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ORIGINAL ARTICLE

WILEY Congenital Heart Disease

The long-term functional outcome in Mustard patients study: Another decade of follow-up

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Abstract

Objective: For over 20 years, we have followed a cohort of patients who underwent the Mustard procedure for d-transposition of the great arteries. The current study follows the same cohort from our last study in 2007 to reassess their functional capacity and quality of life.

Participants: Of the original 45 patients, six patients have required cardiac transplant and 10 patients have died, including two of the transplanted patients. Twenty-five of the remaining patients agreed to participate in this current study.

Design: Patients underwent comparable testing to the previous studies when possible including exercise stress testing, echocardiography, MRI or CT evaluation of cardiac anatomy and function, Holter monitor, and quality of life questionnaire.

Results: Thirty-one percent of patients have experienced cardiac death either in the form of mortality or cardiac transplantation. The major cause of death was systemic right ventricular failure. Sixty-five percent have continuing abnormalities of rhythm. Exercise time and workload showed a statistically significant decrease from the original study (Time 1) to both 10-year (Time 2) and 20-year (Time 3) follow-up points. Right ventricular ejection fraction decreased significantly from the Time 1 to Time 2, and again to this current follow-up. Quality of life measures of energy level decreased significantly from the original study to both the Time 2 and Time 3.

Conclusion: Cardiac mortality for Mustard patients remains high, and over time, systemic right ventricular ejection fraction, rhythm, exercise tolerance, and quality of life assessments show deterioration. There does not appear to be a single clear predictor of poor outcome.

KEYWORDS
adult congenital heart disease, cardiac diseases, d-transposition of the great arteries, Mustard procedure

1 | INTRODUCTION

Until the mainstream introduction of the arterial switch in the mid-1980s, almost all children with d-transposition of the great arteries (DTGA) underwent atrial baffle operations, such as the Mustard and Senning procedures (Figure S1). Although these procedures for DTGA have been largely replaced by the arterial switch operation, cardiologists continue to care for a now-adult population of patients with Mustard physiology. The atrial baffle operations are also still currently used for another group of patients with l-transposition of

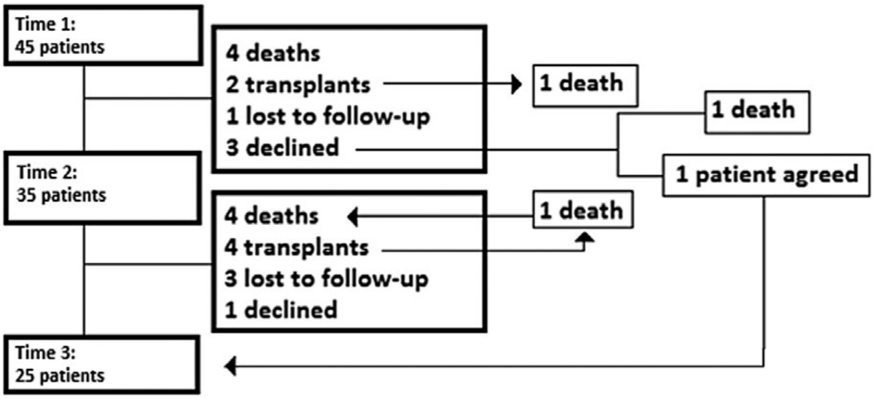

FIGURE 1 Summary of cohort patients across three study time points over 20 years

the great arteries (LTGA) as part of the "double switch" operation. As more atrial baffle survivors travel through adulthood, there is an increasing need to understand long-term outcomes and complications in order to optimize management strategies to improve longevity and quality of life.

For over 20 years, we have followed a cohort of patients who had undergone the Mustard procedure to assess their functional potential. We have previously reported a 13% cardiac mortality during the second and third decades of life in this cohort of patients, and found that despite continuing deterioration in exercise performance, right ventricular function, and cardiac rhythm, many of these patients continued to lead normal lives into the fourth decade.[1,2]

The current study follows the same cohort group 10 years since our last study to reassess their functional capacity and quality of life.

