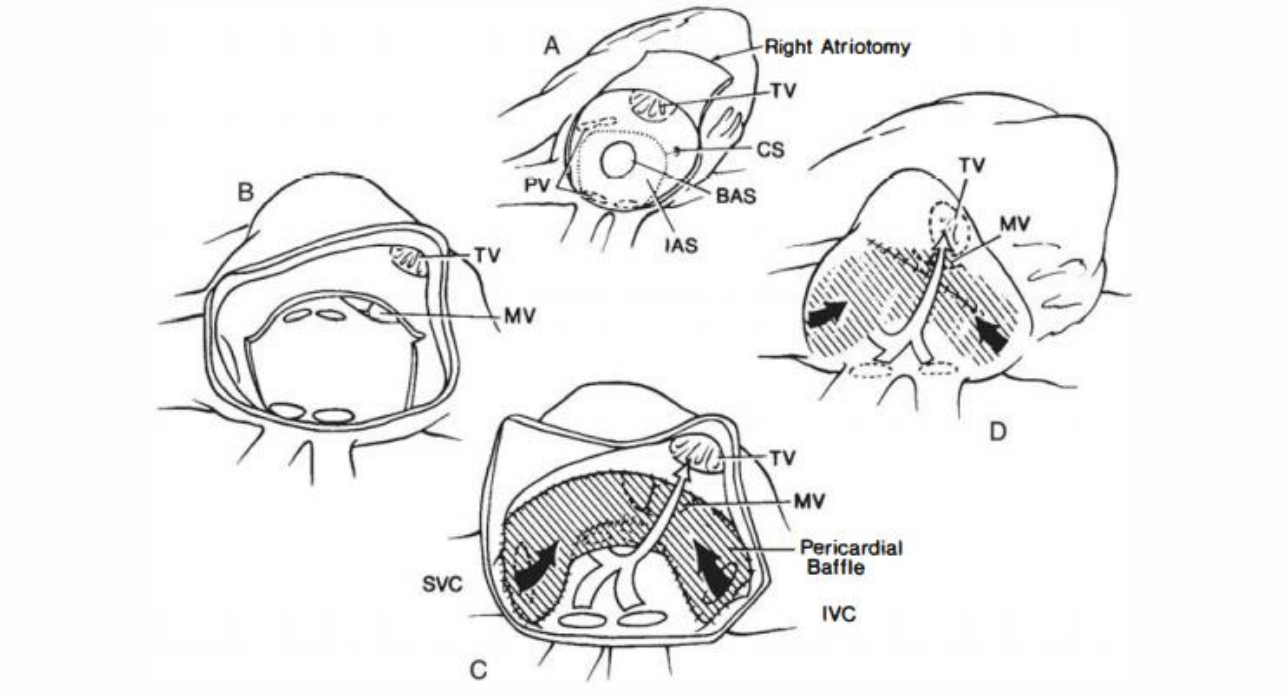


Figure 2: *Adapted from Moss and Adams Heart Disease in infants, children and adolescents ninth edition ASO: Mustard technique: A: the right atrium is opened through an oblique atriotomy incision, exposing the interatrial septum (lAS). B: The atrial septal remnants are excised widely posteriorly, inferiorly, and superiorly but not anteriorly to preserve a small anterosuperior rim of atrial septal tissue between the superior vena cava and tricuspid valve (TV). In all atrial switch operative techniques, the area of the sinus node and the sinus node artery must be scrupulously avoided in order to minimize dysrhythmia complications. C: An appropriate baffle material, usually pericardium (cross-hatched area) is sutured in place. Suturing starts across the floor of the left atrium along a line immediately to the left of the left pulmonary vein orifices. The suturing continues around the orifices of the superior and inferior vena cavae (SVC, IVC) and finally along the anterior atrial septum resection line to complete the baffle conduit. D: The oblique atriotomy is closed. Black arrows indicate systemic vena caval flow patch through the newly fashioned pericardia! (or synthetic material) conduit and systemic venous chamber (cross-hatched area) toward the mitral valve (MV); white arrow indicates*

pulmonary venous flow path in pulmonary venous atrium passing behind, rightward, and anterior to the systemic venous chamber toward the tricuspid valve (TV). PV, pulmonary valve.

In terms of connections, the ASO imposes a discordant AV connection on the existing discordant AV connections; this "double-negative " results in a "normal" circulation with SRV.

Major complications of ASO are: arrythmias, SRV dysfunction, progressive tricuspid valve regurgitation (TR), heart failure, baffle stenosis or leakage, left ventricular outflow tract obstruction (LVOTO), post capillary pulmonary hypertension, death either due to end stage heart failure or to malignant arrhythmias. [4, 5] Long-time survival up to 40 years is 60-75% with a low rate of event free survival. [6-8]

Congenitally corrected transposition of the great arteries (ccTGA)

Congenitally corrected transposition of the great arteries is a rare CHD, characterised by atrioventricular and ventriculoarterial discordance, with a prevalence of 3 over 100000 live births. The risk of recurrence of CHD in first-degree relatives is not uncommon and was estimated at about 2-5%. Almost 5% of patients will have a situs inversus while 25% of patients will demonstrate dextrocardia or mesocardia. Moreover, unlike TGA, ccTGA is frequently associated with other abnormalities such as ventricular septal defect (VSD), pulmonary outflow obstruction, atrial septal defect (ASD) and abnormalities of the conduction system. Late complications of ccTGA are a progressive TR, SRV dysfunction and consequently heart failure, LVOTO, complete atrio ventricular block with 2% loss in AV conduction per year, more frequent in patients with VSD repair and TV replacement. [5]

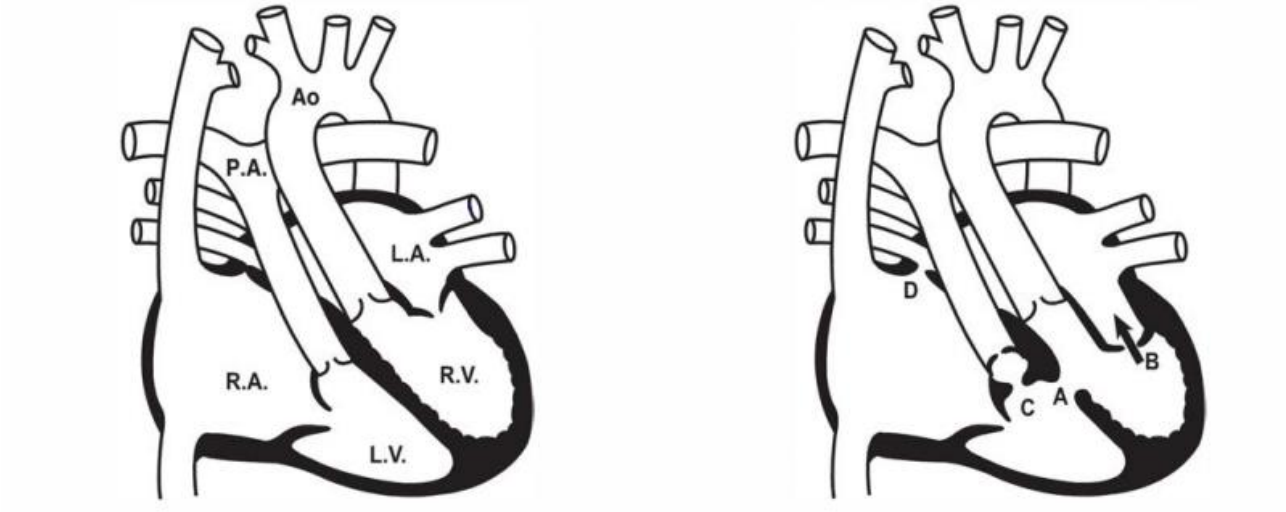


Figure 3: Adapted from Moss and Adams Heart Disease in infants, children and adolescents ninth edition ccTGA without associated lesions (left hand side panel) and ccTGA with associated anomalies. (A) Ventricular septal defect (VSD); (B) Ebstein anomaly of the tricuspid valve; (C) multiple-level left ventricular outflow obstruction; (D) atrial septal defect (ASD).

Systemic right ventricle: evaluation and natural history

Systemic RV has a poorer prognosis comparing to the "normal systemic left ventricle" mainly due to the different morphology, fibromuscular architecture and therefore adaptation to chronic and/or acute pressure or volume overload. SRV dysfunction can be explained by coronary perfusion mismatch especially in patients with ccTGA where the coronary arteries are inverted consequently the RV is supplied only by the left-sided (morphologically right) coronary artery, which can lead to inadequate perfusion of the hypertrophied walls and therefor deterioration of the RV function with aging, tricuspid valve regurgitation or conduction abnormalities. Van Praagh summarised anatomic differences between left and right ventricle that provide a significant advantage for the left ventricle in the systemic circulation. [9]

	Left Ventricle ("Pressure Pump")	Right Ventricle ("Low Pressure/Volume Pump")
Cavity	Cylindric	Crescentic
Contraction pattern	Concentric	Bellows-like
Inlet and outlet valves	Close proximity	Distant
Coronary artery supply	Two coronary arteries	One coronary artery
Developmental origin	Primitive ventricle	Bulbus cordis
Mitral valve	Closure for circular orifice	Closure for crescentic orifice
Papillary muscles	Two large papillary muscles	Multiple small papillary muscles

Figure 4: Anatomic and Physiologic Differences Between the Left and Right Ventricles (after Van Praagh)

Hence, considering the increasing number of adults with congenital heart disease (ACHD) especially complex CHD the management of the SRV remains a huge challenge for the ACHD cardiologists, interventional cardiologists and cardiac surgeons.[10] Cuypers and al. evidenced after a median follow-up of 35 years a cumulative survival of: 84% after 10 years, 80% after 20 years, 77% after 30 years, and 68% after 39 years in ASO patients. However, cumulative survival free of events (heart transplantation, arrhythmias, reintervention, and heart failure) was 19% after 39 years.[8]

Echocardiography

It is well known that the ejection fraction of the left ventricle (EF LV) is one the most important predictors of outcome in patients with acquired cardiac diseases. Right ventricle evaluation at 2D echocardiography might be challenging because of the complex geometry and the lack of specific right-sided anatomic landmarks to be used as reference points. Evaluation of RV is recommended in a modified conventional apical four-chamber view to evaluate properly the free wall of the RV. The normal values of areas, diameters and wall thickening of the RV recommended by the American Society of Echocardiography and the European Association of Cardiovascular Imaging [11] are resumed in table 1.

Table 1: Normal values for RV chamber size

Parameter	Normal range
RV basal diameter (mm)	25-41
RV mid diameter (mm)	19-35
RV longitudinal diameter (mm)	59-83
RVOT PLAX diameter (mm)	20-30
RVOT proximal diameter (mm)	21-35
RVOT distal diameter (mm)	17-27
RV wall thickness (mm)	1-5
RV EDA (cm2)	Men 10-24 Women 8-20
RV EDA indexed to BSA (cm2 /m2)	Men 5-12.6 Women 4.5-11.5
RV ESA (cm2/m2)	Men 3-15 Women 3-11
RV EDV (ml/m2)	Men 35-87 Women 32-74
RV ESV (ml/m2)	Men 10-44 Women 8-36

Systolic evaluation of RV

Systolic function of SRV has an important prognostic value. However, contrary of the LV EF, echocardiographic evaluation of RV EF is problematic due to the shape of the RV which does not allow a geometric formula to calculate it. Therefore, cardiac MRI is the gold standard for RV functional assessment. However, different echocardiographic parameters are routinely recommended to evaluate the systolic function of the RV and a good correlation with the cardiac MRI RV EF have been demonstrated.

