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Hemodynamics and Exercise Tolerance after Senning Operation for Transposition of Great Arteries and Its Limiting Factors: A Longitudinal Study

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Abstract

Objectives: The purpose of this longitudinal study was to assess hemodynamics and exercise capacity in patients after Senning operation and to determine its limiting factors.

Methods: 87 long-term survivors of the Senning operation for transposition of great arteries were recruited for a longitudinal follow-up study consisting of two cross-sectional evaluations at a mean of 12.6 and 22.6 years after surgery, respectively. The protocol included a questionnaire, echocardiography, radionuclide angiocardiography, magnetic resonance imaging and cardiopulmonary exercise test. Decreased exercise capacity was defined as maximum oxygen uptake <-2 Z-scores.

Results: Hemodynamic variables (right ventricular function and degree of tricuspid regurgitation) and chronotropic competence did not change significantly with time. Decreased exercise tolerance was present in 55.6 and 49.3% of patients at the first and second evaluation, respectively (NS) and had multi-variable correlation with lower right ventricular end-diastolic volume (P=0.039, OR 0.963) and increased ventilation/carbon dioxide production slope (P=0.040, OR 1.293). None of other hemodynamic variables correlated with decreased functional capacity.

Conclusions: Long-term survivors of the Senning operation have stable hemodynamics and exercise capacity on longitudinal follow-up. Decreased exercise tolerance is found in approximately half of the patients and is significantly associated with lower ventilation efficiency. This data may point to the usefulness of targeted respiratory rehabilitation in this patient group.

Keywords: Transposition of the great arteries; Exercise tests; Echocardiography; Magnetic resonance imaging; Senning operation

Introduction

Transposition of the great arteries (TGA) is one of the most frequent congenital heart defects presenting with critical cyanosis after the birth. Before the arterial switch operation was introduced to clinical practice, atrial physiological correction saved lives of many children with TGA [1,2]. Concerns about the long-term outcome appeared soon after the introduction of Mustard and Senning procedures. Dysfunction of systemic right ventricle along with tricuspid regurgitation and atrial tachyarrhythmias were described as important causes of morbidity and mortality [3-5]. Several studies have revealed an association between decreased survival and limited exercise intolerance [6-8]. The main purpose of this longitudinal study was to assess the evolution of hemodynamic and functional parameters in a cohort of long-term survivors of the Senning operation.

This study was designed as a single institution prospective longitudinal investigation.

Patients and Methods

Demography

Between 1984-1997 a total of 300 patients underwent the Senning procedure at our institution. Cumulative survival analysis could be performed in 204 of them living in the Czech Republic (Figure 1). The surgical mortality rate was 13.2% (27/204 patients). Nineteen/204 patients (9.3%) died during later follow-up and two were transplanted. All 156 surviving patients living in the Czech Republic were asked to participate in the study to exclude potential bias arising from any other selection. Out of 156 surviving patients 87 (female=23, male=64) were recruited for the longitudinal follow-up study consisting of two cross-sectional evaluations at a mean of 12.6 and 22.6 years after the Senning procedure, respectively. Median age at the time of the physiological repair was 5.8 (IQR 4.8–7.5) months. The remaining 69 patients either refused to participate in the study (N=47) or could not be reached (N=22). Informed consent was obtained from all participants and the medical review board of our institution approved the study.

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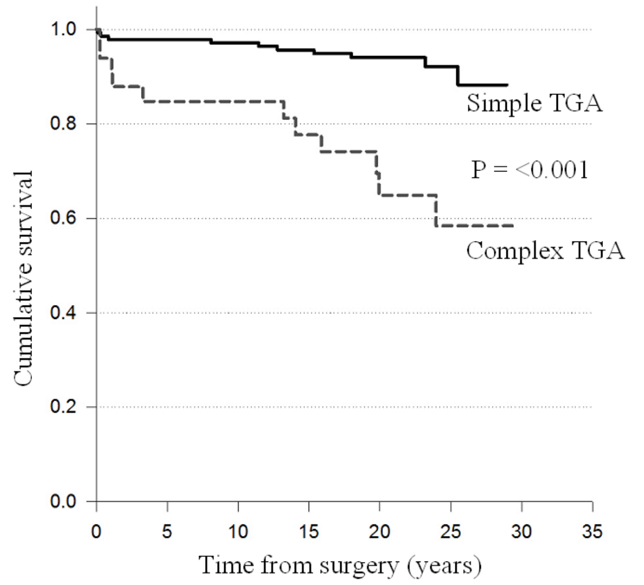

Figure 1: Cumulative survival probability (early deaths excluded) in simple TGA (N=158) and complex TGA (N=46). TGA – transposition of great arteries.