2 | METHODS

2.1 | Patient population

In 1993, all patients who had undergone the Mustard operation for DTGA between 1970 and 1986 at Riley Hospital for Children at Indiana University Health were identified. Of these patients, 45 patients were chose to participate in the original cohort group (Time 1) and underwent data collection from August 1993 to July 1997.[1] Thirty-five of the 45 agreed to participate approximately 10 years later (Time 2).[2] For the current study, we again recruited from this cohort to undergo testing from June 2013 to March 2017 (Time 3). Of the patients who had participated at Time 2, four patients had died, four patients had received cardiac transplantation (including one patient who subsequently died), and four were either lost to follow-up or declined to participate, leaving 24. The authors also attempted to contact participants of the original study who had declined to participate at Time 2: one patient had died and one patient could not be located for follow-up information. One patient who declined to participate in the first follow-up agreed to participate in this current study, bringing the total number of participants for this study to 25. This cohort of participants is summarized in Figure 1 and Table 1. The current study, and the previous studies, have all been approved by the Institutional Review Board of Indiana University.

2.2 | Patient testing

The patients completed testing between June 2013 and March 2017. Patients underwent comparable testing to the previous studies when possible, including a standard Bruce protocol treadmill cardiopulmonary exercise stress test (CPET) with metabolic measurements, echocardiography, Holter monitor with rhythm history, and quality of life questionnaire (Table 2). Instead of radionuclide angiocardiography as in the original study, patients underwent either cardiac MRI or cardiac CT, per current standard of care, for cardiac function and anatomy. Right ventricular systolic function by echo was visually estimated by echocardiographers blinded to the results of the study. The Rand SF-36 Item Health Survey (SF-36) was used to score quality of life.[3] Six health concept scores were again evaluated: physical functioning, role limitation from physical problems, energy level, social functional, bodily pain, and general health. Of note, only four of these six categories were available at Time 1 during the original study.[1]

2.3 | Statistical analysis

Repeated measures ANOVA was used to test for differences over time in SF-36 subscale scores, exercise stress tests, and ejection fractions. Cochran-Mantel-Haenszel chi-square tests for stratified data were used to test for changes over time in rhythm and function. Patients with and without a pacemaker were compared for differences in RVEF and LVEF using two-sample *t* tests. A 5% significance level was used for all tests.

3 | RESULTS

3.1 | Mortality

In total, 10 of 45 patients (22%) died at some point between the original study at Time 1, and the current study at Time 3. Four patients, or 9% of the original cohort, died between Time 1 and Time 2, and six patients, or 13%, of the original cohort, died between Time 2 and Time 3. Two patients had undergone a transplant and subsequently died as a result of complications related to rejection; one of these patients had been excluded at Time 2 and the other had

TABLE 1 Characteristics of patients meeting inclusion criteria

Study group	Total participants	Age at time of study	Years from operation	Exclusions
Time 1: Original cohort	45 31 = M 14 = F	13.1 ± 3.8 (11-30)	14 ± 3.9 years	
Time 2: 10-year follow-up	35 23 = M 12 = F	25.4 ± 4.3 years (19-37 years)	24 ± 3.9 years	4 deaths 2 cardiac transplant 1 lost to follow-up 3 declined
Time 3: 20-year follow-up	25 16 = M 9 = F	36.7 ± 4.9 (29-49)	34.3 ± 3.9 years	4 deaths[a] 4 cardiac transplant[a] 3 lost to follow-up 1 declined

Abbreviations: M = male; F = female.
[a]One patient died after transplantation, counted here in both categories.