1. Tricuspid annular plane systolic excursion (TAPSE)

TAPSE is easily obtainable and represents a measure of RV longitudinal function. Although this index predominantly reflects RV longitudinal function, it has shown good correlations with parameters estimating RV global systolic function, such as radionuclide-derived RV EF, 2D echocardiographic RV FAC, and 2D echocardiographic EF. TAPSE < 17 mm is highly suggestive of RV systolic dysfunction. [11]

Lissin et al. showed a good correlation between TAPSE and MRI-based systemic RVEF in a small cohort of patients with TGA and previous atrial switch procedure. [12] Later, Khattab et al. evaluated the best cut-off of systolic parameters of SRV and their correlation with MRI-based systemic RVEF, TAPSE cut off was identified being less than 14mm. [13]

2. Doppler Tissue Imaging (DTI)-Derived Tricuspid Lateral Annular Systolic Velocity

DTI-Derived Tricuspid Lateral Annular Systolic Velocity velocity is easy to measure, reliable, and reproducible, and it has been shown to correlate well with other measures of global RV systolic function. An S velocity < 9.5 cm/sec measured on the free-wall side indicates RV systolic dysfunction.

3. Fractional area change (FAC)

FAC provides an estimate of global RV systolic function. RV FAC < 35% indicates RV systolic dysfunction. For SVR the cut-off of normality recommended by Khattab et al. was 33%. [13]

4. RV Strain and Strain Rate

Strain and strain rate are useful parameters for estimating RV global and regional systolic function. Longitudinal strain is calculated as the percentage of systolic shortening of the RV free wall from base to apex, while longitudinal strain rate is the rate of this shortening. In the context of the right ventricle, GLS (global longitudinal strain) is a parameter borrowed from LV measurements, and software currently used to measure RV GLS from most manufacturers has been designed for LV measurements and later adapted for the right ventricle. The term RV GLS usually refers to either the average of the RV free wall and the septal segments or the RV free wall segments alone. Pooled data suggest that global longitudinal RV free wall strain > - 20% (< 20% in absolute value) is abnormal.

Indices of myocardial deformation in SRV are reliable and highly reproducible with lower rate of global longitudinal strain (GLS) when compared with the control group -13.2 ± 3.8% versus - 20.6 ± -2.6% (6 segments model) [14]

Kowalik et al evaluated SRV in patients witc ccTGA and evidenced that GLS < -16.3% identified RV EF ≥ 45 % at CMR with an acceptable sensibility. The authors suggest routine use of GLS for evaluation of systolic SRV function. [15]

5. Three-dimensional echocardiographic RV EF

3D RV EF has a particular clinical value in patients after cardiac surgery when conventional indices of longitudinal RV function (TAPSE, DTI S wave) are generally reduced and no longer representative of overall RV performance. 3D RV EF is feasible, reproducible, and highly correlated with MRI evaluation in patients with SRV. [16]

Iriart et al in an interesting review of SRV echocardiographic evaluation [17] suggest the following cutoff for the systolic evaluation of SRV.

Table 2 Cut-offs for systolic right ventricular function evaluation

Parameter	Normal value
TAPSE, (mm)	**>14**
DTI-Tricuspid Lateral Annular Systolic Velocity, cm/sec	**>9.5**
GLS, %	**< -10 a -14.5**
FAC, %	**>33**
3D RV EF, %	**>45**

Cardiovascular magnetic resonance (CMR)

CMR evaluation is the gold standard in patients with SRV either to evaluate the dimensions and the RV systolic function but also to assess the presence of fibrosis detected by late gadolinium enhancement (LGE). RV mass and volumes are depending on the body surface area and the indexed values normally grater in males, moreover volumes normally decrease with aging. A recent review of the "normal CMR values" have been published by Kawel-Boehm et al. [18]

Table 3 Cut-offs for right ventricular volumes and function at the CMR

Parameter	20-29 years	30-39 years	40-49 years	50-59 years
Adult men by age group				
RVEDV/BSA *(ml/m2)*	94 ±15 (63-124)	83 ±13 (57-109)	81 ± 16 (50-112)	80 ± 16 (48-111)
RVESV/BSA *(ml/m2)*	44 ±11 (23-66)	38 ±8 (23-53)	34 ± 8 (18-49)	35 ± 10 (24-54)
RVEF, *(%)*	52 ± 8 (36-69)	55 ± 7 (41-68)	57 ± 8 (40-73)	57 ± 8 (41-74)
Adult women by age group				
RVEDV/BSA *(ml/m2)*	78 ±12 (55-101)	76 ±12 (57-109)	74 ± 14 (46-102)	69 ± 13 (42-95)
RVESV/BSA *(ml/m2)*	33 ± 12 (10-56)	31 ± 8 (15-48)	29 ± 8 (13-45)	28 ± 8 (11-44)
RVEF, *(%)*	56 ± 11 (34-78)	58 ± 9 (39-77)	60 ± 8 (44-76)	61 ± 8 (44-78)

RVEDV right ventricle end diastolic volume, RVESV right ventricle end systolic volume, RVEF right ventricle ejection fraction, mean value ± standard deviation (LL lower limit-upper limit).

Previous studies evidenced a relatively high prevalence of fibrosis which is strongly correlated with a poorer outcome. [19, 20] The presence of fibrosis was confirmed by Roberts at al, who presented an autoptic cohort of 4 patients with a previous ASO aged between 33 and 50 years. SRV had thicker walls and frequent scars who were not evidenced in the LV. Moreover, the myocytes in the wall of the right ventricle were larger than those in the wall of the left ventricle [21]. The distribution of fibrosis more frequent involving the subpulmonary LV suggests adverse ventricular-ventricular interaction at the extracellular matrix level. [22]

Echocardiographic follow up is regularly recommended in patients with ASO every 6/12 months according to the clinical status while cardiovascular magnetic resonance (CMR)/cardiovascular

computed tomography (CCT) are recommended every 3-5 years in stable patients and every year in patients with moderate complications. [23] [24]

Exercise capacity: cardiopulmonary exercise test (CPET)

Adults with SRV have reduced exercise capacity compared with their siblings apparently due to inadequate heart response to exercise [25, 26] or ventricular dysfunction [27]. Farther, chronotropic incompetence seems to be an independent predictor of long-term survival. [28] Winter et al demonstrate an increase in exercise capacity after 10-week training in patients with SRV without any impact on functional status or quality of life [29]. A tree-year follow up of the same cohort of patients evidenced that the benefit of 10-week training was not maintained at 3-year follow-up; however, atients who habitually performed physical activity over 3 years had higher peak VO2 values. [30] These data underline the importance of patients' education and the necessity to avoid a sedentary lifestyle.

Quality of life

Health related quality of life (QOL) has an emergent role in the evaluation of patients with chronic medical conditions. The interest of QOL in the adult population with congenital heart diseases (ACHD) has progressively increased during the last decade. The data are quite surprisingly evidencing that ACHD patients are just as well as their healthy counterparts or have a better QOL; this could be explained by a stronger sense of coherence in patients with CHD reason of their wellbeing despite the complex chronic condition. [31] [32]

Pregnancy

Woman with previous atrial (Senning and Mustard) switch can tolerate pregnancy even if there is an increased risk of maternal complications such as arrhythmias and heart failure (modified WHO risk class III). Furthermore, an irreversible decline in RV function and worsening TR was described. [33] Canobbio et al evidenced a high complication rate both during the pregnancy and after the delivery. [34]

Equally, patients with ccTGA have a high risk of complications including arrhythmias and HF during pregnancy (modified WHO risk class III). Moreover, ccTGA pregnant woman are predisposed to complete AV block. [35] Kowalik et al reported high rate (95%) of successful pregnancies without maternal mortality but, complications such as SRV dysfunction, arrhythmias and AV block requiring pacing were described. [36]

Management of complications during follow-up

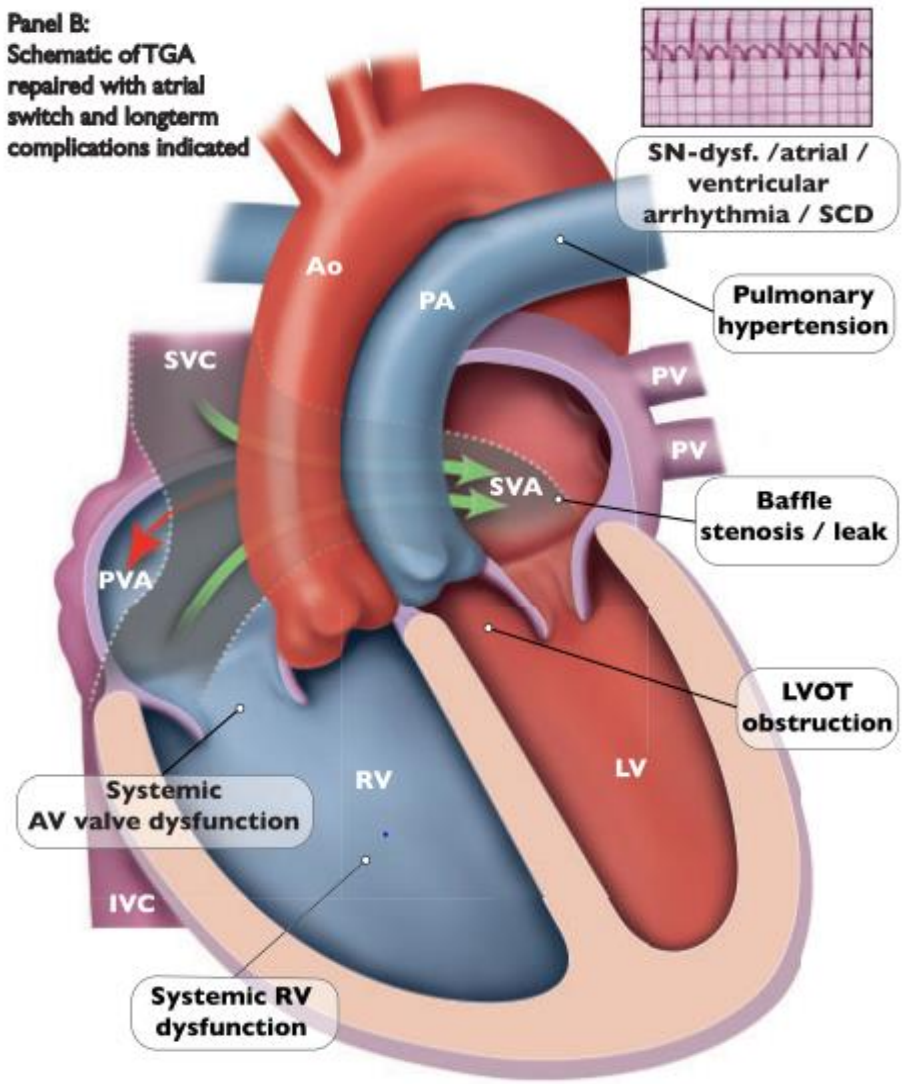


Figure 5: Long-term complications of ASO: adapted from ESC Guidelines 2020 [5]

Heart failure

Almost 22% of patients with a previous ASO procedure and 32% of ccTGA patients develop signs of heart failure (HF) during follow-up. Patients with HF signs have a dramatically increased mortality when compared with asymptomatic SRV patients. Decreased RV EF was associated with the onset of HF symptoms and signs. [37] [38]

The mortality among adult patients with ccTGA was 16% at 40 years of age, the mortality causes were tachyarrhythmia, sudden death, or congestive heart failure. [38]

Unlike the heart failure with reduced EF (HFrEF) in patients with acquired cardiac diseases where medical therapy plays a crucial role in improving survival, only a limited number of studies explored the effectiveness of medical therapy in adults with systemic RV dysfunction and signs of HF with inconclusive results. [39]

Cardiac resynchronization therapy (CRT) on top of optimal medical therapy is an effective treatment option for patients with HFrEF, wide QRS and ventricular dyssynchrony. However, data on ACHD population are limited; the complex anatomy added to the presence of fibrosis can make almost impossible the expected result to the resynchronisation therapy. Diller et al evidenced that only 4–9% of unselected patients with a systemic RV are potentially eligible for CRT. [40]

Ventricular assist device (VAD) can be used in patients with SRV failure as bridge to heart transplantation. [41] However, VAD implantation in SRV is challenging and inflow cannula occlusion due to excessive SRV trabeculations has been described.

