Failure of Stroke Volume Augmentation During Exercise and Dobutamine Stress Is Unrelated to Load-Independent Indexes of Right Ventricular Performance After the Mustard Operation

Graham P. Derrick, BMedSci, BM, BS, MRCP; Indra Narang, BMedSci, BM, BS, MRCP; Paul A. White, PhD; Andrea Kelleher, BM, BS, FRCA; Andrew Bush, MD, FRCP; Daniel J. Penny, MD, MRCP; Andrew N. Redington, MD, FRCP

Background—Impaired right ventricular function has been implicated as a cause of reduced maximal exercise capacity after the Mustard operation for transposition of the great arteries.

Methods and Results—Fourteen asymptomatic survivors of the Mustard operation were studied. Each underwent conventional cardiac catheterization, and after satisfactory hemodynamics were confirmed, load-independent indexes of ventricular function were derived by conductance catheter during dobutamine infusion (0, 5, and 10 \(\mu g \cdot kg^{-1} \cdot min^{-1}\)). Seven patients also underwent upright exercise testing on a bicycle ergometer with analysis of respiratory gas exchange by continuous mass spectrometry. Accessible pulmonary blood flow was measured at each workload with an automated acetylene rebreathing technique. All patients exercised to a satisfactory end point (respiratory quotient \(= 1.1\)). Maximum oxygen consumption during exercise was impaired compared with predicted values (mean, 77%; \(P<0.02\)). Both exercise and dobutamine infusion were associated with an increase in cardiac index and heart rate and a reduced stroke volume index response. This was despite significantly improved indexes of myocardial contraction (end-systolic pressure volume relation, \(P<0.001\)), preload recruitable stroke work index \((P<0.01)\), VA coupling \((P<0.001)\), and isovolumic relaxation \((P<0.001)\) during dobutamine infusion. There were no changes observed in end-diastolic pressure-volume relations, but there was failure to augment ventricular filling manifest by absence of change in \(dV/dt\) \((P=NS)\).

Conclusions—The stroke volume response to exercise stress is reduced in patients after the Mustard operation. A similar failure to augment stroke volume occurs during dobutamine stress despite appropriate responses in load-independent indexes of contraction and relaxation. This is due to failure to augment right ventricular filling rates during tachycardia, presumably as a result of impaired AV transport, consequent to the abnormal intra-atrial pathways. (Circulation. 2000;102[suppl III]:III-154-III-159.)

Key Words: transposition of great vessels ■ hemodynamics ■ exercise

The development of atrial redirection procedures (the Mustard and Senning operations) revolutionized the care of patients with transposition of the great arteries.\(^1\,2\) Although these procedures have largely been superseded by the arterial switch operation, there remains a large cohort of young adults who underwent atrial redirection in childhood. There are a number of concerns regarding the long-term outcome in this patient group. Baffle obstruction,\(^3\) systemic right ventricular (RV) dysfunction,\(^4\,5\) exercise intolerance,\(^6\,7\,8\) and increased risk of arrhythmia and sudden death\(^9\,8\) have all been reported. Impaired function of the systemic RV has been inferred from the almost-uniform findings of increased RV volumes and decreased ejection fraction in mid term survivors.\(^4\,5\,10\) Our own data have shown that segmental wall motion abnormalities are common in these patients and are related to global RV dysfunction and preoperative damage.\(^11\) It has also been suggested that these abnormalities of RV function may underpin the impaired exercise tolerance.\(^7\,8\) However, although one recent study showed a reduction in stroke volume in response to exercise and concluded that this implied ventricular dysfunction,\(^8\) the few available data suggest that measurements of RV volumes and ejection fraction do not predict either functional performance or the likelihood of late deterioration.\(^5\) Furthermore, volumetric indexes are flawed by their dependence on preload and afterload conditions. A detailed analysis of load-independent indexes of RV systolic...
and diastolic performance, the degree of contractile reserve of the systemic RV, and their relationship to exercise performance has yet to be performed.

