The Role of Right and Left Ventricular Function in the Ventilatory Response to Exercise in Chronic Heart Failure

Andrew L. Clark, MA, MRCP; Jonathan W. Swan, MRCP; Robin Laney, MSc; Michael Connelly, MRCP; Jane Somerville, MD, FRCP; Andrew J.S. Coats, DM, FRACP

Background Right ventricular function may be an important determinant of exercise capacity, peak oxygen consumption (VO2), and the ventilatory response to carbon dioxide production (Ve/VCO2 relation) in patients with chronic heart failure (CHF).

Methods and Results We studied the role of right ventricular function in CHF and also investigated the effects of absent right ventricular reserve in patients previously operated on with Fontan's procedure by measuring metabolic gas exchange during exercise in five groups of patients: (1) 10 patients who had previously undergone Fontan's procedure for congenital heart disease in whom the right ventricle is not functional; (2) 11 age-matched control subjects with dilated cardiomyopathy (DCM); (3) 15 age-matched normal subjects; (4) 42 patients with MHS; and (5) 16 age-matched control subjects. Left and right ventricular ejection fractions (LVEF and RVEF) were measured by radionuclide ventriculography in group 4. In the young subjects, the Ve/VCO2 slope was lower in the control subjects than in the other two groups, being 24.4±4.3 against 33.3±6.6 in group 1 (P<.001) and 29.6±8.1 in group 2 (P<.05). The correlation between peak VO2 and Ve/VCO2 was −0.80 (P=.005) in group 1 and −0.76 (P=.007) in group 2. In the older age groups, the Ve/VCO2 slope was significantly greater (38.0±14.9 versus 25.4±3.7; P<.001) in the heart failure group (group 4). In neither control group was there a significant relation between peak VO2 and Ve/VCO2 slope. In group 4, the relation between peak VO2 and Ve/VCO2 was similar to that seen for groups 1 and 2. LVEF was 24.3±14.1%, and RVEF was 32.5±13.1%. There was no correlation between either RVEF or LVEF and peak VO2 or Ve/VCO2 slope in the heart failure group.

Conclusions The relation between excessive ventilation and reduction in peak oxygen consumption is present in patients with no functioning right ventricle. RVEF is not a determining feature of either exercise capacity or the excessive ventilatory response in CHF. (Circulation, 1994;89:2062-2069.)

Key Words • heart failure, congestive • exercise • ventilation

The pathophysiology underlying the symptom of exercise limitation in patients with chronic heart failure remains incompletely explained. Central hemodynamic factors such as cardiac output, left ventricular filling pressures, and left ventricular ejection fraction (LVEF) correlate poorly with exercise capacity as assessed by peak oxygen consumption (peak VO2) during an incremental exercise test,1,2 but other studies have suggested a weak correlation with total pulmonary resistance and a weak correlation with pulmonary artery pressures.3 A modest correlation between pulmonary capillary wedge pressure and peak VO2 was also found by Szlachcic and colleagues.4 It has been suggested that diastolic function of the left ventricle and pulmonary hemodynamics may be limiting features,5 and attention has been drawn to the possible limiting effects of right ventricular dysfunction in chronic heart failure.6 One study showed a weak correlation between increase in right ventricular ejection fraction (RVEF) and improvement in peak VO2 with unspecified treatment.7

There is an excessive ventilatory response to exercise in patients with chronic heart failure as indicated by increased ventilation relative to carbon dioxide production,2,8 and the reduction in exercise capacity correlates with the increase in the slope of ventilation/carbon dioxide production.6 This increase in slope has been attributed to an increase in pulmonary dead space ventilation9,10 and appears to be the best single physiological correlate of reduction in peak VO2.