Heart transplantation (HT) is the only therapy of patients with end stage HF. However, even if CHD patients are younger, they pass longer time in the waiting list for heart transplantation when compared with patients with acquired cardiac diseases. Moreover, CHD patients have a significantly higher early mortality after HT but surprisingly, after the acute phase, they have the best long-term survival. [42]

Arrythmias

Bradycardia

Sinus node dysfunction is frequent in patients with previous ASO due to ischemic sinus node damage after surgery or to fibrosis or interruption of the atrial conduction fibers. Consequently, chronotropic incompetence is frequent in patients after atrial switch. [43]

On the other hand patients with ccTGA have an abnormal AV conduction tissue: with the presence of two AV nodes a normal posterior AV node located at the apex of the triangle of Koch with no AV bundle, and an abnormal right anterior AV node giving rise to the penetrating AV bundle. Hosseinpour et al hypothesized that the development of an AV bundle from the normal posterior AV node to the summit of the interventricular septum is anatomically hindered by the atrial and ventricular septal malalignment. The degree of malalignment is related to the size of the left ventricular outflow tract and the pulmonary trunk. The authors showed that patients with congenitally corrected transposition with a normal conduction system are frequently characterized by the presence of pulmonary atresia or significant pulmonary stenosis because a lower degree of atrial and ventricular septal malalignment.[44, 45] The risk of complete atrio-ventricular block is 3% per annum. [4]

Tachyarrythmias and sudden cardiac death (SDC)

Intra-atrial reentry tachycardia (IART) is the most frequent tachyarrythmia after ASO and is due to atrial conduction barriers caused by fibrosis of the native right atrium and to the presence of suture lines and patches. Often is slower than a typical atrial flutter and may be asymptomatic. The

recurrence of IART in patients with hypokinetic SRV may be a trigger for malignant ventricular arrythmias.

The incidence of sudden cardiac death in the entire CHD population is relatively low and has been estimated to be < 0.1% per year; however tetralogy of Fallot, transposition of the great arteries with Mustard or Senning baffles, congenitally corrected transposition of the great arteries, left-sided obstructive lesions, cyanotic Eisenmenger syndrome, and Ebstein's anomaly have a significantly higher risk. Therefore, ICD therapy may be reasonable in adults with a SRV ejection fraction < 35% particularly in the presence of additional risk factors such as complex ventricular arrhythmias, unexplained syncope, NYHA functional class II or III symptoms, QRS duration ≥140 msec, or severe systemic AV valve regurgitation. [43]

Progressive tricuspid regurgitation (TR)

Tricuspid regurgitation is frequent in patients with SRV. The mechanism of TR is different according to the underling cardiopathy. ASO patients frequently have a functional TR due to tricuspid anulus dilatation whereas patients with ccTGA have an organic TR (Ebstein-type tricuspid valve). Previous studies showed a poorer outcome in patients with severe TR. [46] The recent guidelines recommend tricuspid valve replacement for symptomatic adults with CCTGA, severe TR, and preserved or mildly depressed systemic ventricular function[23] [5]. After atrial switch tricuspid valve repair or replacement should be taken into account for severe TR without significant ventricular systolic dysfunction (EF >40%) regardless of symptoms. [5]

Baffle obstruction or leak in ASO patients

The most frequent cause of re-intervention in ASO patients is the systemic baffle obstruction or leak. Pulmonary baffle obstruction is rare but may cause pulmonary hypertension. [8] The recent ESC guidelines recommend in symptomatic patients with pulmonary venous atrium obstruction or leak, surgical repair or, if feasible, catheter intervention.[5]

INTRODUCTION

Both congenitally corrected transposition of the great arteries (ccTGA) and transposition of the great arteries (TGA) treated with atrial switch operation (ASO) have a right ventricle that sustains the systemic circulation (systemic right ventricle, SRV). Adverse events prevalently arrythmias and heart failure are frequent in this heterogeneous patient population. [37, 38] Severe tricuspid regurgitation, reduced exercise capacity, chronotropic incompetence and the presence of fibrosis have been previously described as predictors of a poorer outcome. [19, 20, 28, 46] Moreover, a reduced exercise tolerance has been described in these population even in asymptomatic patients. [25-29] The aims of this study were to evaluate long term outcome in patients with systemic right ventricle, to identify predictors of a poorer outcome, to assess the exercise capacity and the quality of life.

MATERIAL AND METHODS

This study was designed as a retrospective analysis of SRV in a referral ACHD center. All patients with a previous Senning/Mustard operation or ccTGA evaluated in the out-patient clinic for a routinely clinical follow-up planned between 2014 and September 2020 were enrolled in this study. All patients performed at least 2 planned visits during the study period. All clinical events were recorded.

Definitions and outcomes

Patients were evaluated as clinical routine practice with clinical examination, ECG, HOLTER ECG, echocardiography, cardiopulmonary exercise test (CPET), cardiac MRI. Quality of life was also assessed.

Adverse clinical events were considered death, heart transplantation, active presence in waiting list for HT, heart failure requiring hospitalization, stroke, myocardial infarction, arrythmias requiring hospitalization. During follow-up, survival free from heart transplantation and survival free from adverse events were evaluated.

ECG

Standard 12-lead ECGs were recorded at 25 mm/s speed, and calibrated to 1 mV/cm. Each patient's ECG was analyzed for the presence of arrhythmias, atrioventricular block, bundle branch block, QRS axis as well as QT interval were calculated.

Echocardiography

Echocardiography studies were performed with the IE33, Affinity 50, Affinity 70 or EPIC Philips Medical Systems. Subsequent analysis was performed using the Xcelera system (Philips Medical Systems, Amsterdam, The Netherlands). Strain evaluation were performed using the QLab Philips Healthcare. All exams were re-evaluated offline by a single expert operator to avoid intra-operator variability.

Echocardiography was performed using the European Association of Cardiovascular Imaging/American Society of Echocardiography guidelines and recommendations. [11] [47]

Right ventricular (RV) evaluation was made performed according to the current guidelines and dysfunction was defined as TAPSE < 17mm, two-dimensional FAC < 33%, a S' velocity at DTI less than 9.5 m/sec and a 3D RV EG less than 45%. Right ventricular dilatation was defined either as RV diameters, end diastolic/ end systolic area measured in the 4 chambers view > expected diameters/areas. M-mode measurement of tricuspid annulus plane systolic excursion (TAPSE) was calculated with the cursor aligned through the tricuspid annulus in the apical four-chamber view. Pulsed tissue Doppler imaging (TDI) data from mitral annulus were recorded by placing a tissue Doppler sample volume at the septal and lateral annulus in the apical four-chamber view. Left ventricular ejection fraction (LVEF) was measured using the biplane Simpson technique evaluating end diastolic/ end systolic volume. Atrial evaluation included volume, area, and infero-superior diameter evaluation. For ASO patients the presence of baffle obstruction or leak were evaluated. TR regurgitation was evaluated prevalently the vena contracta. Moreover, the coexistence of LVOTO was evaluated routinely. RV GLS was calculated offline using both the 6 segments model and the free RV wall model. Conventionally for sub-pulmonary RV Free RV GLS > - 20% (< 20% in absolute value) is abnormal. For SRV normal values are lower between -10 and -14.5%. [14, 15] 3D RV was performed for patients who underwent the exam using the EPIC 7 C system. [16]

Cardiopulmonary exercise test (CPET)

All exams were performed on an upright cycle ergometer (Cardioline, Italy) using a continuous ramp protocol (10 watt/min) until muscular exhaustion with continuous monitoring of expiratory gas. Oxygen uptake (Vo2), carbon dioxide production (Vco2), and minute ventilation (VE) were measured with use of a computerized breath-by-breath analyzer. Peak Vo2/kg (determined by the highest value of workload), peak heart rate, and percentage of maximal heart rate were also

measured. The ventilatory anaerobic threshold was calculated by means of the V-slope method. The ventilatory equivalent for carbon dioxide (VE/Vco2) was calculated as the amount of ventilation needed to eliminate a given amount of CO2. The respiratory exchange ratio (RER) was calculated. Chronotropic incompetence was defined using established criteria as an age-adjusted heart rate reserve < 80% or 62% on beta blocker regimen.

Cardiovascular magnetic resonance (CMR)

CMR was performed using a 1.5-Tesla Magnetic Resonance Unit (Philips Medica System, The Neaderlands). The presence of late gadolinium enhancement (LGE) was evaluated using a segmented fast low-angle shot inversion recovery sequence 15 minutes after injection of 0.15 mmol/kg IV gadolinium – DPTA). A standardized CMR protocol for assessment status post Mustard/Senning was performed. A short-axis contiguous stack of 7-mm cine images (3-mm gap) was acquired for quantification of ventricular function and mass using Simpson's method.

Quality of life assessment

The Short Form-36, derived from the General Health Survey of the Medical Outcomes Study by Stewart and colleague, is one of the most widely used generic measures of health-related quality of life and has been shown to discriminate between subjects with different chronic conditions and between subjects with different severity levels of the same disease. [48] The SF-36 is a generic multi-item questionnaire comprising of 36 questions on eight domains: physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health, with a scores range from 0 to 100; higher scores representing better quality of life. The results were compared with those of the Italian population. [49]

Statistical analysis

The statistical analysis was performed with Statistical Package for Social Science (SPSS) 21.0. Continuous variables are reported as mean ± SD and categorical variables as frequencies and percentages. Differences between groups were assessed using the 2-tailed Student t test for continuous variables and by the chi-square test or Fisher exact test for the categorical variables. Changes in echocardiographic measures from baseline to follow-up were compared using a paired T-test. The cumulative incidences of clinical events at follow-up were assessed with the Kaplan-Meier method, and the log-rank test was used for comparison between groups. Cox regression was performed to identify predictors of mortality or HT. All variables with a $p \leq 0.05$ were included in the multivariable analysis. A p value <0.05 was considered statistically significant.