The objectives of this study were to study the hemodynamic responses to exercise and dobutamine stress in patients after the Mustard operation to assess the amount of contractile reserve of the systemic RV and to investigate the possible relationship between exercise and RV dysfunction.

**Methods**

The study design was approved by the Institutional Ethics Committee. Informed consent was obtained for 14 late survivors of the Mustard procedure. Demographic data are summarized in the Table. Original medical records were unavailable for 2 patients. The intra-atrial baffles were constructed from glutaraldehyde-treated autologous pericardium, bovine pericardium, dura mater, or Dacron using the modification of Brom. Eight patients were recruited during an admission for elective catheterization as part of the unit policy for surveillance at late follow-up, and 6 patients were being investigated because of clinical suspicion of baffle stenosis (n=4) or because of recent onset of arrhythmia (n=2). All patients were otherwise well and in sinus rhythm at the time of the study.

**Exercise Testing**

A subgroup of 7 patients underwent detailed exercise testing to ensure that the performance of our study group was representative of previously published data on exercise performance. An electromechanically braked exercise bicycle (SECA 100) was adjusted for the individual size and comfort of each subject. After a period of rest and familiarization with the equipment, a resting recording was made to ensure that the performance of our study group was representative of previously published data on exercise performance. An electromechanically braked exercise bicycle (SECA 100) was adjusted for the individual size and comfort of each subject. After a period of rest and familiarization with the equipment, a resting recording was made. Thereafter, pedaling was begun while subjects were encouraged to maintain a speed of 50 to 70 rpm. Workload began at 25 W/m2 and increased by 15 W/m2 every 3 minutes. Basic monitoring included heart rate (HR) and peripheral transcutaneous oxygen saturation (Nelcor). Continuous respiratory mass spectrometry (Amis 2000, Innovision) was used for metabolic measurements, with subjects breathing orally through a mouthpiece into the instrument while wearing a nose clip. Mean accessible pulmonary blood flow was measured with the mass spectrometer using an automated acetylene rebreathing technique during the last 30 seconds of each workload. This noninvasive technique measures the absorption of 0.3% acetylene from a closed system and has been validated in our laboratory. Exercise testing was performed to maximum volition, confirmed by a respiratory quotient >1.1.

**Invasive Measurements**

Cardiac catheterization was performed while subjects were under a general anesthetic in all cases. Full conventional diagnostic catheterization and angiography were performed, followed by balloon dilatation of significant baffle stenosis (>3 mm Hg mean gradient, n=6). Patients were included in the subsequent research study if there were no residual resting hemodynamic abnormalities, including baffle stenosis or shunts.

**Study Preparation**

The existing arterial and venous valved introducer sheaths were used for access to the vasculature. Figure 1 shows a radiograph of the study preparation. A standard 7F balloon-tipped thermodilution catheter (Baxter Healthcare) was advanced into the pulmonary artery for measurement of cardiac output and connected to a dedicated cardiac output processor (Com 2, Baxter Edwards). The appropriate manufacturer’s computation constant was entered into the processing computer (Com 2, Baxter Edwards). A custom-built integrated conductance and Mikro Tip pressure catheter (Millar Instruments) was placed retrograde arterially into the apex of the RV. The conductance electrodes were connected to a signal conditioning and processing unit (Sigma SDF, Cardiodynamics Corp). The analog volume signal from the Sigma SDF signal processor, the amplified pressure signal (modified Fylyde Isotransducer Amplifier), and the surface ECG signal were all digitized simultaneously by an analog-to-digital converter (Data Translation Ltd) in a customized personal computer running customized software. Digital data were stored for offline analysis.

