Heart Failure and Ventricular Dysfunction in Patients With Single or Systemic Right Ventricles

Sanaz Piran, BSc; Gruschen Veldtman, MD; Samuel Siu, MD; Gary D. Webb, MD; Peter P. Liu, MD

Background—Previous studies suggested a high incidence of congestive heart failure in patients with single and/or systemic right ventricles. The corresponding risk in an adult population is unknown.

Methods and Results—A cohort of 188 consecutive adult patients with single or systemic right ventricles was prospectively assessed with gated radionuclide angiography (n=135) or 2D echocardiography (n=188) and followed up clinically. Clinical assessment showed 82.4% of the patients were in New York Heart Association class I or II, 13.3% were in class III, and 4.3% were in class IV. Heart failure occurred in 22.2% of patients with transposition of the great arteries and a Mustard procedure, 32.3% of patients with congenitally corrected transposition of the great arteries, and 40% of Fontan-palliated patients. Symptomatic patients had significantly lower anaerobic thresholds (10.3±2.8 versus 13.2±4.8 mL · kg⁻¹ · min⁻¹, P=0.006) and peak VO₂ (15.2±4.8 versus 20.3±6.8 mL · kg⁻¹ · min⁻¹, P<0.00029). Systemic ventricular ejection fraction in symptomatic versus asymptomatic patients at rest was 34.8±15.7% versus 46.7±13.4% (P=0.00001). Mortality was 47.1% among symptomatic patients and 5% among asymptomatic patients at 15.7 years of postoperative follow-up. Seven of 12 patients with potentially correctable surgical lesions died or persisted in heart failure despite surgery. Best predictors for mortality were New York Heart Association class, systemic ejection fraction, and age at operation.

Conclusions—Patients with single or systemic right ventricles have significant risk for heart failure accompanied by high mortality. This study suggests the importance of identifying this group of patients who are at risk for heart failure and considering strategies to preserve ventricular function. (Circulation. 2002;105:1189-1194.)

Key Words: heart failure ■ heart defects, congenital ■ follow-up studies ■ Fontan procedure ■ transposition of great vessels

With advances in surgical technique, cardioprotection, and preoperative care in recent decades, increasing numbers of patients with complex congenital heart disease are surviving to adulthood.¹ Many adult patients unfortunately will develop ventricular dysfunction that will evolve to symptomatic heart failure. Patients with single or systemic right ventricles are particularly at risk.² Numerous studies have confirmed the poor prognosis in patients who develop symptomatic heart failure secondary to acquired heart disease.³ Up to 50% may die within 5 years of diagnosis.³ In addition to symptomatic congestive heart failure, more patients have asymptomatic ventricular dysfunction with depressed ejection fraction⁴ or chamber dilation in the absence of symptoms. Asymptomatic ventricular dysfunction is common in acquired heart disease and may persist for prolonged time periods before the onset of symptoms.⁴ Intervention during this asymptomatic phase may improve prognosis in terms of heart failure symptoms, hospitalization, and mortality outcomes.

The purpose of the present study was to determine the frequency of heart failure in adult patients with single and/or systemic right ventricles, describe its evolution, and determine its risk factors. We also attempted to define differences between symptomatic and asymptomatic patients and related these to an age-matched normal control group.

Methods

Patients

One hundred eighty-eight consecutive patients (123 men) with single or systemic right ventricles who were referred to and regularly followed up at our center were identified from the University of Toronto Congenital Cardiac Center for Adults (UTCCCA) database. UTCCCA is a large regional center for adult patients with congenital heart disease, and has a close linkage with the Hospital for Sick Children in Toronto. Patients at the center undergo regularly scheduled prospective functional testing. The UTCCCA database was evaluated for patients with single or systemic right ventricles with the following inclusion criteria: age >18 years, patients who had Mustard operation for transposition of the great arteries (TGA), congenitally corrected transposition of the great arteries (ccTGA), or...
TABLE 1. CHF Data for Different Subgroups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mustard (n=90)</th>
<th>ccTGA (n=65)</th>
<th>Fontan (n=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of CHF, %</td>
<td>22</td>
<td>32.3</td>
<td>40</td>
</tr>
<tr>
<td>No. who died</td>
<td>9</td>
<td>16</td>
<td>6</td>
</tr>
<tr>
<td>No. who died of CHF</td>
<td>4</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>No. of symptomatic patients</td>
<td>19</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td>No. of asymptomatic patients</td>
<td>71</td>
<td>45</td>
<td>18</td>
</tr>
</tbody>
</table>

CHF indicates congestive heart failure.