RESULTS

BASELINE CHARACTERISTICS

Overall, 73 patients with a systemic right ventricle (SRV) were included in this study. The etiology of SRV was 47% atrial switch (22% previous Mustard operation and 25% previous Senning operation) and 53% congenitally corrected transposition of the great arteries.

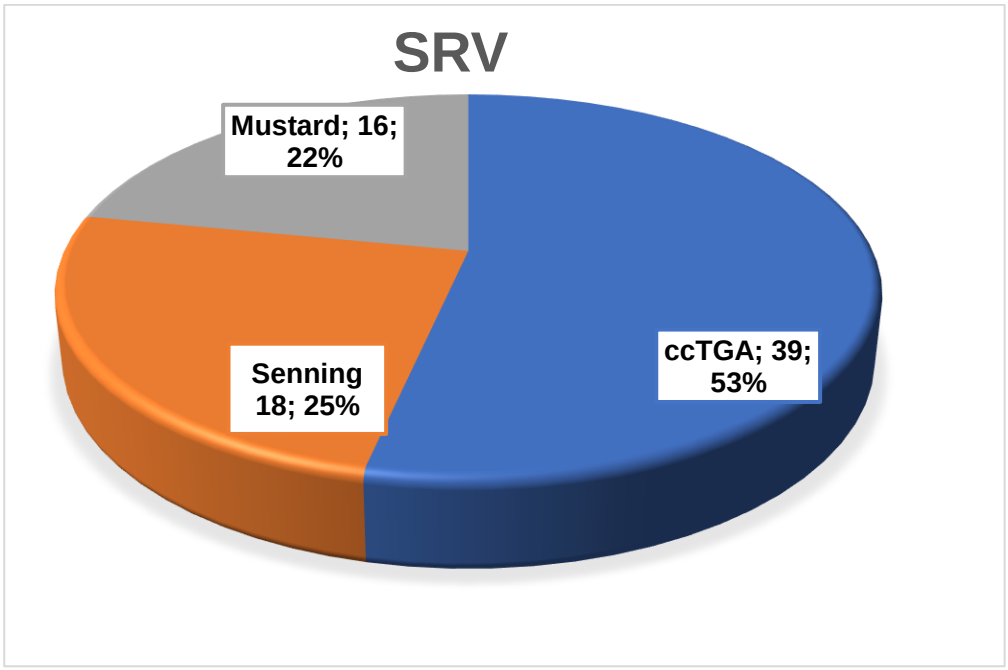


Figure 6: Aetiology of SRV

Mean age at the first evaluation was 29.6 ± 14.2 years. 35 patients (47.9%) were female. Overall, 86.3 % of patients were in good clinical status with functional NYHA class I/II (figure 7) with no significative differences between groups. However, 14% patients had an advanced NYHA class.

Overall, 50 patients underwent at least one surgical intervention: all patients in the ASO group and 17 patients (43.5%) with ccTGA. Indications to surgery in the ccTGA group were prevalently the associated lesions: pulmonary outflow obstruction (58.8%), VSD (41.2%), coartation of the aorta (11.7%), ASD (41%) and severe TR (29.4%). 12 patients (16.4%) underwent a second cardiac surgery (in the ASO group prevalently for baffle obstruction or leak 3patients or systemic AV

valve replacement 2 patients) and 4 patients (5.4%) underwent a third cardiac surgery (2 in the ASO group and 2 in the ccTGA group).

Thirteen patients, 4 with a previous ASO and 9 with ccTGA (37.1% of the female population), had at least one previous pregnancy (range 1-4). Only in one case the pregnancy followed an IVF (in vitro fertilization). In 5 cases complications occurred during pregnancy (25%): 2 miscarriage, 2 cases of heart failure (the pregnancy was followed, and the fetus had no complications), and in one case eclampsia was followed by massive hemorrhage with necessity of hysterectomy (IVF pregnancy). Moreover, in one case a vertical transmission of ccTGA was evidenced while in another case a dextrocardia was present in the newborn without associate cardiac defects.

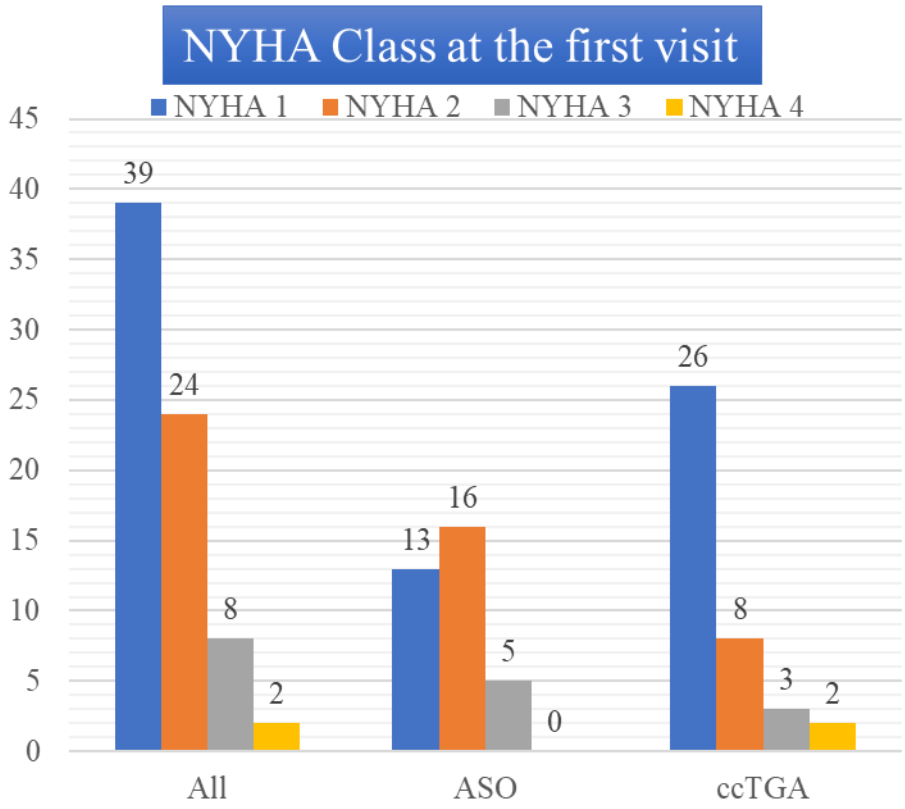


Figure 7: NYHA class according to aetiology of the SRV

ECG

ECG is described in Table 3; 9 patients (12.3%) presented permanent atrial fibrillation while 15 patients (20.5%) had a permanent pacemaker (PM): 9 patients witch a ccTGA (23%) and 6 patients (17.6%) with ASO. Moreover, 5 patients had an ICD and in one case un upgrading of the PM to CRT-P was performed. Mean age of PM/ICD implantation was 30 ±16 years old.

Table 4: ECG

	All (73)	ASO (34)	CcTGA (39)	9
Normal sinus rhythm, *(n, %)*	60 (82.2)	27 (79.4)	33 (84.6)	0.83
Atrial fibrillation, *(n, %)*	9 (12.3)	5 (14.7)	(10.2)	0.1
HR, bpm *(mean ± SD)*	71 ± 13	69 ± 14	72 ± 12	0.44
PR, msec *(mean ± SD)*	174 ± 40	172 ± 46	175 ± 32	0.76
QRS, msec *(mean ± SD)*	115 ± 23	118 ± 21	112 ± 26	0.24
QTc, msec *(mean ± SD)*	434 ± 37	439 ± 41	428 ± 37	0.26

ECHOCARDIOGRAPHY

Echocardiography data at the first evaluation are shown in Table 4. Patients presented dilated right ventricle (RV): overall, end diastolic/systolic area 20.1 ± 5.3 cm2/m2 respectively 12.9 ± 4.4cm2/m2 significantly more dilated was the SRV of ASO patients. Basal and mid RV diameters ware also increased while the longitudinal diameter was normal. Overall, systolic function was normal or slightly impaired: FAC 36.8 ± 10.3%, TAPSE 15.3 ± 3.8mm, S wave DTI 8.7 ± 2.3 cm/sec.

Systemic tricuspid regurgitation (sTR) was common: 23.3% of patients had moderate sTR, 17.8% moderate-to-severe sTR and 8.2% of patients had severe sTR. 10 patients had already a mechanical tricuspid prosthesis (8 patients with ccTGA).

Left atrium was often dilated: volume 39 ± 25ml/m2, area 12.3 ± 4.7cm2/m2 with no difference between groups. Stenosis at the pulmonary outflow was present in 4 patients. Baffle stenosis was present in 6 patients.

Table 5: Echocardiography

	ALL (73)	ASO (34)	CCTGA (39)	P
RV end diastolic area, cm2 (mean ± SD)	34.8 ± 11.1	39.5 ± 10.5	30.6 ± 10.0	< 0.001
RV end systolic area, cm2 (mean ± SD)	22.2 ± 9	25.8 ± 8.4	19.3 ± 8.6	0.002
RV end diastolic area, cm2/m2 (mean ± SD)	20.1 ± 5.3	21.6 ± 5.6	18.7 ± 4.6	0.01
RV end systolic area, cm2/m2 (mean ± SD)	12.9 ± 4.4	14.1 ± 4.3	11.8 ± 4.3	0.03
FAC, % (mean ± SD)	36.8 ± 10.3	36.2 ± 4.3	37.4 ± 11.8	0.65
TAPSE, mm (mean ± SD)	15.3 ± 3.8	14.2 ± 3.8	16.4 ± 3.6	0.02
S wave, DTI RV (mean ± SD)	8.7 ± 2.3	8.4 ± 2.1	9.1 ± 2.3	0.2
RV D1 (mean ± SD)	53 ± 10	57 ± 10	50 ± 10	0.01
RV D2 (mean ± SD)	52 ± 12	55 ± 12	50 ± 12	0.14
RV D3 (mean ± SD)	79 ± 16	86 ± 13	73 ± 15	< 0.001

Free wall LS RV (mean ± SD)	-12.1 ± -5.1	-10.2 ± -3.6	-14.1 ± 15.8	0.002
6 segments RV LS (mean ± SD)	-10.9 ± - 4.5	-9.3 ± -3.4	-12.4 ± -4.8	0.006
RV volume, strain ml	97 ± 52	104 ± 57	89 ± 45	0.25
3D EF %, (mean ± SD)	51 ± 10	46 ± 9	55 ± 10	0.026
3D RVEDV ml/m2 (mean ± SD)	98 ± 40	116 ± 38	83 ± 36	0.027
Tricuspid regurgitation, (n, %)				
1	24 (32.8)	12 (35.2)	12 (30.7)	
2	17 (23.2)	9 (28.1)	8 (20.5)	
3	13 (17.8)	7 (21.8)	6 (18.7)	0.2
4	6 (8.2)	4 (12.5)	2 (5.1)	
Tricuspid prosthesis	10 (13.6)	2 (6.2)	8 (20.5)	<0.001
Left atrial volume, ml/m2 (mean ± SD)	39 ± 25	38 ± 23	40 ± 26	0.65
Right atrial volume, ml/m2 (mean ± SD)	21 ± 13	18 ± 11	24 ± 13	0.06
Left atrial area, cm2/m2	12.3 ± 4.7	11.3 ± 3.8	13.1 ± 5.1	0.1
LA diameter, mm	56 ± 11	57 ± 10	55 ± 12	0.45
RA diameter, mm	47 ± 12	48 ± 11	45 ± 12	0.33
LV EDV ml (mean ± SD)	56 ± 28	57 ± 29	55 ± 27	0.74
LVEF %, (mean ± SD)	63 ± 10	65 ± 9	61 ±10	0.10

CMR

Cardiac magnetic resonance was available for 52 patients. Overall, as evidenced by echocardiography also, ASO patients had more dilated SRV with a lower ejection fraction (RV EF). Left ventricle had normal volumes and EF. Fibrosis was present in 42.3% of cases with no significant differences between groups.