Cross-sectional evaluation

Cross-sectional evaluation consisted of a questionnaire, clinical examination, 12-lead electrocardiogram, 24-hour Holter ECG, echocardiography and cardiopulmonary exercise test. To quantify ventricular function radionuclide angiocardiography was used at the first and magnetic resonance imaging at the second cross-sectional study.

Echocardiography

Echocardiography was performed on Vivid 9 (GE Medical Health Systems) with 2.5-5 MHz convex transducers. Transthoracic examinations were performed in a supine position using standard 2 D grayscale and Doppler techniques. To assess systolic function of the right ventricle (RV), tricuspid annular plane systolic excursion (TAPSE) and semiquantitative visual grading (1-normal, 2-mild dysfunction, 3-moderate dysfunction, 4-severe dysfunction) were utilized [8-9]. Tricuspid regurgitation was semiquantitatively estimated by echocardiography from the apical 4- and 2-chamber views and was reported as 0=absent, 1=mild, 2=moderate, or 3=severe [10].

Radionuclide angiocardiography

Radionuclide ventriculography (N=74) was performed with gamma camera PHO/Gamma LEM (Siemens) and computer system PDP 11/34-Gamma 11 (DEC). Patients' red blood cells were labelled in vivo with 430 MB q 99 mTc per m^2 of body surface area. Left anterior oblique projection providing optimum ventricular separation was used. Detector was equipped with a 30° slant-hole high sensitivity collimator and tilted 5° caudally to provide optimal atrioventricular separation. Data were recorded using electrocardiographic gating into 46 frames per cardiac cycle until the total count of 8 millions. Cycles differing by more than 50 ms from the average RR interval were excluded. The frames were recorded into a 64 × 64 × word matrix. Structures with ventricular dynamics were defined automatically by phase analysis. End-diastolic ventricular regions of interest were defined using phase analysis and automatic detection of ventricular septum. Background regions of interest were automatically generated between end-diastolic and end-systolic ventricular outlines. From the background-free ventricular time-activity curve the first derivative curves were computed. Ejection fractions were calculated from the end-diastolic and the end-systolic counts using the usual formula (Figure 2).

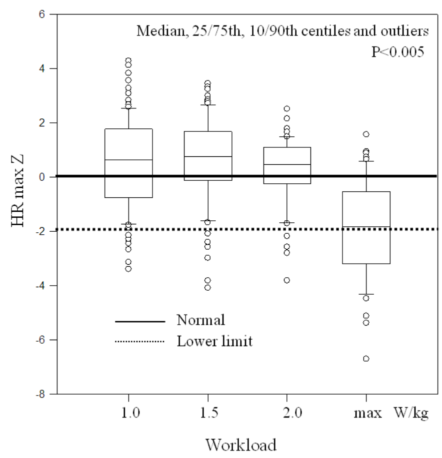

Figure 2: Heart max rate Z-scores during increasing workload (second cross-sectional evaluation). A significant chronotropic incompetence is noted at maximum exercise (P <0.005 versus all other exercise levels). HR – Heart Rate.

Magnetic resonance imaging (MRI)