The Fontan procedure is carried out for patients with a single atrioventricular connection and results in a circulation with no effective right-sided pumping reserve. It is associated in some subjects with exercise limitation and shortness of breath, the cause of which is incompletely understood. The experiments reported in this article were designed to investigate the role of right and left ventricular function in determining exercise capacity in patients with chronic heart failure and to assess the possible contribution of right ventricular function to the increased ventilatory response relative to carbon dioxide production during exercise. We investigated right ventricular function and exercise capacity in a group of patients with chronic heart failure with a mixture of right and left ventricular impairment and in a group of patients who had previously undergone Fontan's operation for congenital tricuspid atresia and who thus have no right ventricular function. In addition,
TABLE 1. Group 1: 10 Patients Who Had Undergone Fontan’s Procedure for Congenital Heart Disease

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, y</th>
<th>Diagnosis</th>
<th>Age at surgery, y</th>
<th>Surgery</th>
<th>Symptoms</th>
<th>Medication, mg/d</th>
<th>Peak Vo2</th>
<th>VE/VCO2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25.0</td>
<td>TA, VSD</td>
<td>22.8</td>
<td>Fontan</td>
<td>2</td>
<td>Dig 0.125, Warf</td>
<td>17.3</td>
<td>34.2</td>
</tr>
<tr>
<td>2</td>
<td>27.5</td>
<td>TA</td>
<td>0.4</td>
<td>Glenn</td>
<td>2</td>
<td>Fruse 40</td>
<td>21.6</td>
<td>30.9</td>
</tr>
<tr>
<td>3</td>
<td>32.9</td>
<td>ASD</td>
<td>8.5</td>
<td>Fontan</td>
<td>1</td>
<td>None</td>
<td>31.0</td>
<td>24.5</td>
</tr>
<tr>
<td>4</td>
<td>35.4</td>
<td>SV, PS</td>
<td>18</td>
<td>Fontan</td>
<td>3</td>
<td>Dig 0.125, Amiod</td>
<td>14.7</td>
<td>40.0</td>
</tr>
<tr>
<td>5</td>
<td>25.5</td>
<td>TA</td>
<td>0.9</td>
<td>Blalock</td>
<td>2</td>
<td>Mod</td>
<td>18.0</td>
<td>46.1</td>
</tr>
<tr>
<td>6</td>
<td>33.0</td>
<td>TA</td>
<td>0.3</td>
<td>Blalock</td>
<td>1</td>
<td>Fruse 80</td>
<td>28.9</td>
<td>26.7</td>
</tr>
<tr>
<td>7</td>
<td>35.7</td>
<td>ASD</td>
<td>28.3</td>
<td>Fontan</td>
<td>Dig 0.125</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>25.0</td>
<td>ASO</td>
<td>28.3</td>
<td>Fontan</td>
<td>2</td>
<td>Dig 0.125</td>
<td></td>
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</tr>
<tr>
<td>9</td>
<td>33.3</td>
<td>SV</td>
<td>17.2</td>
<td>Blalock</td>
<td>3</td>
<td>Fruse 40</td>
<td>16</td>
<td>39.4</td>
</tr>
<tr>
<td>10</td>
<td>19.1</td>
<td>SV</td>
<td>1.1</td>
<td>Blalock</td>
<td>None</td>
<td></td>
<td>24.6</td>
<td>35.1</td>
</tr>
</tbody>
</table>

Average±SD 28.3±6.9 23.3±6.7 33.3±6.6

Symptoms refers to the New York Heart Association classification for breathlessness. Peak Vo2 is the peak achieved oxygen consumption in mL·kg⁻¹·min⁻¹. VE/VCO2 is the slope of the relation between ventilation and carbon dioxide production. TA indicates tricuspid atresia; VSD, ventricular septal defect; ASD, atrial septal defect; SV, single ventricle; PS, pulmonary stenosis; TS, tricuspid stenosis; CA, common atrium; PFO, patent foramen ovale; Dig, digoxin; Warf, warfarin; Fruse, furosemide; Amiod, amiodarone; Burnet, bumetanide; Mod, hydrochlorothiazide 50 mg/amiloride 5 mg; and Aten, atenolol.

we studied two appropriate age-matched control groups with normal right and left ventricular function.

Methods

The study was approved by the ethics committee of the Royal Brompton National Heart and Lung Institute. All subjects gave informed consent. Subjects were asked to undertake a symptom-limited incremental treadmill exercise test with expired gas analysis to determine metabolic gas exchange.

Patient Selection

The ventilatory responses to exercise of three groups of patients and two control groups were investigated.