Table 6 CMR data

CMR	ALL (52)	AS (28)	CCTGA (24)	P
EDV RV, ml/m2 (mean ± SD)	117 ± 40	127 ± 46	106 ±30	0.07
ESV RV, ml/m2 (mean ± SD)	62 ± 34	72 ± 39	50 ± 24	0.02
RV EF, % (mean ± SD) (mean ± SD)	49 ± 12	47 ± 11	53 ± 12	0.06
EDD LV, ml/m2 (mean ± SD)	76 ± 27	74 ± 26	78 ± 29	0.56
ESD LV, ml/m2 (mean ± SD)	32 ± 19	30 ± 16	34 ± 23	0.43
LV EF, % (mean ± SD)	60 ± 12	61 ± 9	59 ± 15	0.53
RVMass, g/m2 (mean ± SD)	41 ± 17	40 ± 20	43 ± 14	0.55
LGE, % (n, %)	22 (42.3)	14 (50)	8 (33.3)	0.14

CPET

Cardiopulmonary exercise test was available for 57 patients. Overall, a moderate impairment of exercise capacity was evidenced peak VO2 24.5 ± 9.4 ml/kg/min 67 ± 20 % of the predicted value. with a significantly lower performance for the patients with a previous atrial switch. Moreover, patients with ASO have an evident cardiogenic limitation to exercise: lower O2 pulse, higher VE/VCO2.

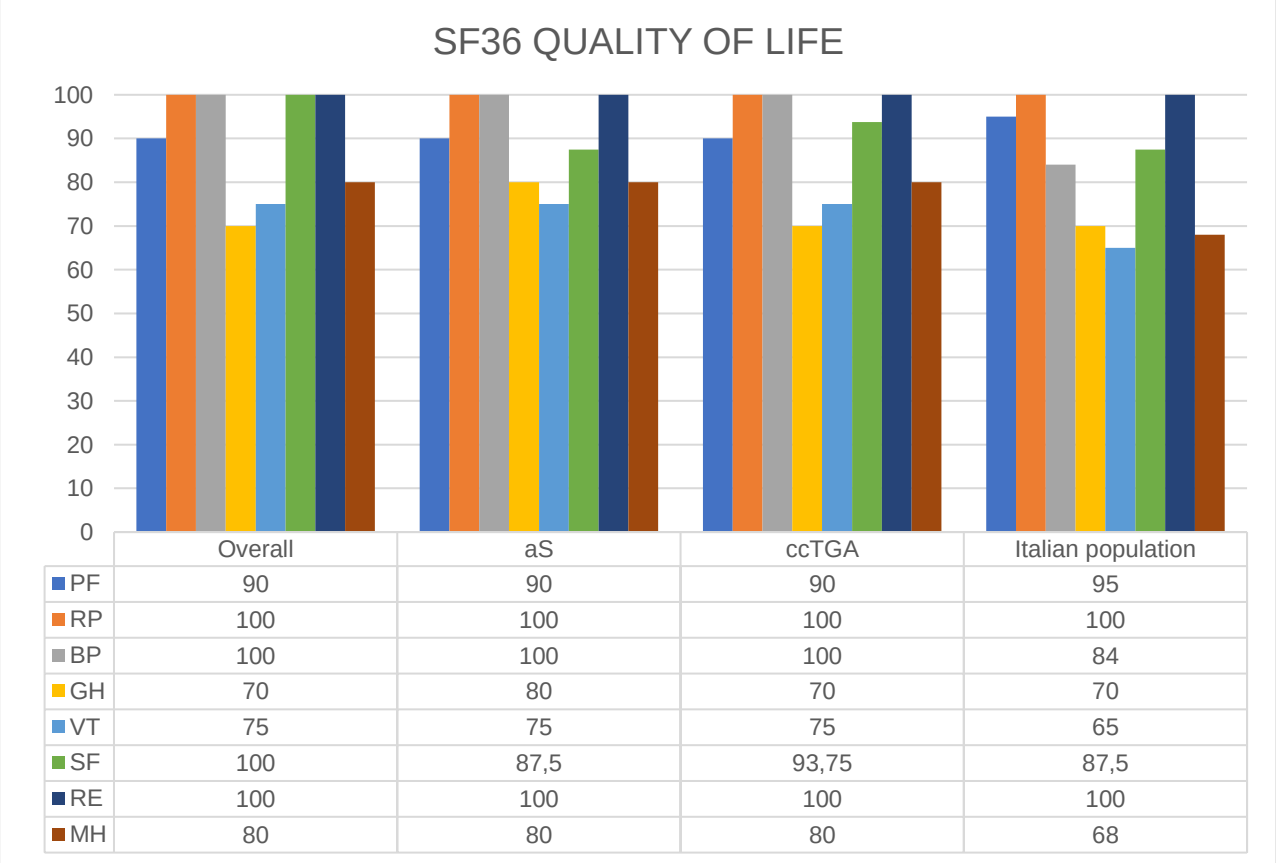
Table 7 CPET data

CPET	Overall (57)	AS (34)	ccTGA (39)	P
Age, mean ± SD	33 ± 11	35 ± 7	30 ± 16	0.1
Baseline HR, mean ± SD	70 ± 15	65 ± 16	75 ± 14	0.02
Chronotropic index, mean ± SD	74 ± 21	72 ± 24	78 ± 17	0.5
Peak SBP, mean ± SD	143 ± 23	144 ± 23	140 ± 23	0.49
Watts, mean ± SD	122 ± 41	122 ±38	121 ± 45	0.93
Peak VO2 (ml/kg/min), mean ± SD	24.5 ± 9.4	22.2 ± 7.2	27.2 ± 11	0.04
Percentage predicted VO2, mean ± SD	67 ± 20	61 ± 16	75 ± 21	0.007
Peak HR, mean ± SD	148 ± 25	142 ± 38	152 ± 26	0.25
RER, mean ± SD	1.2 ± 0.1	1.2 ± 0.09	1.2 ± 0.1	0.6
VAT (ml/kg/min), mean ± SD	17.7 ± 6.8	15.7 ± 4.8	20.3 ± 8.1	0.02
VE/VCO2 slope, mean ± SD	34 ± 8	37 ± 8	31 ± 6	0.02

O2 pulse (VO2/FC) mean ± SD	11.6 ± 3.5	11.1 ± 3.1	12.2 ± 3.9	0.3
O2 pulse (% predicted) mean ± SD	87 ± 27	76 ± 24	101 ± 23	0.001

QUALITY OF LIFE

Quality of life, evaluated with the SF 36 test, was similar between groups and was similar to the QOL of the Italian population. Eight domains were evaluated and the results were: physical functioning (PF) 83.8 ± 19.8; role physical (RP) 89.2 ± 29.9; bodily pain (BP) 90.3 ± 21.1, general health (GH) 67.8 ± 22, vitality (VT) 74 ± 16, social functioning (SF) 86.2 ± 17.8, role emotional (RE) 92.3 ± 25.5, mental health (MH) 78.7 ± 15.9.



	Overall	aS	ccTGA	Italian population
PF	90	90	90	95
RP	100	100	100	100
BP	100	100	100	84
GH	70	80	70	70
VT	75	75	75	65
SF	100	87,5	93,75	87,5
RE	100	100	100	100
MH	80	80	80	68

Figure 8: Quality of life of SRV patients compared with the Italian population

FOLLOW-UP

Mean follow-up was 6.4 ± 1 years. Mean age at follow-up was 36 ± 14 years.

Overall, one and 5-year survival free from heart transplantation was 97.4 ± 2.6 % and 92 ± 4.4 % respectively (Figure 9). Survival rate was not statistically different between groups (p 0.09). Two patients died during follow up: a 35-year old man with ccTGA, VSD, ASD, pulmonary outflow stenosis and coarctation of the aorta previously treated de-coarctation and subsequently VSD, ASD closure, treatment of sub-pulmonary stenosis in tricuspid valve replacement with a mechanical prosthesis Carbomedics 25mm. The patient had a PM for complete AV block and a permanent atypical atrial flutter; he presented a severe dilatation and dysfunction of the SRV. He was admitted for end stage heart failure complicated by ventricular arrythmias and underwent ventricular assistance device implantation (VAD) during hospitalization as bridge to transplantation but died because of multiorgan failure one month after the VAD implantation. The second patient was a 51-year-old woman with end stage HF affected by ccTGA and a tricuspid mechanical prosthesis with a severe SRV dysfunction, severe pulmonary hypertension and a severe restrictive pulmonary disease not eligible for HT.

Moreover, a 52-year patient underwent heart transplantation during follow-up. He had a ccTGA with a severe SRV dysfunction.

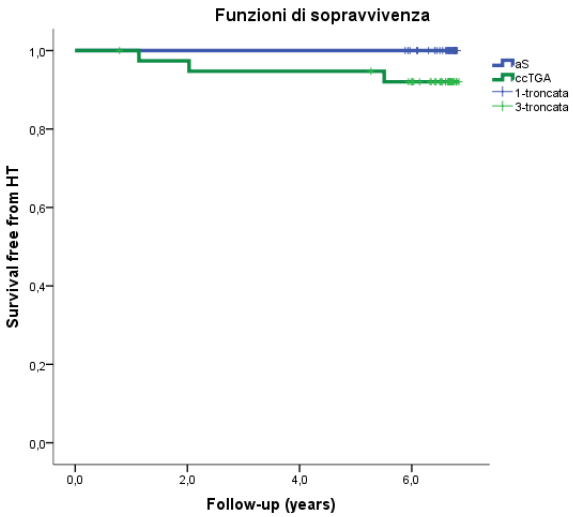


Figure 9: Survival free from HT

Composite endpoint was defined as survival free from heart transplantation, end stage heart failure in patients in waiting list for heart transplantation, heart failure, arrythmia requiring hospitalisation or MACEs.

Survival free from adverse events was 98.6% at one year and 95.8% at 5-year follow-up without difference between the two groups.