All MRI examinations (N=71) were performed by 1.5 T MRI scanner (Avanto, Siemens Medical Systems, Germany). Static steady-state free precession (SSFP) consecutive images in axial, coronal and sagittal plane were performed for anatomical overview (slice thickness 8 mm, gap 0). Cine SSFP retrospectively ECG-gated images in the right ventricular long axis and 4-chamber view were done (slice thickness 6 mm, 25 phases). Consecutive cine SSFP images in the short axis and axial plane (slice thickness 8 mm, gap 2 mm, 25 phases except two patients with 16 phases due to higher heart rate) were obtained and used for volumetric measurement of the left and right ventricle, respectively. The MRI protocol also included fast low angle shot (FLASH) cine tagging (slice thickness 7 mm, grid spacing 7 mm) in 3 short axis planes, 4-chamber and right ventricular long axis, 3-dimensional SSFP (slice thickness 1.5 mm), contrast-enhance MR angiography (slice thickness 1.4 mm) and SSFP phase sensitive inversion recovery (PSIR) single shot consecutive images in short axis, right ventricle long axis and 4-chamber view for detection of late-gadolinium enhancement. Gadobutrol (Gadovist; Schering, Berlin, Germany) at 0.15-0.2 mmol/kg was used as contrast medium. Post-processing including the left and right ventricular volume measurements. Calculation of stroke volume and ejection fraction was done using dedicated software (Argus, Syngo, Siemens Medical Systems, Germany). The end-diastole and end-systole were determined visually on cine images as the largest and the smallest area respectively in the transversal plane. The delineation of endocardial border was outlined manually and trabecullae and papillary muscles were excluded from the ventricular lumen. Abnormal right ventricular ejection fraction at rest was defined as less than 47% (-2 SD of normal) [11].

Cardiopulmonary exercise test

Exercise testing was performed at the same day as MRI and echocardiography. A graded stepwise maximal exercise test was performed on bicycle ergometer (Ergoline Ergoselect 100, Ergoline GmbH Germany). Exercise stress protocol started with a load of 0.5 W* kg^{-1}* min^{-1} increased after each 3 minutes by 0.5 W* kg^{-1}* min^{-1} until hard work was subjectively reported (Borg scale 15) and then followed by continuous increase of load until exhaustion within 2–4 minutes. Continuous recording of ECG and oxygen saturation was performed and blood pressure measurement was measured manually at the end of each stage. Gas exchange was monitored by breath – by – breath analyzer (Oxycon – Pro, Jaeger, Germany). The respiratory quotient exceeding 1.1 together with Borg scale indicating peak exercise was used as an indicator of maximum effort. Data were expressed as Z-scores using own published age-related normal values [12] (Figure 3).

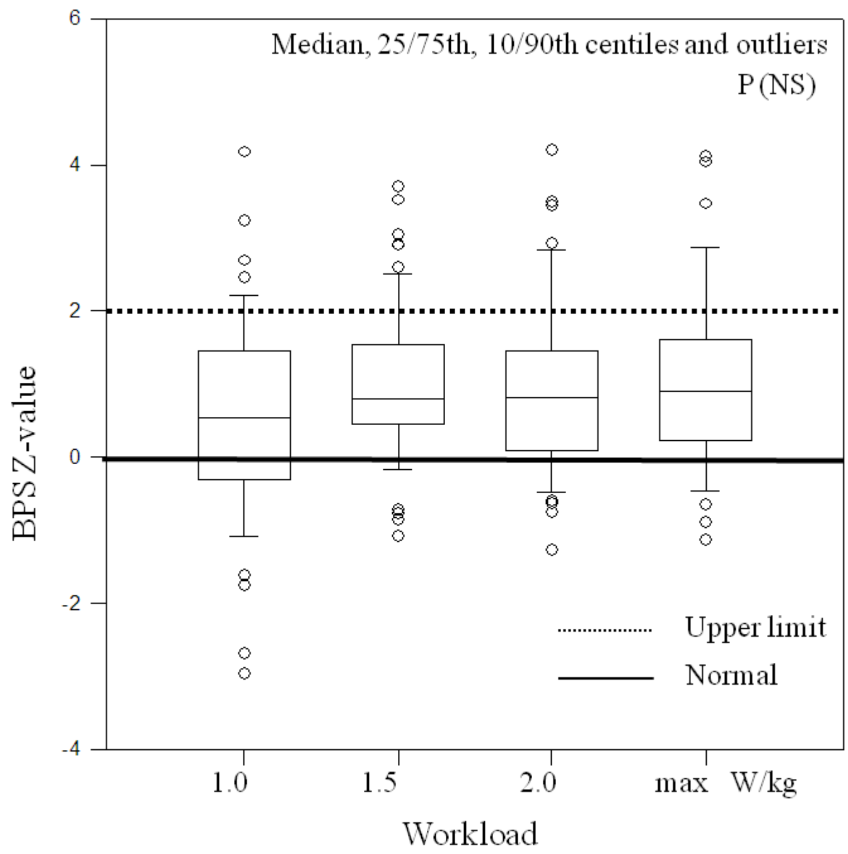

Figure 3: Systolic blood pressure Z-scores during increasing workload (second cross-sectional evaluation). BPS – systolic blood pressure.