Group 1 consisted of 10 young adults (average age±SD, 28.3±7 years) who had undergone Fontan’s (or modified Fontan’s) procedure for tricuspid atresia. Clinical details relating to these patients are presented in Table 1. All patients had been clinically stable for at least the preceding 3 months and were limited by symptoms of shortness of breath or fatigue on exercise. All had normal systemic ventricular function by echocardiography (n=9) except subject 9, in whom the systemic ventricle appeared to be of right ventricular morphology. Exclusion of this subject did not materially affect the results.

Group 2 consisted of 11 age-matched patients with dilated cardiomyopathy (age, 28.3±8 years). Clinical details of these patients are presented in Table 2. All patients had been clinically stable for at least the preceding 3 months and were limited by symptoms of shortness of breath or fatigue on exercise.

Group 3 consisted of 15 age-matched normal subjects (average age, 30±5 years). Normal subjects were recruited from the hospital staff. All were healthy. None had a past history of cardiovascular disease, and none were current smokers.

Group 4 consisted of 42 patients with chronic heart failure (average age, 59±6 years). The cause of heart failure was not considered as a selection criterion. All patients were clinically stable for at least 3 months before inclusion in the study and were limited by shortness of breath or fatigue on exercise. None were limited by angina or claudication. Clinical details are given in Table 3.

Group 5 consisted of 16 normal subjects age-matched to group 4. None had a past history of cardiopulmonary illness. One was a current smoker. None were taking any medication. Subjects were recruited from hospital staff and from subjects attending for medicals as part of routine health screening. All were sedentary subjects.

Exercise Protocol

All subjects undertook a symptom-limited treadmill exercise test. All patients had previously undergone exercise testing and were familiar with the protocol. The standard Bruce protocol was used, with the addition of a stage 0 (3 minutes of exercise at 1 mph with a 5% gradient). Subjects breathed through a one-way valve, allowing the collection of expired air. Expired air was mixed with an inert indicator gas in a mixing chamber, and samples taken every 10 seconds were analyzed by mass spectrometer (Amis 2000). Ventilation (Ve), carbon dioxide production (VCO2), and oxygen consumption (Vo2) were derived on line every 10 seconds. The exercise tests were carried out in an air-conditioned room at a temperature...
of 20°C to 22°C. The exercise protocol was started after it was
ensured that baseline readings were constant for at least 1
minute, and subjects were encouraged to exercise to
exhaustion.

Peak VO₂, the VE/VCO₂ slope, and the respiratory exchange
ratio (VCO₂/VO₂) at peak exercise were calculated for each
exercise test.

Technique for Measuring RVEF and LVEF

Resting RVEF and LVEF were measured in the patients in
group 4. It was thought unethical to expose the other groups to
radiation. Each subject was injected intravenously with 0.03
mg·kg⁻¹ of stannous fluoride red cell labeling agent (Amer-
sham International). After a period of 15 to 30 minutes was
allowed for equilibration of the red blood cells, the subject was
connected to a 19-gauge cannula in the right antecubital
vein. The patient was positioned supine on a scanning couch,
with the gamma camera, a Sopha medical DS-X rectangular
field of view, positioned in the 45° right anterior oblique
projection. To allow for synchronization of events, the patient
was connected to an ECG with the output of chest lead V₆
monitored. A bolus of 740 MBq of ⁹⁹mTcO₄⁻ in 0.3 to 0.5 mL
was rapidly injected via the cannula, the camera acquiring
first-pass, list mode image data for 45 seconds. The gamma
camera was then moved to a position optimal for imaging the
left ventricle: 45° left anterior oblique with 10° of cranio-
caudal tilt. An equilibrium radionuclide ventriculogram was then
acquired: 16 frames are acquired in each RR interval and
summed repeatedly until the end-diastolic image contains
300 000 counts to ensure an accurate estimation of LVEF. The
first-pass data were re-framed into a 16-frame R-wave-syn-
chronized study to facilitate calculation of RVEF. For each of
the studies, ventricular ejection fraction was calculated by
comparison of background-subtracted images at end diastole
and end systole as

Ejection Fraction =

\[
\frac{\text{End-Diastolic} - \text{End-Systolic Counts in Ventricle}}{\text{End-Diastolic Counts in Ventricle}} \times 100
\]

Statistical Methods

Between-group analysis was made by factorial ANOVA, and
when significant, individual comparisons were made by
Scheffé's procedure. Within-subject comparisons were made
with paired Student's t test, with corrections for multiple
comparisons by Scheffé's procedure. Linear regression analysis
by the least-squares method was used. Corrected values of
P<.05 were taken to be statistically significant. In the text,
results are quoted as mean±SD.