TABLE 2 Current study testing participants

Testing	Number of participants	Reasons for exclusion
Holter monitor	23	Monitor returned without any data
Treadmill cardiopulmonary exercise test	14	Deep vein thrombosis, chronic pain, orthopedic contraindication, did not present for testing, patient declined
MRI/CT	18	Severe allergy to contrast dye, patient declined, patient claustrophobia, orthopedic contraindication
Echocardiography	21	Patient declined or did not present for testing
Quality of life survey	21	Patients did not return questionnaire

declined to participate. These patients are counted as both a post-Mustard transplant and a mortality, but not double counted toward cardiac death statistics. Therefore, a total of six patients underwent cardiac transplantation, including two prior to, and four patients since, Time 2. All told, 14 patients from the original cohort of 45 (31%) experienced cardiac death, either in the form of a mortality or cardiac transplantation or both (Table 3). Although most of the mortalities are male, due to the small sample size, there was no statistically significant difference in mortality or transplant based on gender ($P = .17$).

3.2 | Cardiac rhythm

Rhythm data was obtained on 23 patients. Of these patients, 15 (65%) have continuing abnormalities of rhythm. Seven of the 23 patients (30%) have undergone pacemaker placement either for sick sinus syndrome or complete heart block; only one of these devices was placed in the 10 years since Time 2. Five of the 23 (22%) have undergone cardioversion, including three patients that were previously identified at Time 2. Five of the 23 patients (22%) underwent an electrophysiology (EP) study for either supraventricular tachycardia or ventricular tachycardia. Statistically significant increases were found in the number of patients undergoing EP studies from Time 1 to Time 3 ($P = .046$), and from Time 2 to Time 3 ($P = .046$). Other findings on Holter monitoring included first degree atrioventricular block ($n = 4$), junctional rhythm ($n = 4$), interventricular conduction delay ($n = 3$), supraventricular ectopy ($n = 11$), and ventricular ectopy ($n = 9$). Two patients had runs of supraventricular tachycardia, one of whom also had a brief run of ventricular tachycardia. The number of patients with abnormal rhythm and need for cardioversion increased and trended toward significance but did not attain statistical significance due to the small sample size. These findings are summarized in Figure 2.

3.3 | Exercise stress testing

Exercise time and workload in METS showed a statistically significant decrease from Time 1 to both Time 2 and Time 3, but the decreases

TABLE 3 Cumulative mortality and cardiac transplantation of the entire cohort

Patient	Gender	Death/transplant	Age (years)	Reason/cause
4	**M**	**Transplant**	**26**	**Acute biventricular heart failure/ acute cellular rejection**
		Death	**29**	
6	F	Death	19	Sudden chest pain/syncope
8	**M**	**Death**	**31**	**Unknown**
16	F	Transplant	16	Right ventricular failure
		Death	29	Coronary artery disease due to transplant vasculopathy
19	M	Death	24	Right ventricular failure/atrial flutter
22	**M**	**Death**	**37**	**Unexpected, unknown**
25	M	Death	23	Pulmonary hypertension
28	**M**	**Death**	**26**	**Congestive heart failure**
31	M	Death	17	Right ventricular failure
32	**M**	**Transplant**	**45**	**Right ventricular failure**
33	**M**	**Death**	**27**	**Pulmonary hypertension**
34	**M**	**Transplant**	**38**	**Right ventricular failure**
43	M	Transplant	19	Chest pain/ischemia
44	**M**	**Transplant**	**33**	**Right ventricular failure**

Note: Patients in bold reflect data since the second study (Time 2).