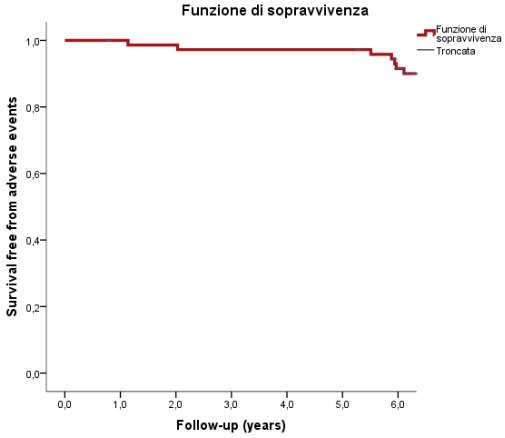


Figure 10: Survival free from adverse events

The most common adverse event during follow-up was the presence of arrhythmia requiring hospitalisation (18 patients = 24.6%) followed by signs of heart failure requiring hospitalisation (11 = 15%) one patient had a stroke during follow-up due to a non-optimal adherence to anticoagulation therapy (a 55 years old woman with a ccTGA and a mechanical tricuspid valve with a low INR value 1.7).

Arrythmia presented during follow-up were: 41% atrial fibrillation, 39% atypical atrial flutter and 20% IART. Moreover, 3 patients underwent transcatheter ablation for atypical atrial flutter.

Considering the entire medical history of patient's survival free from adverse events was assessed every ten years and was: 97.2% at 10 years, 94.1% at 20 years, 90.9% at 30 years, 69.4% at 40 years and 41.2% at 50 years with no differences between groups. (figure 11)

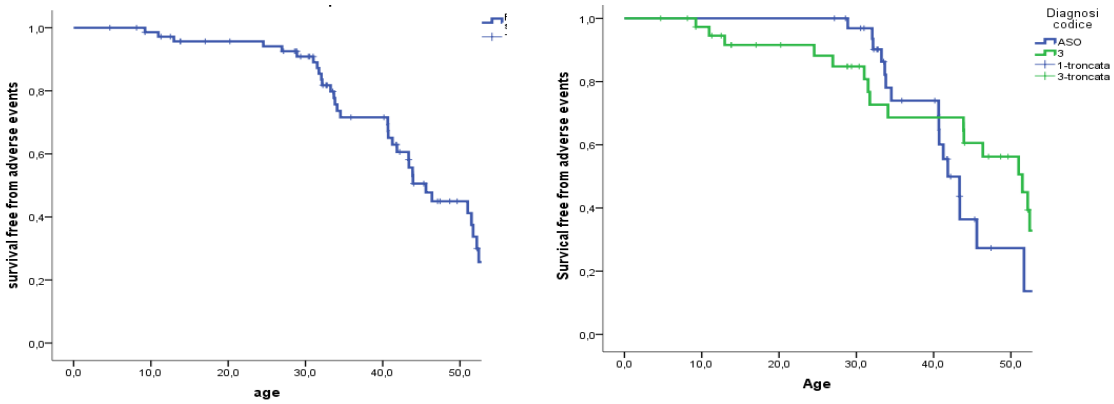


Figure 11: Survival free from adverse events considering the entire period of follow-up not just the study period

Second echocardiography evaluation:

There was no statistically significant variation between the first and the second echography evaluation except for an increasing in left atrial volume. End diastolic/ systolic RV area 19.6 ± 5.6 cm2/m2 respectively 12.6 ± 5.6 cm2/m2; FAC 37.7 ± 10%, TAPSE 15 ± 4mm, S wave DTI 8.6 ± 2.1cm/sec. Free wall/ 6 segments GLS was -12.9 ± - 5.2% and respectively -11.9 ± -4.7%. 27.1% of patients had moderate-to-severe or severe sTR. The pressure in the sub-pulmonary LV was 33 ±18mmHg. An increasing left atrium volume was noticed: volume 43 ± 27ml/m2, area 12.8 ± 9.5 cm2/m2.

NYHA class valuation at the last clinical evaluation did not evidenced significant differences comparing with the first evaluation.

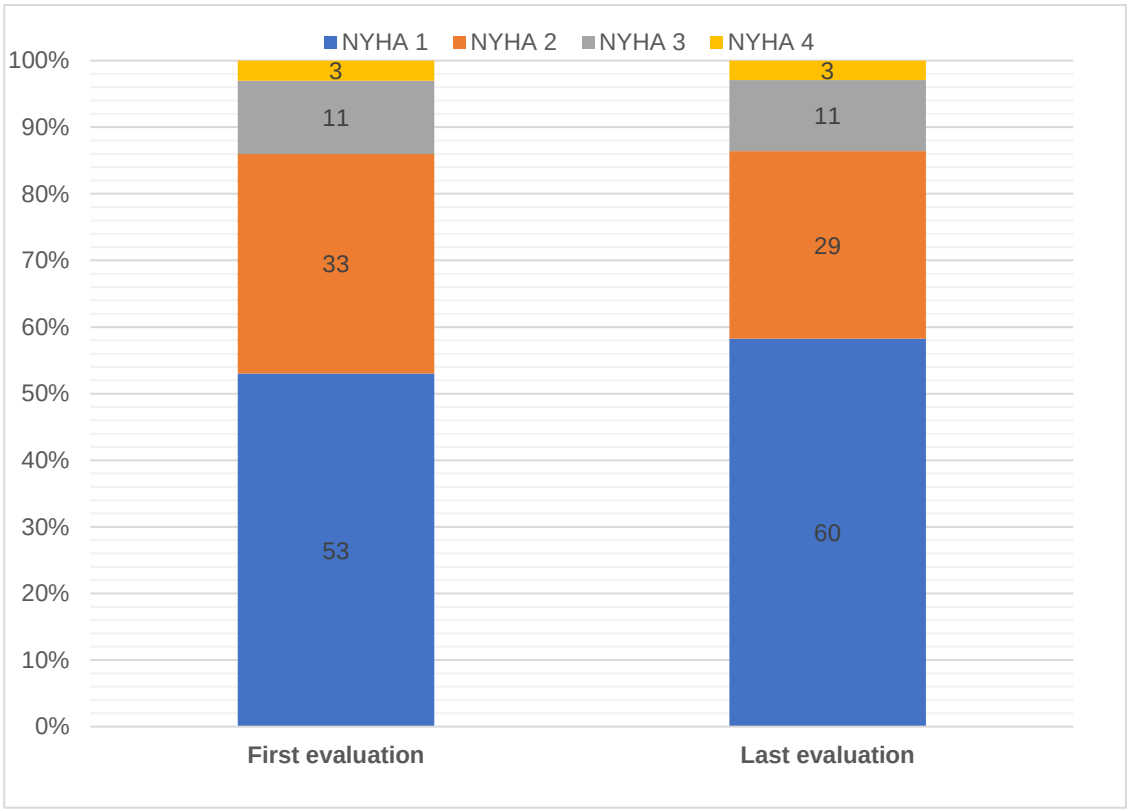


Figure 12: NYHA class variation between the first and the last evaluation

Medical therapy was registered. Almost one third of patients received diuretics, more than 40% received beta-blockers or ACE-I/ARBs.27.1% of patients received oral anticoagulation therapy prevalently warfarin even if in 3 patients a new oral anticoagulant therapy was preferred.

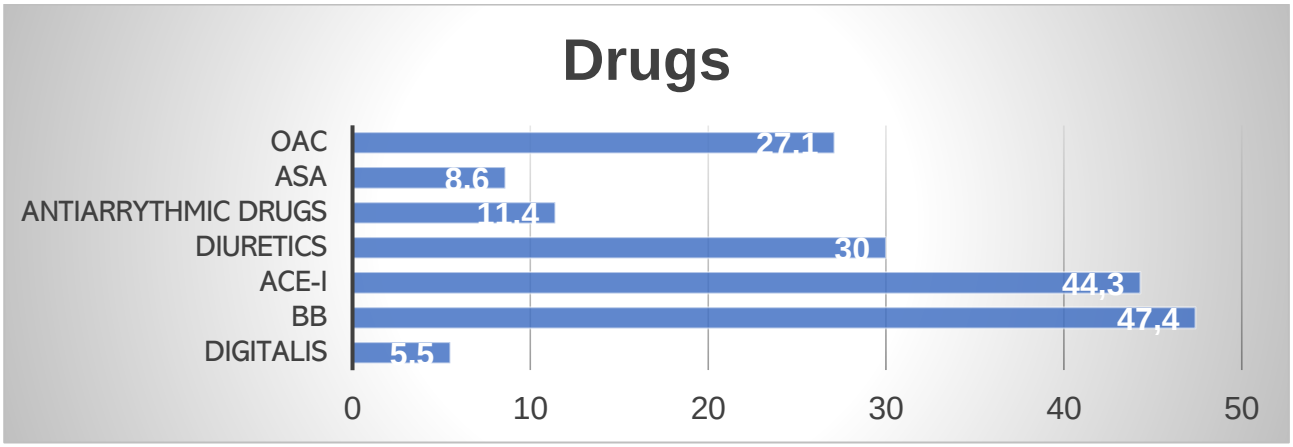


Figure 13: Drugs implementation at the last follow-up (% of alive patients)

PREDICTORS OF OUTCOME

A univariate analysis was performed in order to identify the predictors of poorer outcome and that includes a higher NYHA class, a more dilated and dysfunctional SRV, a higher degree of TR a lower exercise capacity and the presence of fibrosis documented at CMR.

Table 8 Univariate analysis

	HR	95% CI	p
NYHA class	**2.8**	**1.8-4.7**	**<0.0001**
EDA RSV (cm^2)	**1.1**	1.0- 1.2	**0.07**
ESA RSV (cm^2)	**1.1**	**1.0-1.2**	**0.02**
FAC (%)	**0.9**	**0.8-0.96**	**<0.001**
TAPSE (cm)	**0.86**	**0.7-0.99**	**0.01**
S' (cm/sec)	**0.7**	**0.6-0.9**	**0.01**
TR>2	**3.2**	**1.2-9.1**	**0.02**
RV DI (cm)	**1.7**	**1.1-2.7**	**0.001**
RV DII (cm)	**1.9**	**1.3-2.7**	**0.001**
GLS 2D SRV strain free wall	**0.89**	**0.8- 0.98**	**0.01**
GLS 2D SRV strain 6 segments	**0.87**	**0.78 – 0.98**	**0.01**
Left atrium volume ml/m2	**1.03**	**1.01-1.05**	**<0.001**
Right atrium volume ml/m2	**1.03**	**1.0-1.06**	**0.008**
QRS (ms)	**1.04**	**1.02-1.06**	**<0.001**
% VO2 teor	**0.96**	**0.93-0.99**	**0.05**
EDV SRVi (ml/m^2)	**1.02**	**1.01-1.03**	**<0.001**
ESV SRVi (ml/m^2)	**1.02**	**1.01-1.03**	**<0.001**
FE SRV (%)	**0.9**	**0.8-0.99**	**0.008**
LGE	**12**	**2.6-59**	**0.009**

DISCUSSION

Congenital heart diseases with a systemic right ventricle are a challenging situation for clinicians and need a multidisciplinary approach and a systematic follow-up to guarantee an optimal management. Clinical evaluation should assess the NYHA class, the physiological state, as well as the coexistence of signs of heart failure, persistent or paroxysmal arrythmias or other symptoms such as syncope, angina palpitation.

In the last decades the treatment of heart failure associated with acquired cardiac disease changed dramatically with a considerable improvement of survival and quality of life. [50] However, very few studies were conducted in ACHD patients with SRV and the results are contrasting.