TABLE 2. Symptomatic Versus Asymptomatic Patients: Operative and Chest X-Ray Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Symptomatic (n=51)</th>
<th>Asymptomatic (n=137)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex, %</td>
<td>54.9</td>
<td>59.9</td>
</tr>
<tr>
<td>Age, y</td>
<td>34.5±11.3</td>
<td>28.6±7.8</td>
</tr>
<tr>
<td>Height, cm</td>
<td>168.5±8.7</td>
<td>169.9±9.4</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>68.0±12.0</td>
<td>68.5±17.8</td>
</tr>
<tr>
<td>No. of surgeries</td>
<td>2.3±1.6</td>
<td>2.3±1.3</td>
</tr>
<tr>
<td>Age at 1st surgery*</td>
<td>15.9±14.3</td>
<td>8±10</td>
</tr>
<tr>
<td>Cardiotoracic ratio*</td>
<td>0.58±0.07</td>
<td>0.53±0.08</td>
</tr>
</tbody>
</table>

*Statistically significant.

Laboratory Testing in Follow-Up

Of the 188 patients, 135 patients had both RNA assessment of ventricular function and cardiopulmonary testing, whereas 17 had RNA only and 7 had cardiopulmonary testing only. The details of the testing procedures are outlined below.

Cardiopulmonary Exercise Testing

Graded exercise with an electrically braked cycle ergometer was performed in the upright position or semi-upright position for cardiopulmonary testing and RNA to assess cardiopulmonary performance as previously described by our group.5

Radionuclide Ventriculography

Before initial exercise testing, each patient received red blood cell labeling with 20 mCi of 99mTc pertechnetate by a standard modified procedure. Gated RNA (Apex 409 Elscint camera) was performed at rest in 3 views (anterior, lateral, and best septal view in vivo technique. Gated RNA (Apex 409 Elscint camera) was performed at rest in 3 views (anterior, lateral, and best septal view in vivo technique). This method was described previously by our group.5

Clinical Assessment During Follow-Up

Patients were classified according to their symptomatic status on the basis of the presence of orthopnea, paroxysmal nocturnal dyspnea, dyspnea on exertion, and peripheral edema. Patients were considered symptomatic if they had signs and symptoms of congestive heart failure as defined by Marantz et al.6 Effort-related dyspnea was graded according to the New York Heart Association functional classification.7 To determine the diagnosis of heart failure, the Framingham criteria were used, incorporating parameters of symptoms, physical findings, and laboratory tests.8 The only exception was the criterion of vital capacity <33% of predicted for age and sex, which was not available for all patients. For classification purposes, systemic ventricular dysfunction was defined as those with an echocardiographic ventricular function grade ≥2.

Echocardiography

All echocardiographic studies were performed within 1 year of cardiopulmonary studies and were reviewed by 2 experienced, unbiased echocardiographers for systemic ventricular function, pulmonary ventricular function, and AV valve regurgitation.5 The evaluation of ventricular function is based on expert visual assessment supplemented by objective measurements, including ventricular diameter and fractional shortening.