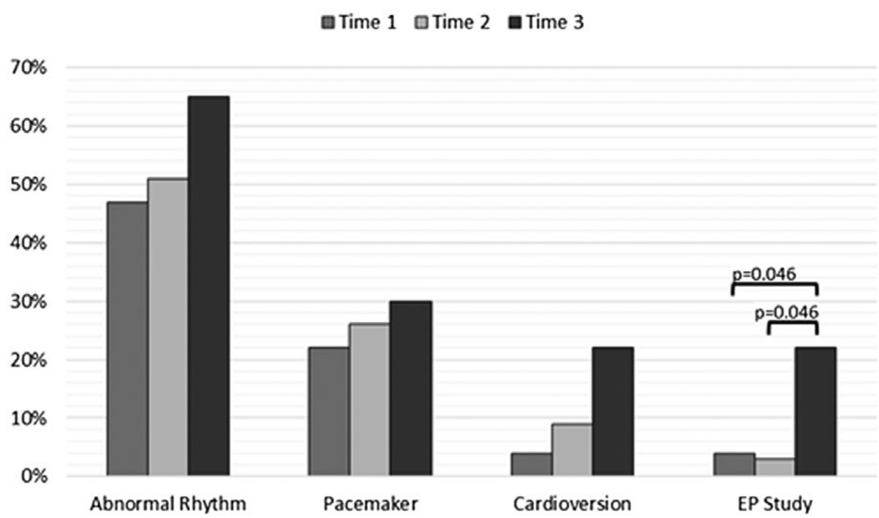

FIGURE 2 Rhythm abnormalities in Mustard cohort across the three time points

in exercise time and workload between Time 2 and Time 3 were not significant. These findings are summarized in Figure 3A. Average exercise time dropped significantly from 11.2 minutes (±2.1) at Time 1 to 9.1 minutes (±2.9 minutes) at Time 2 (P = .001), but only to 8.9 minutes (±3.8) at Time 3 (P = .77). The overall workload decreased significantly from 12.3 METS (±1.9) at Time 1 to 7.4 METS (±2.9) at Time 2 (P < .001), but only to 7.3 METS (±1.8) at Time 3 (P = .91). Average peak oxygen consumption (peak VO_2) for this group decreased from 28 (±6.7) mL/kg/min in the previous study Time 2 to 23.6 (±7.8) mL/kg/min in the current study. Although trending toward significance, this decrease was not statistically significant (P = .062). Peak VO_2 data were not available at the time of the original study.

There was a downward trend in maximum achieved heart rate, as one would expect, over the 20-year follow-up time, from 174.4 bpm (±20.6) at Time 1, to 166.6 bpm (±24.7) at Time 2, to 152.3 bpm (±38.4) at Time 3. When correcting for age, there were no significant differences between the percent predicted maximal heart rates between studies, fluctuating between 85.1% (±9.6%, P = .33) at Time 1, 88.7% (±12.5%, P = .111) at Time 2, and 79.7% at Time 3 (Figure 3B). All three groups attained lower heart rates than would be expected for a healthy cohort.

3.4 | Cardiac function

Right and left ventricular ejection fraction (RVEF and LVEF, respectively) data were obtained in a large subset of the cohort. The original study at Time 1 included data on 44 patients, all of whom had ejection fractions measured with radionuclide angiocardiography. Thirty-four patients at