Results

There was no complication from any of the exercise
tests. All subjects other than one of the patients in
group 1 (patient 1) were able to exercise until the
respiratory exchange ratio (VCO₂/VO₂) exceeded 1.0,
indicating at least near maximal exercise. In all subjects,
the relation between ventilation and carbon dioxide
production (VE/VCO₂ slope) was well described by a
linear regression equation with a correlation coefficient
>.9 in all cases.

Groups 1, 2, and 3

The patients in groups 1, 2, and 3 were well matched for
age (see Table 4). The peak VO₂ was significantly
greater in the control subjects than in either the Fontan
group or the dilated cardiomyopathy group (P=.0001)
(40.3±6.3 in group 3 versus 23.3±6.7 in group 1

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, y</th>
<th>Symptoms</th>
<th>Medication, mg/d</th>
<th>Peak VO₂</th>
<th>VE/VCO₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17.6</td>
<td>1</td>
<td>L 2.5</td>
<td>35.5</td>
<td>24.7</td>
</tr>
<tr>
<td>2</td>
<td>19.1</td>
<td>1</td>
<td>L 2.5</td>
<td>33.5</td>
<td>26.5</td>
</tr>
<tr>
<td>3</td>
<td>34.2</td>
<td>2</td>
<td>E 5</td>
<td>27.6</td>
<td>23.2</td>
</tr>
<tr>
<td>4</td>
<td>32.5</td>
<td>2</td>
<td>E 5</td>
<td>28.2</td>
<td>29.4</td>
</tr>
<tr>
<td>5</td>
<td>29.9</td>
<td>3</td>
<td>Fruse 160</td>
<td>22</td>
<td>29.9</td>
</tr>
<tr>
<td>6</td>
<td>46.8</td>
<td>2</td>
<td>BZF 5</td>
<td>22.2</td>
<td>33.3</td>
</tr>
<tr>
<td>7</td>
<td>22.0</td>
<td>4</td>
<td>Fruse 80</td>
<td>9.2</td>
<td>53.5</td>
</tr>
<tr>
<td>8</td>
<td>32.1</td>
<td>3</td>
<td>Fruse 80</td>
<td>16.4</td>
<td>26.5</td>
</tr>
<tr>
<td>9</td>
<td>25.3</td>
<td>1</td>
<td>Warf</td>
<td>31.8</td>
<td>28.6</td>
</tr>
<tr>
<td>10</td>
<td>30.0</td>
<td>1</td>
<td>Fruse 40</td>
<td>32.1</td>
<td>24.0</td>
</tr>
<tr>
<td>11</td>
<td>22.0</td>
<td>2</td>
<td>Fruse 40</td>
<td>26.1</td>
<td>25.9</td>
</tr>
</tbody>
</table>

Average±SD 28.3±8.4

Angle-1n-clearing enzyme inhibitors are given as single initials: C indicates captopril; E, enalapril; and L,
lisinopril. Amiod indicates amiodarone; Fruse, furosemide; Warf, warfarin; Dig, digoxin; and BZF, bendrofluazide.
TABLE 3. Group 4: 42 Patients With Chronic Heart Failure

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Diagnosis</th>
<th>Symptoms</th>
<th>EF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DCM</td>
<td>IHD</td>
<td>I</td>
</tr>
<tr>
<td>59.3</td>
<td>13</td>
<td>29</td>
<td>7</td>
</tr>
<tr>
<td>(7.9)</td>
<td>(13.1)</td>
<td>(14.1)</td>
<td></td>
</tr>
</tbody>
</table>

DCM indicates dilated cardiomyopathy; IHD, ischemic heart disease; EF, ejection fraction; RV, right ventricle; and LV, left ventricle. In this group of patients, the average dose of diuretic was 90.8 (45.3) mg furosemide daily. Thirty patients were taking angiotensin-converting enzyme inhibitors, 3 were taking isosorbide dinitrate, 15 were taking digoxin, and 4 were taking amiodarone. Values in parentheses indicate SD.