Data Analysis

Data were analyzed with Statistical Analysis Systems software (SAS Institute). We compared clinical parameters, such as exertional fatigue, cyanosis, and syncpe, using logistic regression analysis, and we used χ² tests for comparisons between the symptomatic and asymptomatic groups (Table 3). Laboratory testing variables, such as those from the cardiopulmonary and radionuclide tests (Table 4), were also compared between symptomatic and asymptomatic patients by ANOVA with Newman-Keuls post hoc subgroup testing. Measured data are presented as mean±SD unless otherwise indicated. A linear regression model was used to assess determinants of anaerobic threshold and peak V̇O₂ in the 3 clinical groups. If the variables were not normally distributed, the Mann-Whitney test was applied where appropriate. A P value of <0.05 was regarded as statistically significant.
Clinical Characteristics and Follow-Up

Of the 188 patients, 155 (82.4%) were in New York Heart Association functional class I or II, 25 (13.3%) were in functional class III, and 8 (4.3%) were in functional class IV (Figure 1). For the purpose of subsequent analysis, patients in functional class II or higher or those with 2 or more symptoms were classified as having heart failure symptoms (symptomatic group). Of the 188 patients, 31 died during follow-up (overall mortality rate of 16.5%), including 9 patients with TGA and a Mustard procedure, 16 with ccTGA, and 6 with Fontan palliation for univentricular physiology. Average age at death was 31.5 years (range 18 to 62 years), a mean of 15.7 years after the initial operation. The heart failure–related mortality rate was 32.7% in symptomatic patients and 0% in asymptomatic patients. The overall mortality rate in asymptomatic patients was 5% compared with 47.1% in the symptomatic group on subsequent follow-up. The clinical characteristics of the patients are shown in Table 2.

Exercise Capacity

The mean peak workload was significantly lower in the symptomatic group (491.2±272.8 kilopounds per minute [kpm]) than in the asymptomatic group (587.2±199.3 kpm), and both were significantly lower than in the control population (1094±190 kpm, P<0.0001; Figure 2). The symptomatic group reached a mean peak heart rate of 124.5±20.3 bpm, which was significantly lower than that reached by the asymptomatic group (146.7±29.6 bpm) or the healthy population (187±11 bpm; P<0.001). As shown in Figure 3, anaerobic threshold and VO2max were significantly lower in symptomatic patients than in the asymptomatic group and were significantly lower in both groups than in the control cohort. Anaerobic threshold was 10.3±2.8 mL·kg⁻¹·min⁻¹ in symptomatic patients, 13.2±4.9 mL·kg⁻¹·min⁻¹ in asymptomatic patients, and 23.6±4.6 mL·kg⁻¹·min⁻¹ in the control group (P<0.0003). Peak oxygen consumption was

### Table 4. Comparison Between Symptomatic and Asymptomatic Patients for Cardiopulmonary Study Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Symptomatic</th>
<th>Asymptomatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVEFe,* %</td>
<td>39.0±17.2</td>
<td>52.3±14.1</td>
</tr>
<tr>
<td>SVEFr,* %</td>
<td>44.2±17.1</td>
<td>53.4±13.6</td>
</tr>
<tr>
<td>PVEFr,* %</td>
<td>48.85±19.7</td>
<td>59.5±16.8</td>
</tr>
<tr>
<td>BPrest, mm Hg</td>
<td>112.4±15.1/27.5±16.3</td>
<td>117.1±19.9/71.6±12.3</td>
</tr>
<tr>
<td>BPepe, mm Hg</td>
<td>146.1±23.2/78.3±17</td>
<td>154.3±22.9/83.8±18</td>
</tr>
<tr>
<td>PeakVO2, mL·kg⁻¹·min⁻¹</td>
<td>15.2±4.8</td>
<td>20.3±6.8</td>
</tr>
<tr>
<td>PeakAT,* mL·kg⁻¹·min⁻¹</td>
<td>10.3±2.8</td>
<td>13.2±4.9</td>
</tr>
<tr>
<td>DyspInx, %</td>
<td>58.9±16.1</td>
<td>55.3±17.9</td>
</tr>
<tr>
<td>PeakWk,* kpm</td>
<td>491.2±272.8</td>
<td>587.2±199.3</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>73.3±14.3</td>
<td>75.7±18.3</td>
</tr>
<tr>
<td>PeakHR,* bpm</td>
<td>131.4±18.9</td>
<td>146.7±29.6</td>
</tr>
</tbody>
</table>

SVEFr and SVEFe indicate systemic ventricular ejection fraction at rest and during exercise, respectively; PVEFr and PVEFe, pulmonary ventricular ejection fraction at rest and during exercise, respectively; BPrest and BPepe, systolic and diastolic blood pressure at rest and during exercise, respectively; Peak VO2, peak oxygen uptake; AT, anaerobic threshold; DyspInx, dyspnea index; PeakWk, peak work; kpm, kilopounds per minute; HR, heart rate; and PeakHR, peak heart rate.