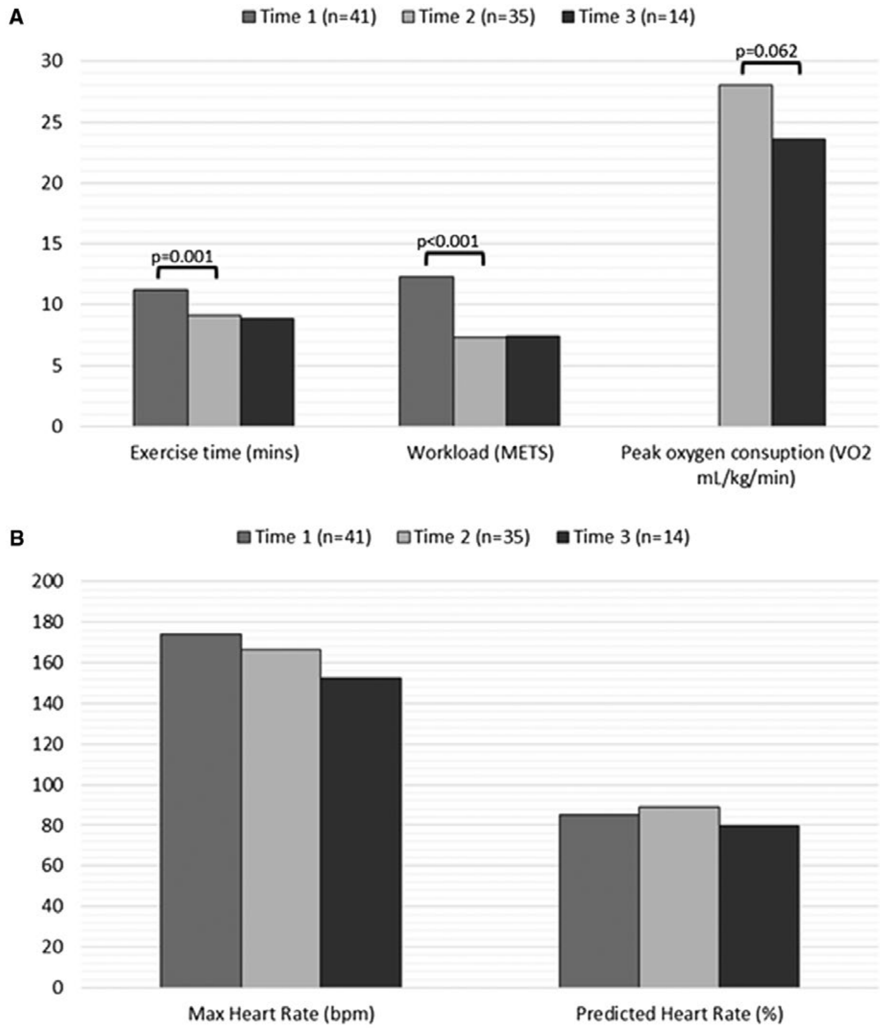

FIGURE 3 A and B, Summary of exercise stress test findings

Time 2 and 18 patients in the current study were evaluated with cardiac MRI or cardiac CT. These values were compared with the previously obtained RVEF data from the nuclear medicine studies. These newer modalities have been shown to be equally as accurate as nuclear studies with good correlation and are now the standard of care for complex cardiac disease.[4,5] These data were compared to the previous data of the same patients. RVEF decreased significantly to 45% (±11%) in this current study from 54% (±10%) at Time 1 (P = .003) and from 53% (±10%) at Time 2 (P = .011). There was no statistically significant LVEF change. LVEF was 62% (±8%) in this current group as compared with 61% (±11%, P = .673) at Time 1 and 62% (±8%, P = .868) at Time 2.

Subjective estimation of right ventricular function was obtained by echocardiography in 21 patients. These data were compared to the previous data of the same 21 patients over all three study time periods. Three patients (14%) of this current study were classified as having normal appearing right ventricular systolic function. Twenty-nine percent and 26% of these patients had a normal EF at the Time 1 and Time 2, respectively. Fifty-seven percent of patients had mild or mild-moderately decreased function. This number compares with 39% and 50% who had mild or mild-moderately decreased function at Time 1 and Time 2, respectively. Approximately 29% of participants in this current follow-up have moderate or moderate-to-severely decreased right ventricular systolic function. Thirty-two percent had moderate or moderate-to-severely diminished function at Time 1, which improved to 24% at the Time 2. Of note, statistical analysis of this current cohort of 21 did not find a statistically significant change in subjective echocardiography derived right ventricular function over time as compared with overall study data of all participants at the other time points.

3.5 | Anatomy

Anatomic data was obtained on 21 of the participants using echocardiography and radiographic imaging with cardiac MRI or CT when possible. Cardiac CT was the preferred radiographic modality for patients with a pacemaker (n = 7) while the remaining patients were referred for cardiac MRI. Fifteen of these patients (71%) had patent systemic and pulmonary venous baffles, including 1 who had previously undergone systemic venous baffle stent placement. Three patients (14%) had mild SVC venous baffle obstruction and three patients (14%) had significant or severe SVC baffle obstruction, including one patient who had previous stent placement in the IVC. All six of these patients had unobstructed baffles during the previous study. At Time 2, there were five patients (14%) with mild-to-moderate systemic venous baffle obstructions. None of these patients were in the death or transplant groups, but one patient declined to participate in this study, and one patient was lost to follow-up. One of the patients required a Mustard baffle repair and the other two appeared to have normalized at the time of this study without any intervention.