[P<.001] and 25.9±7.6 in group 2 [P<.001]. Exercise time was longer in the control subjects than in the other two groups. The VE/VCO₂ slope was lower in the control subjects than in the other two groups (P=.008), being 24.4±4.3 against 33.3±6.6 in group 1 (P<.001) and 29.6±8.1 in group 2 (P<.05). There were no significant differences between groups 1 and 2.

The relation between the VE/VCO₂ slope and peak VO₂ in these three groups can be seen in Fig 1. The relation for the patients with dilated cardiomyopathy and with Fontan’s operation is similar to that previously described for patients with heart failure and is indistinguishable between the two groups. This is in distinction to the control group, who display no such relation, as previously described.¹³

Groups 4 and 5

The two groups were well matched for age (see Table 5). Peak VO₂ was significantly higher in the control group (34.3±8.5 versus 16.8±4.1 mL·kg⁻¹·min⁻¹; P<.001), and the VE/VCO₂ was significantly greater in the heart failure group (38.0±14.9 versus 25.4±3.7; P<.001). There was a relation between peak VO₂ and VE/VCO₂ in group 4 similar to that seen for groups 1 and 2, but again, no such relation was seen in the normal control subjects (see Fig 2).

In group 4 (heart failure group), the average LVEF was 24.3±14.1% and RVEF was 32.5±13.1%. If the patients were divided into two groups on the basis of their New York Heart Association symptom classification, there was no significant difference in LVEF between the two groups (symptom classes I and II, 28.4±16.5% [n=12]; class III and IV, 22.6±12.9% [n=30]; P=NS). RVEF was significantly lower in the more symptomatic group (symptom classes I and II, 39.9±10.6%; classes III and IV, 29.6±13.0%; P=.02). There was, however, no correlation between RVEF and exercise capacity as assessed by peak VO₂ and exercise time or the VE/VCO₂ slope (see Fig 3). Similarly, there was no correlation between LVEF and either peak VO₂ or VE/VCO₂ slope (see Fig 4). There was a weak correlation between right and left ventricular ejection fraction (r=.3; P=.05).

Combining groups 2 and 4 (patients with heart failure and dilated cardiomyopathy) and the two control groups (3 and 5) (see Fig 5) further emphasizes the importance of the relation between the VE/VCO₂ slope and the reduction in peak VO₂ in patients with heart failure and the fact that this relation does not extend to normal subjects.

Discussion

We found that the relation between an increased VE/VCO₂ slope and reduction in peak VO₂ seen in patients with chronic heart failure is also seen in a group of patients who have no right ventricular function. Furthermore, we demonstrated no constant relation between RVEF and either exercise performance or the ventilatory response to exercise.

Central to an understanding of the pathophysiology of exercise limitation in patients with chronic heart failure is the need to explain the increase in the VE/VCO₂ slope seen in such patients and the association of this increase with the reduction in peak VO₂.⁴¹³ What might be called the "central hemodynamic hypothesis" would predict that indexes of cardiac function such as cardiac output or left ventricular filling pressures should predict exercise performance, but this has been shown experimentally not to be the case.¹² It has also been proposed that a ventilatory abnormality, demonstrated by the increased ventilation relative to carbon dioxide production, may be the principal abnormality limiting exercise capacity. In particular, an increase in dead space ventilation has been suggested as the physiological basis for this abnormality.¹⁰¹¹ The question remains as to why such a primary increase in dead space