Our study confirms a high incidence of adverse events during follow up. The most common are supraventricular arrythmias requiring hospitalisation (27.1%) supporting data presented in previous studies by Cuypers et al (28%). [8] Almost one third of patients received oral anticoagulant therapy (OAC); the main indications were mechanical prosthesis or atrial arrhythmias. However, non-vitamin K antagonist oral anticoagulants (NOACs) were used in a relatively low percentage of patients. Further studies or trials are needed to verify long-term safety and efficacy of NOACs in these patients.

The second cause of hospitalisation was the worsening of heart failure (12.3%) similar with the data presented by Cuypers, where 14% of developed heart failure the last decade of follow-up. [8] Optimization of the medical therapy is crucial in these patients, but it needs evidenced based trials therefor it will be interesting thinking at trials using dapagliflozin such as DAPA-HF [51, 52] or sacubitril/valsartan as Paradigm-HF trial [53].

The young adults should be empowered concerning their clinical condition and therapeutic/follow-up strategies should be shared with patients to achieve a better compliance. Clinical evaluation

should be performed every year or more frequently if necessary. View the frequency of arrhythmic events a regular follow-up with HOLTER ECG should be performed and, in selected cases, longer monitoring could be considered.

Echocardiographic evaluation is crucial and should be performed as the clinical evaluation every year; together with the standard evaluation including RV diameters, areas, and systolic function (TAPSE, S wave DTI RV, FAC%) the longitudinal evaluation should be routinely performed. CMR should be preferred because it characterise better the myocardium allowing the study and quantification of fibrosis and it avoids radiations. Alternatively, cardiovascular computed tomography can be performed in claustrophobic patients or with contraindications to MRI.

A progressive dilatation of the right ventricle was observed, with documented myocardial fibrosis in 42% of patients. In previous studies extended fibrosis was documented at the autoptic heart examination. [21] Moreover, Rydman et al evidenced that LGE was present in half of patients and was associated with poorer outcome as proved in our analyses LGE had an important predictive value HR 12, 95% CI 2.6-59, p 0.009. [20] As demonstrated by Giardini et al the fibrosis is associated with older age; in our study mean age of patients with LGE was 34 years while the mean age of patients without evidence of LGE was 27 years. [19]

In our study RV dimensions and function independently if evaluated with echocardiography or CMR were strongly associated with poorer outcome. Even if RV systolic function might be difficult to evaluate at 2D echocardiography in these patients with previous surgical intervention, non-exceptional dextrocardia or mesocardiac, we think, considering the prognostic value, that it should be routinely assessed during outpatient clinic evaluation and change should be promptly confirmed by a CMR or cardiac tomography when CMR is not feasible. Different cut-off values have been proposed for the evaluation of SRV. [17] Moreover, an impairment in longitudinal function of the SVR is observed even in the presence of normal systolic function FAC, TAPSE, S DTI ant it correlates with a poorer outcome with no significant difference if a 6 segments or the

free wall GLS is used: GLS 2D SRV strain free wall HR 0.89, 95% CI 0.8- 0.98, p 0.01; GLS 2D SRV strain 6 segments HR 0.87, 95%CI 0.78 – 0.98, p 0.01; this data are similar to previous studies Kalegeropoulos et al. assessed that a SRV GLS < - 10% was associated with poorer outcome [14] while Diller et al established with a sensibility of 72% and a specificity of 63% that GLS lower than -13.3% identify higher risk of MACEs. Probably, the longitudinal evaluation is able to identify earlier the changes in myofiber organization in the SRV. The myofiber disorganization is an anatomic substrate for heart failure and arrhythmias.[54]

Moreover, the presence of moderate to severe or severe tricuspid regurgitation, previously described as associated with a higher incidence of adverse events especially in ccTGA patients [46], was an important predictor of outcome HR 3.2 95%CI 1.2-9.1, p = 0.02. The current guidelines suggest tricuspid valve replacement for severe TR in symptomatic adults with preserved or mildly depressed systemic ventricular function (ccTGA) and regardless symptoms in ASO patients without significant ventricular systolic dysfunction (EF >40%). [23] [5].

Exercise tolerance should be assessed every 24/36 month according to the clinical status; the evidence of worsening of the exercise capacity with an evidence of cardiogenic limitation: lower O2 pulse, higher VE/VCO2 corroborate by the clinical condition could indicate an invasive evaluation with cardiac catheterization. Advanced imaging evaluation should be regularly performed every 3-5 years in stable patients and eventually every other year or less in patients with complications.

Exercise capacity in patients with SRV is reduced with a peak VO2 24.5 ± 9.4ml/kg/min (67±20% of the predicted value) similar to previous published data: VO2 27.14 ± 4.3 ml/kg/min [25] VO2 28.6 ± 8.3 ml/kg/min for ASO patients and 25.6 ± 7.1 ml/kg/min for ccTGA patients [28] 21.5 ± 5.8 ml/kg/min (57 ± 14% of the predicted value)[26], 23.3 ± 6.9 ml/kg/min (68 ± 16.6% of the predicted value)[27] 27 ± 7 ml/kg/min[29]. The chronotropic incompetence, frequent in this category of patients [26], was associated with a poorer outcome [28].

Moreover, pregnancy should be discussed and supported by a multidisciplinary ACHD team involving cardiologists, gynaecologists, obstetricians, cardiac surgeons, radiologists, and psychologists. An interesting data of our study is the high number of pregnancies that was relatively well tolerated with no maternal deaths with a complication rate of 25% prevalently HF, no sustained arrhythmia was evidenced in our population. A case of vertical transmission of ccTGA was evidenced. Our data confirm data described previously. [33] [34] [36] Given the risk of an irreversible decline in RV function during pregnancy we suggest an exhaustive multidisciplinary counselling in fertile women searching a pregnancy. [35]

ACHD patients experience a chronic disease therefor the quality of life is important in these cohort of patients; every therapeutical change should evaluate the clinical benefit and the Qol and we believe that this aspect should be considered as a protagonist of the multidisciplinary management. For disease related-Qol evaluation in patients with acquired heart diseases, different questionnaires are available such as Minnesota living with heart failure questionnaire (MLHFQ) or the Kansas City Cardiomyopathy Questionnaire (KCCQ). The Qol evaluation in ACHD does not have a typical questionnaire and we choose for our study a well-known generic instrument, the SF -36, because it has been used in the ACHD patients and it has been validated for the Italian population. Contrary to the expectation the health-related quality of life of these patients was similar to the QOL of the Italian population. These was explained generally for ACHD population by a stronger sense of coherence. [31, 32] General Qol, defined by the World Health Organization as individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns, should also be evaluated.

CONCLUSIONS

Long term follow-up of patients with systemic right ventricle is characterized by a good survival though with a high incidence of clinical events, prevalently arrhythmias and heart failure which cause most of the unscheduled hospitalisations.

Despite a lower exercise tolerance, relatively high incidence of clinical events ACHD patients with SRV have a quality of life similar to the general population probably due to a stronger sense of coherence.

REFERENCES

1. Samanek M, Slavik Z, Zborilova B, Hrobonova V, Voriskova M, Skovranek J: **Prevalence, treatment, and outcome of heart disease in live-born children: a prospective analysis of 91,823 live-born children**. *Pediatr Cardiol* 1989, **10**(4):205-211.
2. Senning A: **Surgical correction of transposition of the great vessels**. *Surgery* 1959, **45**(6):966-980.
3. Mustard WT: **Successful Two-Stage Correction of Transposition of the Great Vessels**. *Surgery* 1964, **55**:469-472.
4. Brida M, Diller GP, Gatzoulis MA: **Response by Brida et al to Letter Regarding Article, "Systemic Right Ventricle in Adults With Congenital Heart Disease: Anatomic and Phenotypic Spectrum and Current Approach to Management"**. *Circulation* 2018, **138**(3):326-327.
5. Baumgartner H, De Backer J, Babu-Narayan SV, Budts W, Chessa M, Diller GP, Lung B, Kluin J, Lang IM, Meijboom F *et al*: **2020 ESC Guidelines for the management of adult congenital heart disease**. *Eur Heart J* 2020.
6. Raissadati A, Nieminen H, Sairanen H, Jokinen E: **Outcomes after the Mustard, Senning and arterial switch operation for treatment of transposition of the great arteries in Finland: a nationwide 4-decade perspective**. *Eur J Cardiothorac Surg* 2017, **52**(3):573-580.
7. Gelatt M, Hamilton RM, McCrindle BW, Connelly M, Davis A, Harris L, Gow RM, Williams WG, Trusler GA, Freedom RM: **Arrhythmia and mortality after the Mustard procedure: a 30-year single-center experience**. *J Am Coll Cardiol* 1997, **29**(1):194-201.
8. Cuypers JA, Eindhoven JA, Slager MA, Opic P, Utens EM, Helbing WA, Witsenburg M, van den Bosch AE, Ouhlous M, van Domburg RT *et al*: **The natural and unnatural history of the Mustard procedure: long-term outcome up to 40 years**. *Eur Heart J* 2014, **35**(25):1666-1674.
9. Van Praagh R, Jung WK: **The arterial switch operation in transposition of the great arteries: anatomic indications and contraindications**. *Thorac Cardiovasc Surg* 1991, **39 Suppl 2**:138-150.
10. Marelli AJ, Ionescu-Ittu R, Mackie AS, Guo L, Dendukuri N, Kaouache M: **Lifetime prevalence of congenital heart disease in the general population from 2000 to 2010**. *Circulation* 2014, **130**(9):749-756.
11. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T *et al*: **Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging**. *J Am Soc Echocardiogr* 2015, **28**(1):1-39 e14.
12. Lissin LW, Li W, Murphy DJ, Jr., Hornung T, Swan L, Mullen M, Kilner P, Gatzoulis MA: **Comparison of transthoracic echocardiography versus cardiovascular magnetic resonance imaging for the assessment of ventricular function in adults after atrial switch procedures for complete transposition of the great arteries**. *Am J Cardiol* 2004, **93**(5):654-657.
13. Khattab K, Schmidheiny P, Wustmann K, Wahl A, Seiler C, Schwerzmann M: **Echocardiogram versus cardiac magnetic resonance imaging for assessing systolic function of subaortic right ventricle in adults with complete transposition of great arteries and previous atrial switch operation**. *Am J Cardiol* 2013, **111**(6):908-913.
14. Kalogeropoulos AP, Georgiopoulou VV, Giamouzis G, Pernetz MA, Anadiotis A, McConnell M, Lerakis S, Butler J, Book WM, Martin RP: **Myocardial deformation**