One patient had mild systemic venous baffle obstruction and also had mild pulmonary venous baffle obstruction. This finding was stable from testing at Time 2, and both sets of baffles had been patent at Time 1. This patient represents the only patient with both systemic and pulmonary venous baffle obstruction in this study as well as the previous study.

No patients in the current study had only pulmonary venous baffle obstruction without systemic venous baffle obstruction. We previously reported two patients (4%) with mild and one patient with severe pulmonary baffle obstruction Time 1.[1] The patient with severe pulmonary baffle obstruction had a surgical repair, showed patent baffles at Time 2, and ultimately received a transplant and died of acute cellular rejection. The other patient with mild pulmonary venous baffle obstruction at Time 1 had patent pulmonary venous baffles at both Time 2 and Time 3 follow-up. There were an additional three patients with mild pulmonary venous baffle obstruction identified at Time 2. Of these patients, one did not repeat imaging, one was lost to follow-up, and one underwent cardiac transplantation. No patients at Time 3 demonstrated any signs of pulmonary hypertension by imaging.

3.6 | Quality of life

Energy decreased significantly from Time 1 to both Time 2 ($P = .025$) and Time 3 ($P = .011$). Although there were numerical trends downward in Social Functioning ($P = .165$), Pain ($P = .745$), and General Health ($P = .067$), these did not attain statistical significance (Figure 4). The current Mustard cohort showed lower scores in all concept areas as compared with healthy adult norms, with statistically significant differences in general health, physical function, and energy ($P < .05$). They also had comparable or lower scores in all areas as compared to other adult patients with acyanotic congenital heart disease, with statistically significant differences in general health and energy ($P < .05$).[6]

Survey data also revealed that 19 patients (90%) had completed high school education or equivalent. Of these, 12 (57%) also reported completing college or vocational school. Ten patients (48%) were working full time, with another four patients (19%) working part time. One patient (5%) was actively seeking work. Five patients (24%) reported that they were unemployed due to disability.

3.7 | Correlation and prediction

General health, RVEF, LVEF, exercise time, and need for pacemaker placement were compared with one another to assess for correlation across all three data points in order to determine predictors of poor quality of life or poor outcome. General health and RVEF correlated only at Time 1 ($P = .02$) and not at the other points in time. There was no statistically significant correlation at the Time 2 or 3 follow-up studies. General health and exercise time were correlated at the first two time points, with a weak trend toward significance at the third study ($P = .047$, .019, .066). Although the correlation at Time 3 did not reach statistical significance due to the small sample size, the correlation value was .50, indicating a moderate correlation during this study between general health and exercise time.

Patients with and without a pacemaker were compared for differences in RVEF and LVEF using two sample *t* tests. No significant differences were found for RVEF. Patients with a pacemaker had significantly lower LVEF than patients without a pacemaker at Time 1 ($P = .019$) and Time 3 ($P = .011$), but no difference was found at Time 2.

Exercise time, workload, and percent predicted peak VO_2 did not appear to be significantly different between patients with cardiac mortality and survivors. Most patients showed at least mildly diminished cardiac function. As a group, all patients who died or went to