TABLE 4. Comparison Between Two Patient Groups and Control Subjects

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Peak VO₂</th>
<th>VE/VCO₂</th>
<th>Exercise Time, s</th>
<th>R at Peak</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 3</td>
<td>30.4</td>
<td>40.3</td>
<td>24.4</td>
<td>929</td>
</tr>
<tr>
<td>(Control subjects)</td>
<td>(4.4)</td>
<td>(6.3)</td>
<td>(4.3)</td>
<td>(229)</td>
</tr>
<tr>
<td>Group 1</td>
<td>28.3</td>
<td>23.3*</td>
<td>33.3*</td>
<td>621†</td>
</tr>
<tr>
<td>(Fontan)</td>
<td>(6.9)</td>
<td>(6.7)</td>
<td>(6.6)</td>
<td>(199)</td>
</tr>
<tr>
<td>Group 2</td>
<td>28.3</td>
<td>25.9*</td>
<td>29.6‡</td>
<td>738‡</td>
</tr>
<tr>
<td>(DCM)</td>
<td>(8.4)</td>
<td>(7.6)</td>
<td>(6.1)</td>
<td>(194)</td>
</tr>
</tbody>
</table>

Exercise time indicates the total exercise time; R, respiratory exchange ratio (VCO₂/VO₂) achieved at peak exercise; and DCM, dilated cardiomyopathy. Values in parentheses indicate SD.

⁎P<.001; †P<.01; ‡P<.05. P values refer to comparisons made between patient groups and control subjects.
ventilation should occur and how it is sensed by the body.

Right ventricular function may be implicated in exercise limitation in patients with chronic heart failure. Weak correlations have been shown between exercise capacity and pulmonary artery wedge pressure and mean pulmonary arterial pressure. Baker et al using a first-pass radionuclide technique, showed a close correlation between peak \( V_O_2 \) and RVEF in a study of 25 patients with chronic heart failure. It is attractive to propose that a limiting feature in chronic heart failure may be the inability of the right ventricle to eject blood into the pulmonary circulation during exercise sufficiently to perfuse all areas, and thus there will be areas of lung ventilated but unperfused—increased dead space ventilation. Central to this hypothesis should be a relation between right ventricular function and the increased \( V_E/V_CO_2 \) slope, but this has not been reported previously.

**TABLE 5. Comparison Between Patients With Chronic Heart Failure (Group 4) and Their Control Subjects (Group 5)**

<table>
<thead>
<tr>
<th></th>
<th>Group 4 (Heart Failure)</th>
<th>Group 5 (Control Subjects)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>59.3</td>
<td>55.0</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>(7.9)</td>
<td>(7.4)</td>
<td></td>
</tr>
<tr>
<td>Peak ( V_O_2 )</td>
<td>16.8</td>
<td>34.3</td>
<td>&lt; .001</td>
</tr>
<tr>
<td></td>
<td>(4.1)</td>
<td>(8.5)</td>
<td></td>
</tr>
<tr>
<td>( V_E/V_CO_2 )</td>
<td>38.0</td>
<td>25.4</td>
<td>&lt; .001</td>
</tr>
<tr>
<td></td>
<td>(14.9)</td>
<td>(3.7)</td>
<td></td>
</tr>
<tr>
<td>( R )</td>
<td>1.12</td>
<td>1.22</td>
<td>.008</td>
</tr>
<tr>
<td></td>
<td>(0.12)</td>
<td>(0.11)</td>
<td></td>
</tr>
<tr>
<td>Time</td>
<td>436</td>
<td>888</td>
<td>&lt; .001</td>
</tr>
<tr>
<td></td>
<td>(182)</td>
<td>(124)</td>
<td></td>
</tr>
</tbody>
</table>

\( R \) indicates respiratory exchange ratio \( (V_CO_2/V_O_2) \). \( P \) values refer to comparisons between controls and patients with heart failure. Values in parentheses indicate SD.

Our study was specifically designed to examine the contribution of right ventricular function to exercise capacity, and specifically the possibility that RVEF is a predictor of exercise capacity and the increased \( V_E/V_CO_2 \) slope in chronic heart failure. We used two different approaches to answer this question. We chose to study the responses of a group of patients who had undergone Fontan's procedure for congenital heart disease and those of appropriate control groups. In Fontan's procedure and its modifications, the right ventricle (if present) is effectively excluded from the circulation. The operation was originally described for tricuspid atresia but is now more widely used for palliation of double inlet left ventricle and other complex anomalies in which it is not possible to create a biventricular circulation. The operation allows the systemic venous return to be routed into the pulmonary circulation through a conduit or right atrium. The exercise performance of patients who have undergone Fontan surgery seems to be relatively unchanged up to 13 years after the procedure.