*Statistically significant.
15.2±4.8 mL · kg⁻¹ · min⁻¹ in symptomatic patients, 20.3±6.8 mL · kg⁻¹ · min⁻¹ in asymptomatic patients, and 42.1±10.0 mL · kg⁻¹ · min⁻¹ in the control population (P<0.0003).

**Ventricular Function**

Systemic ventricular ejection fractions at rest and during exercise are shown in Figure 4. In the symptomatic group, the mean systemic ventricular ejection fraction at rest was 34.8±16.0%, which was significantly less than in the asymptomatic group (46.7±13.4%; P<0.0001). Ejection fraction during exercise remained significantly lower in the symptomatic group than in the asymptomatic group (P<0.0001). For patients with a biventricular circulation, the mean pulmonary ventricular ejection fraction in the symptomatic group was 44.2±17.1%, which was significantly less than in the asymptomatic group (53.4±13.6%; P=0.004). Pulmonary ventricular ejection fraction during exercise also remained significantly lower in the symptomatic population than in the asymptomatic group (P=0.008). Table 5 provides an overview of the systemic ventricular function.

**Arrhythmias**

At last follow-up, 42 (82%) of the symptomatic patients and 71 (52.5%) of the asymptomatic patients had documentation of clinically significant arrhythmia (arrhythmia that lasted for at least 30 minutes or that caused important symptoms). All of the patients also had 24-hour ambulatory ECG monitoring. Sinus rhythm predominated in 68.6% of symptomatic patients and 76.6% of asymptomatic patients. Among symptomatic patients, 76.1% had a history of heart block compared with 52.1% of asymptomatic patients (Table 3). Fifty-eight percent of symptomatic patients and 23.9% of asymptomatic patients had a history of clinically significant tachyarrhythmia (atrial fibrillation, atrial flutter, or ventricular tachycardia).

Overall, 54 patients had pacemakers, and 106 had second-degree or complete heart block or sick sinus syndrome. Seventy-two percent of patients with frank heart failure had some degree of heart block, and 68% of those patients had a pacemaker. Of the patients who died with heart failure, 91% had arrhythmias or sick sinus syndrome, and 76% had second-degree heart block or higher, with 62% requiring a pacemaker.

**Systemic Ventricular Hypertrophy**

Left ventricular hypertrophy on an ECG is a potential risk factor in the evolution of systemic heart failure.9 Of the patients in the present study who had systemic right ventricles, 76.4% developed hypertrophy of the systemic ventricle as determined by ECG. According to Kannel et al,9 the risk of left ventricular heart failure is significantly associated with ECG parameters of ventricular hypertrophy. In the present study, 99% of patients with systemic right ventricular hypertrophy had developed some degree of systemic ventricular dysfunction as determined by echocardiography (grade 2 or higher; Table 5) or RNA (<2 SDs below normal).

**Heart Failure Frequency Analysis**

Using the modified Framingham criteria, we determined the frequency of documented heart failure in the symptomatic population (56.3%) versus the asymptomatic population (10%) as a whole. In addition, we analyzed the frequency of heart failure in the diagnostic subgroups outlined in Table 1. The mortality rate was 10% in the Mustard group, 25% in those with ccTGA, and 36% in the Fontan subgroup.