Statistical analysis

Whenever appropriate data were expressed as Z-scores and pathologic limits were defined as those exceeding 2 Z. Sigma Plot for Windows Version 12·0 (Systat Software Inc., San Jose, California, USA) was used for statistical analysis. Continuous variables were expressed as mean (standard deviation, SD) or median (inter-quartile range, IQR) as appropriate according to the data distribution pattern. An unpaired t-test or the Mann-Whitney rank sum test was used for comparison of two different patient groups. Paired t-test or paired sample Wilcoxon signed rank sum test was used for intra-patients comparisons of continuous variables. Differences between proportions were evaluated by the Chi-square test. Relationship between two continuous variables was assessed by linear regression. The prognostic value of independent variables showing significant univariate correlation with VO_2 max was assessed by multiple logistic regressions. In case of highly correlated independent variables only the variable with a stronger univariate correlation was entered into the model. P values <0.05 were considered significant.

Results

Demographic and anamnestic data

Eighteen of the 87 patients had a complex TGA with various combinations of additional heart lesions (ventricular septal defect in

15, pulmonary stenosis in 5 and coarctation of the aorta in 1 patient). Two patients underwent an additional surgical procedure at 9.5 (resection of coarcation of the aorta) and 21.6 (tricuspid valve replacement) years after the Senning operation, respectively. None of the patients suffered from baffle obstruction during follow-up. Table 1 summarizes the demographic and anamnestic data at the time of the two cross-sectional evaluations performed in adolescence and early adulthood. A significant increase in the body mass index was noted. At the 2nd evaluation 18 (20.7%) patients exhibited overweight (BMI=25 - 29.9) and 7 (8.0%) obesity (BMI >30). The proportion of patients on cardiovascular drugs increased, mainly due to higher prescription of angiotensin-converting-enzyme inhibitors. Three patients (3.4%) suffered from additional comorbidities potentially associated with the heart lesion: epilepsy, brachial artery and pulmonary artery thromboembolism in 1 patient each). Questionnaire data revealed favourable social status and frequent participation in recreational sports (Table 1).

	1st cross-sectional evaluation	2nd cross-sectional evaluation	P
N	87	87	-
Age at evaluation [years]	mean13.1 (3.3)	mean23.1 (3.5)	-
Time from surgery [years]	mean12.6 (3.3)	mean22.6 (3.4)	-
BMI	mean19.3 (3.6)	mean23.7 (4.7)	<0.001
NYHA class ≥ 2	22/85 (25.9%)	32/87 (36.8%)	NS
Cardiovascular drugs	10/87 (11.5%)	31/87 (36%)	<0.001
- ACE inhibitors	4 (4.6%)	24 (27.6%)	<0.001
- Beta-blockers	0 (0.0%)	3 (3.4%)	NS
- Digoxin	9 (10.3%)	6 (6.9%)	NS
- Antiarrhythmic	4 (4.6%)	5 (5.7%)	NS
Social status			
- Studying	NA	29 (33.3%)	-
- Employed	NA	56 (64.4%)	-
-Unemployed	NA	2 (2.3%)	-
-Disability pension	NA	1 (1.1%)	-
Participation in sports	NA	73 (83.9%)	-

Table 1: Demographic and anamnestic data. ACE: Angiotensin-Converting-Enzyme Inhibitor; BMI: Body Mass Index; NYHA: New York Heart Association Class; NA: Not Available.

Hemodynamic data

Table 2 summarizes the echocardiographic, radionuclide and magnetic resonance imaging evaluations. The reported patient group showed in general stable hemodynamic parameters. There was an increase in the proportion of patients with a visually observed decrease in RV function on echocardiography, which reached statistical significance. Quantitative measurement, however, did not confirm these findings and showed a stable RV ejection fraction being in normal range in about 80% of the patients during both evaluations. The number of patients showing at least moderate tricuspid regurgitation also did not increase over time.