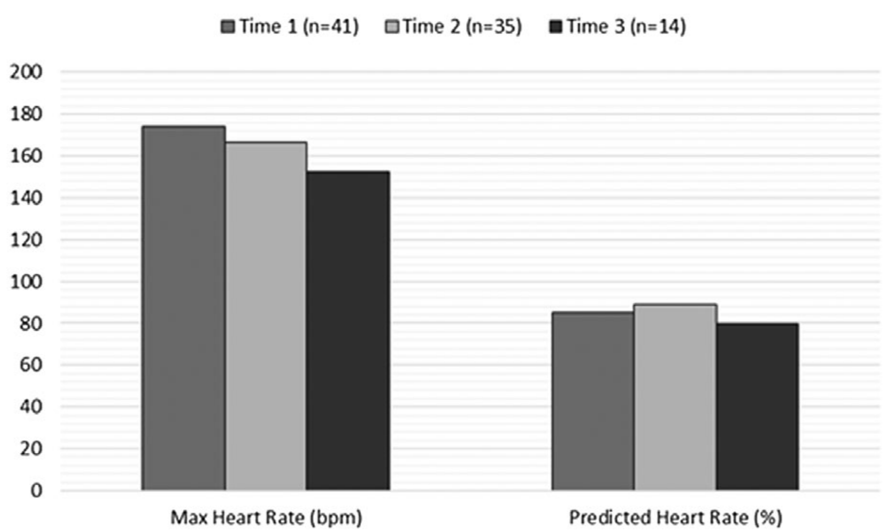

FIGURE 4 Quality of life average scores. A higher score is indicative of a better quality of life in each specific concept area. Social function and pain were not measured in the original study

transplant fell below the mean in all quality of life concept areas at Time 1, but did not show any specific area of underperformance.[7] Surprisingly, as a group, the patients who died or went to transplant after Time 2 had outperformed the group mean in nearly all quality of life concept areas and matched the mean in the Pain concept area.

In patients who died or went to transplant since Time 2, RV function ranged from mildly diminished (n = 4) to severely diminished (n = 1) at that time, making it difficult to predict outcome based solely on right ventricular function. Two patients had pacemakers, but no other rhythm issues had been identified by Holter monitoring. There was no history of cardioversion or EP study. All but one patient had average exercise time for the group. Interestingly, this patient was significantly below average in exercise time, maximum predicted heart rate, workload, and peak VO_2, however, this patient's right ventricular function was mildly diminished.

Of note, women participants had generally lower quality of life (QOL) scores in role limited and energy areas as well as lower exercise time, workload, and peak oxygen consumption. There was no difference between male and female participants in QOL areas of physical function, social function, pain; in general health; or in maximum and percent predicted heart rates.

4 | DISCUSSION

This study has followed a cohort of patients for over 20 years who underwent the Mustard procedure for DTGA. The patients range from 31 to 41 years from their initial surgery, offering an opportunity to assess long-term complications.

Of our original cohort of 45 patients, we have found that cardiac mortality (death or transplant) remains high, with an overall cardiac mortality of 31% (22% actual mortality, including two patients who died after transplant, and 13% cardiac transplantation), with just over half of the deaths and transplantations occurring after age 25 years. These data are comparable to other long-term studies of this patient population, which demonstrate survival rates approaching 76%-77% after 30 years.[8,9] Other studies have suggested that systemic RV failure and arrhythmia are the primary causes of mortality in Mustard patients.[9] The majority of deaths in our patient population are secondary to systemic right ventricular failure rather than sudden cardiac death. Right ventricular failure was also the primary reason for transplantation in our population. The systemic right ventricle is not only distinct from the LV on a cellular level, but often has intrinsic abnormalities of the tricuspid valve, and is vulnerable to abnormalities in electrical conduction and pressure or volume overload over time in adults with CHD and a systemic RV.[10] In our cohort, the systemic right ventricle showed significant decrease in function over time, although the LV function was maintained. This finding is consistent with other studies.[8]

The majority of participants (65%) in our study show some degree of rhythm dysfunction. Of the seven participants with pacemaker placement, only one had a pacemaker placed in the last 10 years, which could be suggestive that, aside from postoperative heart block, sick sinus syndrome issues will occur within the first two-to-three decades following the surgery and are less likely to occur further long term. It has been shown that late arrhythmia occurs in a relative minority of Mustard patients but can be a surrogate marker for ventricular dysfunction.[11] However in our population, the number of patients requiring an EP study showed statistically significant increases over time. Moreover, it is known that adults with congenital heart disease (ACHD) are at a higher risk of premature death from sudden cardiac arrest, with a higher risk in the population with transposition-type physiology after a Mustard-type procedure, thus highlighting the need for long-term rhythm surveillance.[12,13] Three patients in our cohort died of sudden or unexplained deaths with no documented arrhythmia history. It has been shown that among ACHD patients, those with TGA following atrial switch are among the highest risk for sudden cardiac death.[10] However, the indications for primary prevention with intracardiac cardioverter-defibrillators for Mustard patients is still uncertain, as the largest multicenter study to investigate this question only had 37 patients.[14] Known risk factors for sudden cardiac death in this patient population include older age, advanced RV failure or fibrosis, impaired LV function, precapillary pulmonary hypertension, widened QRS, VSD, and atrial tachycardias.[10,12] Exercise is a known risk factor as it may promote 1:1 conduction of malignant arrhythmias.[15]