**TABLE 5. Systemic Right Ventricular Functional Classification Assessed by Echocardiography**

<table>
<thead>
<tr>
<th>Grade</th>
<th>2</th>
<th>2.5</th>
<th>3</th>
<th>3.5</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic</td>
<td>9%</td>
<td>9%</td>
<td>18%</td>
<td>21%</td>
<td>42%</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>19.6%</td>
<td>33%</td>
<td>36.6%</td>
<td>9.8%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Grade 2 indicates mild dysfunction (ejection fraction=40% to 59%); grade 3, moderate dysfunction (ejection fraction=20% to 39%); and grade 4, severe dysfunction (ejection fraction<20%).
Impact of Surgically Correctable Lesions
In this cohort, 12 patients were diagnosed as having potentially surgically correctable lesions that contributed to their heart failure (2 had baffle obstruction, 6 had AV valvular regurgitation, and 4 had conduit obstruction). Of these, 3 were successfully corrected with good outcome (2 baffle and 1 conduit obstruction), but 7 developed heart failure or died despite surgical correction, and 2 were deemed not operable owing to advanced heart failure.

Multivariate Risk Prediction Analysis
We analyzed the cardiopulmonary data for the possible differences between the symptomatic and asymptomatic subgroups of the Mustard patients, ccTGA patients, and Fontan patients. Using exercise capacity and mortality as potential primary end points, we modeled its determinants using stepwise multiple regression analysis with the following variables: sex, age at operation, time since operation, age at follow-up, symptomatic status, systemic ventricular ejection fraction at rest and during exercise, and peak heart rate or oxygen consumption where appropriate. For peak workload, the model revealed that female sex, age at operation, and age at follow-up were significant negative determinants. For peak oxygen consumption, the major predictors were peak heart rate and systemic ventricular ejection fraction. For anaerobic threshold, the major predictors were systemic ventricular ejection fraction both at rest and during exercise. Finally, for overall mortality, the best predictors from modeling were symptomatic status, systemic ejection fraction at rest, and age at operation.

Discussion
Summary of Results
The present study provides some insights into the evolution of heart failure based on 20 years of follow-up of these patients for the development of first onset of heart failure in relation to risk factors and impaired systemic ventricular function. In this group of 188 patients with a systemic right ventricle or single ventricle, the frequency of heart failure was very high (32%). In particular, at the time of most recent follow-up, patients with symptomatic limitation were particularly at risk (mortality in the symptomatic and asymptomatic groups was 47.1% and 5%, respectively). In addition, functional or image-based ventricular assessment demonstrated a high frequency of asymptomatic ventricular dysfunction, which underscores the high frequency of heart failure and asymptomatic ventricular dysfunction, as well as its relation to mortality.

Diagnosis of Heart Failure
Heart failure may be defined as the inability of the heart to meet the metabolic demands of the body, and it remains a clinical diagnosis. We have used Framingham criteria for the diagnosis of congestive heart failure. These are the most widely used criteria in epidemiological studies of heart failure and have been shown to correlate with prognosis for patients without congenital heart disease. To determine functional class, we used the New York Heart Association functional classification because of its long-established relationship to outcomes in heart failure.

Heart Failure Rates Between Symptomatic and Asymptomatic Patients
In our cohort of patients with a systemic right ventricle or single ventricle, symptomatic patients showed a significantly higher incidence of subsequent heart failure than did asymptomatic patients (P<0.05; Table 3). Interestingly, the presence of symptoms was also associated with worse degrees of ventricular dysfunction, eg, systemic ventricular ejection fraction at rest was 34.8±16.0% in symptomatic patients versus 46.7±13.4% in asymptomatic patients. This suggests that there is a strong and important association between symptoms, ventricular function, and the mortality of heart failure. Many associated features of heart failure also fell into the same pattern. The incidence of arrhythmia in symptomatic patients was 82.0% compared with 52.5% in asymptomatic patients (P<0.0001). Rates of atrial tachyarrhythmias, cyanosis, syncope, and fatigue were also significantly higher in symptomatic patients than in asymptomatic patients (P<0.00001, P<0.00001, P=0.02, and P<0.00001, respectively; Table 3).