Exercise data

In correspondence with the hemodynamic findings there was no significant worsening of exercise capacity (Table 3). On the contrary, a slight increase in maximum oxygen uptake was observed. Maximum exercise heart rates were uniformly decreased (Figure 2). The chronotropic incompetence, however, did not worsen over time. Systolic blood pressure was increased but still within normal limits in the majority of patients throughout the exercise (Figure 3). Risk factors for decreased exercise capacity at the second evaluation were analyzed and are summarized in Table 4. There was a univariate correlation between decreased maximum oxygen uptake and increased body mass index, higher systolic blood pressure at exercise, lower right (but not left) ventricular end-diastolic and end-systolic volumes, higher minute ventilation and higher minute ventilation/carbon dioxide production slope. None of the other parameters, specifically RV ejection fraction, degree of tricuspid regurgitation, heart rate at maximum exercise, tricuspid annular plane systolic excursion or the New York Heart Association class correlated with decreased VO_2 max. In the multivariable analysis decreased right ventricular end-diastolic volume and increased minute ventilation/carbon dioxide production slope were the only significant predictors of decreased VO_2 max, respectively.

	1st cross-sectional evaluation	2nd cross-sectional evaluation	P
RV dysfunction grade ≥ 2	11/85 (12.9%)	22/84 (26.2%)	=0.048
TAPSE [mm]	NA	median15 (13 – 17)	-
TR grade ≥ 2	13/87 (14.9%)	17/86 (19.8%)	NS
RV EDVi [ml/m² BSA]	NA	median83 (66 - 99)	-
RV ESVi [ml/m² BSA]	NA	median39 (30 - 47)	-
RV EF [%]	mean52 (8)*	mean53 (9)**	NS
Abnormal RV EF <47%	15/74 (20%)	13/71 (18%)	NS
LV EDVi [ml/m² BSA]	NA	median60 (52 - 71)	-
LV ESVi [ml/m² BSA]	NA	median36 (30 - 42)	-
LV EF [%]	NA	median61 (55 - 66)	-
Abnormal LV EF <55%	NA	7/71 (9.9%)	-

Table 2: Hemodynamic data. BSA: Body Surface Area; EDVi: End-Diastolic Volume Index; ESVi: End Systolic Volume Index; LV: Left Ventricle; NA: Not Available; RV: Right Ventricle; RVEF: Ejection Fraction of Right Ventricle; TAPSE: Tricuspid Annular Plane Systolic Excursion; TR: Tricuspid Regurgitation; *RNACG: Radionuclide Angiocardiography; **MRI: Magnetic Resonance Imaging.

Arrhythmias

There was an insignificant increase in the number of patients with implanted pacemakers and on antiarrhythmic drug treatment, respectively (Table 5). Pacemakers were implanted due to sinus node dysfunction and atrioventricular block in 6/1 patients, respectively. One patient received a primary preventive implantable cardioverterdefibrillator for non-sustained ventricular tachycardia. Antiarrhythmic drugs were used for the following symptomatic tachyarrhythmias at the 1st/2nd evaluation: atrial flutter (3/3 patients) and supraventricular tachycardia (1/2 patients). Two patients underwent a successful radiofrequency catheter ablation of intraatrial reentrant tachycardia. There was an increase in the number of patients with resting junctional rhythm between the first and second evaluation. The progression of bradycardia was, however, clinically negligible if comparing the minimum and mean heart rates and maximum RR intervals as derived from 24-hour Holter recordings (Table 5).

Discussion

Due to complete change in surgical strategy decades ago patients after the atrial baffle procedure for transposition of great arteries represent a non-increasing population offering the possibility to study long-term sequelae of systemic right ventricular circulation. Our study focused on longitudinal follow-up of this specific patient group and revealed a picture of well-preserved systemic RV function in the majority, decreased but not worsening exercise tolerance and favourable social status. The number of arrhythmias requiring treatment was low and chronotropic competence did not worsen over time. This is in line with other reports showing rather favourable results in long-term survivors [13-16].