Overall exercise capacity was found to diminish in this group of patients over the three time points in our study. Exercise time, peak heart rate, and workload showed significant decreases over time. Others have reported decreases in peak VO_2 as well as statistically lower peak VO_2 in Mustard patients as compared with arterial switch patients.[7,16-18] Fredricksen and colleagues also reported a non–statistically significant decrease in maximal oxygen uptake in Mustard patients ages 18-28 years.[16] In looking at patients with complex congenital heart disease, patients with Mustard procedures have been shown to perform lower than patients with repaired l-transposition of the great arteries and repaired tetralogy of Fallot, but were higher than patients who have had a Fontan procedure for single ventricle physiology.[16] A review of 27 studies showed that most patients subjectively reported normal exercise tolerance following the Mustard procedure but in fact had significant abnormalities as compared to normal subjects when undergoing CPET.[19] Exercise capacity may be affected by several factors, including impaired systemic ventricular function, chronotropic insufficiency, and overall level of conditioning.

In our original study, there was correlation of general health with the ejection fractions of both RV and LV; however, in the present study there was no correlation in patients' perception of general health with actual RVEF or LVEF. Participants' perceptions of their general health was correlated with exercise time at all time points reviewed in this study, although in this most recent study, the correlation did not reach a statistical significance due to the smaller study group size. North American adults with congenital heart disease have been shown to have a higher risk of psychosocial difficulties.[20] A previous study also suggested there may be underreporting of issues with self-reported data as compared with researcher-conducted interviews, which may inflate some of the quality of life questionnaire findings.[21] In a review of 31 studies, Fteropoulli and colleagues found that the quality of life of ACHD patients is compromised in the physical domain compared with the general population, but did not find a corresponding difference in the psychosocial and environmental or occupational categories.[22] Risk factors for worse quality of life in ACHD patients include female sex; lower exercise capacity; greater social impediments, such as poor social support, loneliness, or social anxiety; lack of employment or financial strain; and orthopedic problems.[20,21]

In conclusion, cardiac mortality for Mustard patients remains high, and over time, systemic RVEF, exercise tolerance, and quality of life assessments show deterioration. There does not appear to be a single clear predictor of poor outcome, although deteriorating RVEF is associated with mortality and cardiac transplantation. It is still a minority of patients who, after three to four decades after Mustard surgery, continue to have normal appearing cardiac function and normal rhythm. Interesting, patients who had not yet required a pacemaker after the initial follow-up were unlikely to require one over the latest 10-year interval; however, the small sample size makes this a hypothesis-forming observation rather than a suggestion that clinicians should stop routine rhythm monitoring in these patients. While overall health and other factors continue to deteriorate over time, and these patients are significantly less healthy than their acyanotic ACHD peers, some aspects, such as social functioning and pain, remain near to others with ACHD, allowing these patients to maintain relatively productive adult lives. Continued close monitoring of cardiac function, rhythm, and quality of life in these patients is warranted to manage deterioration in clinical status and quality of life over time.

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CONFLICTS OF INTEREST

The authors have no commercial or other conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS

Nayan T. Srivastava, MD, involved in drafting the article, data collection, and data interpretation.

Roger Hurwitz, MD, involved in concept/design and funding.

W. Aaron Kay, MD, performed data interpretation and approval of the article.

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Alisha Kuhlenhoelter, MS, EP-C, performed data collection.

Nicole DeGrave, MS, performed data collection.

Eric S. Ebenroth, MD, involved in concept/design, data analysis/interpretation, drafting the article, funding, and approval of the article.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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