Systemic Ventricular Dysfunction in Symptomatic Versus Asymptomatic Patients
Symptoms do not necessarily correlate with ventricular dysfunction in the classic left heart failure setting, which commonly is due to coronary disease or cardiomyopathy. According to Thomas et al, heart failure symptoms could be due to a variety of different mechanisms, such as degree of hemodynamic impairment, peripheral muscle function, pulmonary function, diastolic function, and neurohormonal activation. Interestingly, in our patient cohort, there was a defined relationship between symptoms and degree of functional impairment. This suggests that these parameters are more limited because of ventricular and cardiovascular functional impairment rather than other factors such as neurohormonal or physical conditioning parameters. This issue is important because these patients with systemic right ventricles have a lower functional capacity than a normal population of adults with systemic left ventricles and may continue to be exposed to high risk in terms of developing heart failure in the future.

Modifiable Predisposing Risk Factors
The predisposing correctable risk factors for heart failure in the general adult population with congenital heart disease include older age at operation, severe AV valve regurgitation, duration of cyanosis, and pregnancy. As shown in Table 2, age at first operation was significantly lower in asymptomatic patients. The current practice of operating at a younger age may lessen the prevalence of ventricular dysfunction and heart failure. Three of the patients developed heart failure during the last trimester of pregnancy, 2 of whom became asymptomatic after delivery. Most of the patients with severe AV regurgitation, who were symptomatic, became asymptomatic after corrective operation. Decreasing the age at corrective operation would also decrease the duration of cyanosis, which is another important risk factor in these
Mechanisms of Functional Limitations

A number of investigations have attempted to define the mechanism of cardiac response to exercise in different groups of adult congenital cardiac patients. In our patients, the heart rate at rest was normal and was seen to increase with exercise. However, peak heart rate in response to exercise was significantly lower in symptomatic patients than in the asymptomatic and control groups. This pattern of heart rate response to exercise has also been observed by other investigators who have studied Fontan patients. Right and left ventricular ejection fractions at rest and exercise were significantly lower in symptomatic patients than in asymptomatic patients or in the control population. These variables were also significantly lower in asymptomatic patients than in controls, which suggests the importance of asymptomatic systemic ventricular dysfunction and silent ventricular remodeling in this population of adults with congenital disease. Peak oxygen consumption, anaerobic threshold, peak workload, and peak heart rate were not only significantly lower in symptomatic than asymptomatic patients but were also significantly lower in asymptomatic patients than in controls. These observations reaffirm the importance of the link between ventricular dysfunction, symptoms, and mortality. This also suggests the potential of preservation of ventricular function in this population as a potential viable strategy to affect both symptoms and survival.

Impact of Cardiomegaly on Incidence of Heart Failure

The incidence of heart failure in patients who have cardiomegaly was significantly higher than in patients who had a normal cardiothoracic ratio \( (P<0.0001) \). Also, the cardiothoracic ratio was generally significantly higher in symptomatic patients than in asymptomatic patients \( (P<0.00001; \text{Tables 3 and 4}) \). This, together with previous observations on ventricular hypertrophy, suggests that cardiac remodeling does affect the development and mortality of heart failure in this unique population. This would again suggest preservation of ventricular function and structure as a future goal in the care of these patients.

Summary

We observed poorer objective measures of cardiac function in this adult population with systemic right ventricles or single ventricles that were significantly worse among symptomatic patients than asymptomatic patients. These objective measures of cardiac function among asymptomatic patients were also significantly lower than in the normal population of adults. The discrepancy of being asymptomatic while having significant cardiopulmonary dysfunction highlights the difficulty that physicians caring for these adult patients may have in judging the condition and prognosis of these patients. Access to objective and comprehensive exercise data can assist in determining such factors. The frequency of heart failure was significantly higher among all the study groups than in the general population and was higher in the Fontan population than in other groups included in the present study. These observations document significant hemodynamic limitations among patients with systemic right ventricles or single ventricles, a sign of deteriorating functional capacity and early mortality in some of these patients.

Acknowledgments

This research study was supported in part by the Canadian Institutes for Health Research and the Heart and Stroke Foundation of Ontario. Dr. Liu holds the Heart and Stroke/Polo Chair Professorship at University of Toronto.

References

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Circulation. 2002;105:1189-1194; originally published online March 4, 2002;
doi: 10.1161/hc1002.105182
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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