It has been well documented that patients after the Senning procedure have subnormal exercise capacity [9,17,18]. Decrease in exercise capacity has been attributed to a variety of factors including impaired ventricular filling [19], decrease in RV systolic function with inadequate increase in stroke volume during exercise due to missing force-frequency relationship[17,18,20], decreased myocardial perfusion reserve and chronotropic incompetence [21-23]. In our study, ~50% of patients presented with significantly decreased exercise tolerance at both the 1st and 2nd cross-sectional evaluation. We could not confirm; however, a decrease in individual exercise capacity over time as reported elsewhere [9]. Actually, there was a slight but significant improvement. This may have been caused by overprotective parents prohibiting sport activity of their children while in adulthood this restriction disappeared [24].

Limited exercise capacity is crucial for prognosis. Subjects with a decreased maximum oxygen consumption and increased minute ventilation/carbon dioxide production (eVE/VCO_2) slope were shown to have a substantially higher 4-year risk of a combined endpoint of death or cardiac related emergency hospital admission after the atrial switch operation [5]. Peak oxygen uptake during exercise stress testing also carries a prognostic value in adults with heart failure related to acquire heart disease [7]. The role of ventilatory efficiency is an even stronger prognostic marker in patients with heart failure [8,25,26]. In our patients, the eVE/VCO_2 slope was a significant predictor of decreased exercise capacity. Ventilation inefficiency thus seems to be an important factor pointing towards the importance of targeted respiratory rehabilitation in this patient group.

	1st cross-sectional evaluation	2nd cross-sectional evaluation	P
Maximum HR [Z-score]	median -1.43 (-2.32 - -0.58)	median -1.54 (-3.07 - -0.17)	NS
VO_2 max [Z-score]	mean -2.05 (1.09)	mean -1.74 (0.88)	0.034
VO_2 max Z-score < -2Z	37/68 (54.4%)	33/67 (49.3%)	NS
Pulse oxygen at 1.5 W/kg [Z-score]	NA	median -0.84* (-1.79 – 0.11)	-
Pulse oxygen at maximum exercise [Z-score]	median -1.27 (-2.15 – -0.51)	median -1.31* (-2.19 – -0.63)	NS
Arterial systolic hypertension at rest	NA	9/87 (10.3%)	-
Arterial systolic hypertension at 1.5 W/kg	NA	9/79 (11.4%)	-

Table 3: Exercise stress testing data, HR: Heart Rate; VO_2 max: Maximum Oxygen Uptake. *P <0.001 by paired t-test.

The influence of RV end-diastolic volume index on maximum oxygen uptake is a surprising finding without a simple explanation. Volume deprivation is regarded to be one of the significant factors negatively influencing hemodynamic performance after the Senning operation. Stiffness of the systemic venous pathway has been described to progressively affect left ventricular filling [19,27]. Lower RV end-diastolic volumes may be a reflection of this diastolic derangement although no correlation could be found between the right and left ventricular volumes in this study. Larger right ventricles may also better adapt to increased workload in the presence of disturbed force-frequency relationship of the RV myocardium. Interestingly, decreased exercise capacity could not be predicted by any other measured hemodynamic variable (specifically RV systolic function and tricuspid regurgitation grade) confirming a weak relationship between objective RV functional findings and exercise tolerance. Unlike other available studies [9,17,28] we have assessed ventricular function more precisely including magnetic resonance imaging and used it for correlation with maximum oxygen uptake.

In contrast to other reports [18,29] we also have not seen any correlation between chronotropic competence and exercise tolerance. The heart rate adaptation during exercise was maintained until a workload of 2 W/kg body weight and showed a significant decrease at maximum exercise without any difference between patients with normal and decreased maximum oxygen uptake. Thus chronotropic incompetence was not responsible for diminished exercise capacity in our study group. There was, however, a striking decrease in pulse oxygen between medium and maximum exercise levels pointing towards the inability to increase stroke volume adequately. The reason may lie in a missing force frequency relationship of the systemic right ventricle, limited ventricular filling or both.