In the experiments on Fontan patients, we showed that right ventricular function or its absence is not the determining feature of exercise capacity. This group of patients exhibits a relation between \( V_O_2 \) and \( V_E/V_CO_2 \) similar to that seen in patients with dilated cardiomyopathy, but in this group, right ventricular dysfunction cannot be responsible for the progressive increase in \( V_E/V_CO_2 \) seen with worsening exercise performance, since all have negligible right-sided functional reserve. The range of performance seen in the Fontan patients, with some subjects having normal exercise capacity and ventilatory responses, precludes right ventricular function from being the limiting factor.

The second part of the present study has been to examine RVEF by radionuclide techniques. Although Baker et al showed a good correlation between RVEF and peak \( V_O_2 \), this result has not been replicated. In a study conducted on 27 patients, Szlachcic et al, although finding a reduced RVEF in patients with severe heart failure compared with a group with less severe symptoms, found no correlation between peak \( V_O_2 \) and RVEF using an
equilibrium technique. We deliberately used patients with a wide range of functional capacity and left ventricular dysfunction to try to reduce the possible bias that may be introduced by considering only subjects who were preselected on grounds of, for example, LVEF. In this latter case, it becomes almost inevitable that LVEF will not correlate with peak VO₂, because there will not be enough variability in LVEF within the group. Any variation in peak VO₂ is, in this instance, likely to correlate with some other measure of severity of heart failure, such as RVEF or circulating noradrenaline.

We again used an equilibrium technique for determining ventricular ejection fractions and found no direct relation between RVEF and either peak VO₂ or VE/VCO₂ slope. It thus appears unlikely that RVEF, and more broadly, right ventricular function, is a major determinant of exercise capacity in patients with chronic heart failure, and in particular, the steepness of the VE/VCO₂ slope cannot be explained by variations in right ventricular functional capacity.

The reasons for the reduced exercise capacity and the increased ventilatory response to exercise seen in patients with chronic heart failure remain unexplained. Much recent work has focused on the possible role of skeletal muscle abnormalities in the pathogenesis of symptoms in heart failure. The existence of a neural connection between active skeletal muscle and the ventilatory response to exercise has been known for many years. It is tempting to speculate that exercise capacity in chronic heart failure is limited by muscle metabolism, whereas the increased ventilatory response is due to an increased ventilatory stimulus caused by the abnormal muscle metabolism. The observed increase in dead space ventilation may thus be seen as a response to, rather than a cause of, increased ventilation in chronic heart failure.

**Limitations to This Study**

The use of patients who have had Fontan's operation results in inevitable heterogeneity in the physiology of
the studied group. Nevertheless, the fact that we have demonstrated a wide variation in exercise capacity and VE/VCO₂ in such patients argues that the heterogeneity cannot be a result of that which they share in common—an effectively absent right ventricle.

It may be argued that ejection fractions are not good measures of ventricular function and that some other index should be used; however, since the right and left ventricular outputs must necessarily be identical, the ejection fractions required to generate the same output seem a reasonable estimate of the functions of the two ventricles. A further limitation is that we have not measured the right ventricular response to exercise, but we were interested principally in the possible predictive value of resting right ventricular function for exercise capacity.

The data we have presented are incomplete with regard to ejection fractions, since we felt it unethical to submit control subjects and young adults to unnecessary radiation. However, the results presented regarding the older patients with chronic heart failure remain valid, and the control groups were included to demonstrate how the relation between VO₂ and VE/VCO₂ differed in patients with heart failure. The younger group with cardiomyopathy was included to demonstrate that the relation between VO₂ and VE/VCO₂ was a function of heart failure and exercise limitation and not of age and that the relation was disrupted in a similar fashion in the Fontan group.

Acknowledgments

This work was supported by the British Heart Foundation and the Clinical Research Committee of the Royal Brompton National Heart and Lung Hospital. Dr Clark is supported by the Robert Luff Foundation. Dr Swan is supported by the Squibb Foundation. Dr Coats is supported by the Viscount Royston Trust.
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Circulation. 1994;89:2062-2069
doi: 10.1161/01.CIR.89.5.2062
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

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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