imaging of the systemic right ventricle by two-dimensional strain echocardiography in patients with d-transposition of the great arteries. *Hellenic J Cardiol* 2009, **50**(4):275-282.
15. Kowalik E, Mazurkiewicz L, Kowalski M, Klisiewicz A, Marczak M, Hoffman P: **Echocardiography vs magnetic resonance imaging in assessing ventricular function and systemic atrioventricular valve status in adults with congenitally corrected transposition of the great arteries**. *Echocardiography* 2016, **33**(11):1697-1702.
16. Kutty S, Li L, Polak A, Gribben P, Danford DA: **Echocardiographic knowledge-based reconstruction for quantification of the systemic right ventricle in young adults with repaired D-transposition of great arteries**. *Am J Cardiol* 2012, **109**(6):881-888.
17. Iriart X, Roubertie F, Jalal Z, Thambo JB: **Quantification of systemic right ventricle by echocardiography**. *Arch Cardiovasc Dis* 2016, **109**(2):120-127.
18. Kawel-Boehm N, Hetzel SJ, Ambale-Venkatesh B, Captur G, Francois CJ, Jerosch-Herold M, Salerno M, Teague SD, Valsangiacomo-Buechel E, van der Geest RJ *et al*: **Reference ranges ("normal values") for cardiovascular magnetic resonance (CMR) in adults and children: 2020 update**. *J Cardiovasc Magn Reson* 2020, **22**(1):87.
19. Giardini A, Lovato L, Donti A, Formigari R, Oppido G, Gargiulo G, Picchio FM, Fattori R: **Relation between right ventricular structural alterations and markers of adverse clinical outcome in adults with systemic right ventricle and either congenital complete (after Senning operation) or congenitally corrected transposition of the great arteries**. *Am J Cardiol* 2006, **98**(9):1277-1282.
20. Rydman R, Gatzoulis MA, Ho SY, Ernst S, Swan L, Li W, Wong T, Sheppard M, McCarthy KP, Roughton M *et al*: **Systemic right ventricular fibrosis detected by cardiovascular magnetic resonance is associated with clinical outcome, mainly new-onset atrial arrhythmia, in patients after atrial redirection surgery for transposition of the great arteries**. *Circ Cardiovasc Imaging* 2015, **8**(5).
21. Roberts WC, Jameson LC, Bahmani A, Roberts CS, Rafael AE, Hall SA: **Morphological and Functional Characteristics of the Right Ventricle Functioning as a Systemic Ventricle for Decades After an Atrial Switch Procedure for Complete Transposition of the Great Arteries**. *Am J Cardiol* 2019, **123**(11):1863-1867.
22. Cheung YF, Lam WWM, So EKF, Chow PC: **Differential myocardial fibrosis of the systemic right ventricle and subpulmonary left ventricle after atrial switch operation for complete transposition of the great arteries**. *Int J Cardiol Heart Vasc* 2020, **30**:100612.
23. Writing Group M, Doherty JU, Kort S, Mehran R, Schoenhagen P, Soman P, Rating Panel M, Dehmer GJ, Doherty JU, Schoenhagen P *et al*: **ACC/AATS/AHA/ASE/ASNC/HRS/SCAI/SCCT/SCMR/STS 2019 Appropriate Use Criteria for Multimodality Imaging in the Assessment of Cardiac Structure and Function in Nonvalvular Heart Disease: A Report of the American College of Cardiology Appropriate Use Criteria Task Force, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and the Society of Thoracic Surgeons**. *J Am Soc Echocardiogr* 2019, **32**(5):553-579.
24. Stout KK, Daniels CJ, Aboulhosn JA, Bozkurt B, Broberg CS, Colman JM, Crumb SR, Dearani JA, Fuller S, Gurvitz M *et al*: **2018 AHA/ACC Guideline for the Management of Adults With Congenital Heart Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines**. *J Am Coll Cardiol* 2019, **73**(12):1494-1563.

25. Rog B, Salapa K, Okolska M, Dluzniewska N, Werynski P, Podolec P, Tomkiewicz-Pajak L: **Clinical Evaluation of Exercise Capacity in Adults with Systemic Right Ventricle**. *Tex Heart Inst J* 2019, **46**(1):14-20.
26. Iriart X, Le Quellenec S, Pillois X, Jaussaud J, Jalal Z, Roubertie F, Douard H, Cochet H, Thambo JB: **Heart rate response during exercise predicts exercise tolerance in adults with transposition of the great arteries and atrial switch operation**. *Int J Cardiol* 2020, **299**:116-122.
27. Gavotto A, Abassi H, Rola M, Serrand C, Picot MC, Iriart X, Thambo JB, Iserin L, Ladouceur M, Bredy C *et al*: **Factors associated with exercise capacity in patients with a systemic right ventricle**. *Int J Cardiol* 2019, **292**:230-235.
28. Helsen F, Claus P, Van De Bruaene A, Claessen G, La Gerche A, De Meester P, Claeys M, Gabriels C, Petit T, Santens B *et al*: **Advanced Imaging to Phenotype Patients With a Systemic Right Ventricle**. *J Am Heart Assoc* 2018, **7**(20):e009185.
29. Winter MM, van der Bom T, de Vries LC, Balducci A, Bouma BJ, Pieper PG, van Dijk AP, van der Plas MN, Picchio FM, Mulder BJ: **Exercise training improves exercise capacity in adult patients with a systemic right ventricle: a randomized clinical trial**. *Eur Heart J* 2012, **33**(11):1378-1385.
30. van der Bom T, Winter MM, Knaake JL, Cervi E, de Vries LS, Balducci A, Meregalli PG, Pieper PG, van Dijk AP, Bonvicini M *et al*: **Long-term benefits of exercise training in patients with a systemic right ventricle**. *Int J Cardiol* 2015, **179**:105-111.
31. Apers S, Moons P, Goossens E, Luyckx K, Gewillig M, Bogaerts K, Budts W, i Di: **Sense of coherence and perceived physical health explain the better quality of life in adolescents with congenital heart disease**. *Eur J Cardiovasc Nurs* 2013, **12**(5):475-483.
32. Moons P, Luyckx K: **Quality-of-life research in adult patients with congenital heart disease: current status and the way forward**. *Acta Paediatr* 2019, **108**(10):1765-1772.
33. Bowater SE, Selman TJ, Hudsmith LE, Clift PF, Thompson PJ, Thorne SA: **Long-term outcome following pregnancy in women with a systemic right ventricle: is the deterioration due to pregnancy or a consequence of time?** *Congenit Heart Dis* 2013, **8**(4):302-307.
34. Canobbio MM, Morris CD, Graham TP, Landzberg MJ: **Pregnancy outcomes after atrial repair for transposition of the great arteries**. *Am J Cardiol* 2006, **98**(5):668-672.
35. Regitz-Zagrosek V, Roos-Hesselink JW, Bauersachs J, Blomstrom-Lundqvist C, Cifkova R, De Bonis M, Iung B, Johnson MR, Kintscher U, Kranke P *et al*: **2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy**. *Eur Heart J* 2018, **39**(34):3165-3241.
36. Kowalik E, Klisiewicz A, Biernacka EK, Hoffman P: **Pregnancy and long-term cardiovascular outcomes in women with congenitally corrected transposition of the great arteries**. *Int J Gynaecol Obstet* 2014, **125**(2):154-157.
37. Piran S, Veldtman G, Siu S, Webb GD, Liu PP: **Heart failure and ventricular dysfunction in patients with single or systemic right ventricles**. *Circulation* 2002, **105**(10):1189-1194.
38. Dobson R, Danton M, Nicola W, Hamish W: **The natural and unnatural history of the systemic right ventricle in adult survivors**. *J Thorac Cardiovasc Surg* 2013, **145**(6):1493-1501; discussion 1501-1493.
39. Zaragoza-Macias E, Zaidi AN, Dendukuri N, Marelli A: **Medical Therapy for Systemic Right Ventricles: A Systematic Review (Part 1) for the 2018 AHA/ACC Guideline for the Management of Adults With Congenital Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines**. *Circulation* 2019, **139**(14):e801-e813.
40. Diller GP, Okonko D, Uebing A, Ho SY, Gatzoulis MA: **Cardiac resynchronization therapy for adult congenital heart disease patients with a systemic right ventricle: analysis of feasibility and review of early experience**. *Europace* 2006, **8**(4):267-272.

41. Peng E, O'Sullivan JJ, Griselli M, Roysam C, Crossland D, Chaudhari M, Wrightson N, Butt T, Parry G, MacGowan GA *et al*: **Durable ventricular assist device support for failing systemic morphologic right ventricle: early results**. *Ann Thorac Surg* 2014, **98**(6):2122-2129.
42. Ross HJ, Law Y, Book WM, Broberg CS, Burchill L, Cecchin F, Chen JM, Delgado D, Dimopoulos K, Everitt MD *et al*: **Transplantation and Mechanical Circulatory Support in Congenital Heart Disease: A Scientific Statement From the American Heart Association**. *Circulation* 2016, **133**(8):802-820.
43. Khairy P, Van Hare GF, Balaji S, Berul CI, Cecchin F, Cohen MI, Daniels CJ, Deal BJ, Dearani JA, Groot N *et al*: **PACES/HRS expert consensus statement on the recognition and management of arrhythmias in adult congenital heart disease: developed in partnership between the Pediatric and Congenital Electrophysiology Society (PACES) and the Heart Rhythm Society (HRS). Endorsed by the governing bodies of PACES, HRS, the American College of Cardiology (ACC), the American Heart Association (AHA), the European Heart Rhythm Association (EHRA), the Canadian Heart Rhythm Society (CHRS), and the International Society for Adult Congenital Heart Disease (ISACHD)**. *Can J Cardiol* 2014, **30**(10):e1-e63.
44. Hosseinpour AR, McCarthy KP, Griselli M, Sethia B, Ho SY: **Congenitally corrected transposition: size of the pulmonary trunk and septal malalignment**. *Ann Thorac Surg* 2004, **77**(6):2163-2166.
45. 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**(17):1293-1302.
46. Prieto LR, Hordof AJ, Secic M, Rosenbaum MS, Gersony WM: **Progressive tricuspid valve disease in patients with congenitally corrected transposition of the great arteries**. *Circulation* 1998, **98**(10):997-1005.
47. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, Solomon SD, Louie EK, Schiller NB: **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**(7):685-713; quiz 786-688.
48. Stewart M: **The Medical Outcomes Study 36-item short-form health survey (SF-36)**. *Aust J Physiother* 2007, **53**(3):208.
49. Apolone G, Mosconi P: **The Italian SF-36 Health Survey: translation, validation and norming**. *J Clin Epidemiol* 1998, **51**(11):1025-1036.
50. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA *et al*: **2016 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure**. *Rev Esp Cardiol (Engl Ed)* 2016, **69**(12):1167.
51. Kosiborod MN, Jhund PS, Docherty KF, Diez M, Petrie MC, Verma S, Nicolau JC, Merkely B, Kitakaze M, DeMets DL *et al*: **Effects of Dapagliflozin on Symptoms, Function, and Quality of Life in Patients With Heart Failure and Reduced Ejection Fraction: Results From the DAPA-HF Trial**. *Circulation* 2020, **141**(2):90-99.
52. McMurray JJV, Solomon SD, Inzucchi SE, Kober L, Kosiborod MN, Martinez FA, Ponikowski P, Sabatine MS, Anand IS, Belohlavek J *et al*: **Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction**. *N Engl J Med* 2019, **381**(21):1995-2008.
53. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K *et al*: **Angiotensin-neprilysin inhibition versus enalapril in heart failure**. *N Engl J Med* 2014, **371**(11):993-1004.

54. Campanale CM, Scherrer B, Afacan O, Majeed A, Warfield SK, Sanders SP: **Myofiber organization in the failing systemic right ventricle**. *J Cardiovasc Magn Reson* 2020, **22**(1):49.