	VO_2 max.				
Parameter	≥ -2 z (N=34)	<-2 z (N=33)	P univariate	P multi-variable	OR

					(CI)
BMI	median22 (20-23)	median25 (21-29)	0.012	NS	1.223 (0.911 - 1.642)
Complex TGA [%]	14.7	27.3	NS	-	-
RV dysfunction grade ≥ 2 [%]	18.2	21.9	NS	-	-
TAPSE [mm]	median16 (12 - 17)	median15 (12 - 17)	NS	-	-
TR grade ≥ 2 [%]	14.7	21.2	NS	-	-
RV EF [%]	mean54 (7)	mean56 (7)	NS	-	-
RVEDVi [ml/m^2 BSA]	median90 (71 -109)	median75 (58 - 92)	0.016	0.039	0.963 (0.930 - 0.998)
RVESVi [ml/m^2 BSA]	median43 (37 - 54)	median34 (26 - 46)	0.016	-	-
LV EF (%)	median62 (54 - 67)	median61 (57 - 65)	NS	-	-
LVEDVi [ml/m^2 BSA]	mean60 (13)	mean60 (13)	NS	-	-
LVESVi [ml/m^2 BSA]	median35 (30 - 43)	median36 (30 - 41)	NS	-	-
Maximum HR [Z-score]	mean-1.74 (1.87)	mean-1.75 (1.77)	NS	-	-
Minute ventilation at 1.5 W/kg [ml/kg]	mean44 (11)	mean52 (12)	=0.006	NS	1.002 (0.901 - 1.115)
eVE/VCO2 at 1.5 W/kg	mean29.9 (4.6)	mean32.7 (3.7)	=0.014	0.040	1.293 (1.012 - 1.651)
Systolic blood pressure at rest [Z-score]	median0.54 (-0.34 - 1.46)	median0.54 (-0.12 - 1.41)	NS	-	-
Systolic blood pressure at 1.5 W/kg load [Z-score]	median0.30 (-0.23 - 1.30)	median1.06 (0.09 - 1.87)	=0.036	NS	2.212 (0.993 - 4.93)

Table 4: Risk factors for decreased exercise capacity at 2nd cross-sectional evaluation, eVE/VCO_2 – minute ventilation/carbon dioxide production, for other abbreviations see Tables 1 – 3.

Study Limitations

The study has several limitations. First, the study evaluates long-term survivors of the Senning operation. Patients with poor hemodynamics were likely to have died or undergo heart transplantation prior to inclusion. The attrition rate between the first and second evaluation was, however, low as displayed in Figure 1 being in favor of a generally stable Senning population in the majority. Some demographic, hemodynamic and functional parameters were not available at the 1st evaluation. RV function was measured by two different methods (radionuclide ventriculography and MRI, respectively) making the intra-patient comparison between the 1st and 2nd evaluation potentially inaccurate. Also, data on maximum oxygen consumption were not available in all subjects due to the fact that some patients were not able to achieve maximum exercise levels. Nonetheless, we believe that these limitations do not significantly weaken the main conclusions of this study.

	1st cross-sectional evaluation	2nd cross-sectional evaluation	P
Implanted pacemaker	4 (4.6%)	8 (9.2%)	NS
Resting sinus rhythm	61 (70.1%)	55 (63.2%)	NS
Resting junctional rhythm	2 (2.3%)	13 (14.9%)	0.006
Sinus and junctional rhythm	16 (18.4%)	8 (9.2%)	NS
Ectopic atrial rhythm	4 (4.6%)	5 (5.7%)	NS

Paced rhythm	4 (4.6%)	6 (6.9%)	NS
minimum HR* [BPM]	median 40 (37.8 - 44)	median 38.5 (35.3 – 42.0)	<0.001
mean HR* mean [BPM]	mean 68.5 (9.2)	mean 66.3 (9.3)	NS
maximum RR interval* [s]	median 1.64 (1.50 – 1.80)	median 1.70 (1.53 – 1.99)	NS

Table 5: Heart rhythm at first and second evaluation. Data are derived from resting 12-lead ECGs and 24-hour Holter recordings (*), respectively. BPM: Beats Per Minute; HR: Heart Rate.

Conclusions

Long-term survivors of the Senning operation have stable hemodynamics and exercise capacity on longitudinal follow-up. Decreased exercise tolerance is found in approximately half of the patients and is significantly associated with lower ventilation efficiency. This data may point to the usefulness of targeted respiratory rehabilitation in this patient group.

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Contributors: All authors meet uniform requirements of the Journal of Clinical & Experimental Cardiology criteria for authorship. All authors critically revised the manuscript and approved the final version of the paper.

This study complies with the Declaration of Helsinki, that the locally appointed ethics committee has approved the research protocol and that informed consent has been obtained from the subjects.

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