**Protocol**

Our protocol for both left ventricular and RV pressure-volume relationships using a conductance catheter has been described in detail elsewhere. Briefly, blood resistivity was measured from a

---

**Demographic Data Describing the Study Population**

<table>
<thead>
<tr>
<th>Sex, DOB, M/F</th>
<th>DOB</th>
<th>Diagnosis</th>
<th>Other Lesion</th>
<th>Age at Surgery, mo</th>
<th>Baffle Material</th>
<th>Prior Baffle Obstruction</th>
<th>Age at Study, y</th>
<th>Catheter Intervention</th>
<th>Medication</th>
<th>Exercise Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>F 1/24/87</td>
<td>TGA</td>
<td>LMB stenosis</td>
<td>2</td>
<td>Autologous pericardium</td>
<td>N</td>
<td>10.8</td>
<td>N</td>
<td>Digoxin</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>M 1/22/89</td>
<td>TGA</td>
<td>Sub PS, vascular ring</td>
<td>5</td>
<td>Autologous pericardium</td>
<td>N</td>
<td>9.5</td>
<td>N</td>
<td>Digoxin</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>M 1/18/86</td>
<td>TGA</td>
<td></td>
<td>8</td>
<td>Autologous pericardium</td>
<td>N</td>
<td>11.6</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>F 12/29/71</td>
<td>TGA</td>
<td></td>
<td>12</td>
<td>Autologous pericardium</td>
<td>N</td>
<td>25.6</td>
<td>SVC, IVC</td>
<td>Y</td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>F 8/18/82</td>
<td>TGA</td>
<td></td>
<td>6</td>
<td>Bovine pericardium</td>
<td>Y</td>
<td>15.0</td>
<td>N</td>
<td>Digoxin</td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>M 5/7/84</td>
<td>TGA</td>
<td></td>
<td>7</td>
<td>Dacron</td>
<td>Y</td>
<td>13.3</td>
<td>SVC, IVC</td>
<td>Y</td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>M 4/24/66</td>
<td>TGA</td>
<td>VSD</td>
<td>63</td>
<td>Dacron</td>
<td>N</td>
<td>31.4</td>
<td>SVC, IVC</td>
<td>Y</td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>M 2/28/85</td>
<td>TGA</td>
<td></td>
<td>3</td>
<td>Dura mater</td>
<td>Y</td>
<td>11.0</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>M 12/6/77</td>
<td>TGA</td>
<td></td>
<td>4</td>
<td>Dura mater</td>
<td>N</td>
<td>19.6</td>
<td>SVC, IVC</td>
<td>Y</td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>F 1/29/81</td>
<td>TGA</td>
<td></td>
<td>13</td>
<td>Dura mater</td>
<td>N</td>
<td>16.7</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>F 8/21/79</td>
<td>TGA</td>
<td>VSD</td>
<td>18</td>
<td>Dura mater</td>
<td>N</td>
<td>18.7</td>
<td>SVC, IVC</td>
<td>Y</td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>M 2/16/78</td>
<td>TGA</td>
<td></td>
<td>19</td>
<td>Dura mater</td>
<td>N</td>
<td>21.1</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>M 6/27/71</td>
<td>TGA</td>
<td></td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>24.5</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>F 3/22/81</td>
<td>TGA</td>
<td></td>
<td>NA</td>
<td>NA</td>
<td>Y</td>
<td>15.9</td>
<td>SVC, IVC</td>
<td>Y</td>
<td>Y</td>
<td></td>
</tr>
</tbody>
</table>

DOB indicates date of birth; TGA, transposition of the great arteries; LMB, left main branch; PS, pulmonary stenosis; SVC, superior vena cava; IVC, inferior vena cava; and VSD, ventricular septal defect.
5-mL sample of blood drawn from an in-dwelling line for calibration of the Sigma 5DF signal processing unit. After steady-state conditions were confirmed, ventilation was stopped at end expiration, and RV pressure and volume were measured during injection of 7 mL of 10% sodium chloride into the pulmonary artery to calculate parallel conductance. Ventilation was restarted, and after recovery, with ventilation held at end expiration, hemodynamic recordings were made during preload reduction by inflation of the occlusion balloon.

Cardiac output was measured by a 10-mL cold saline bolus injection into the injectate port of the thermodilution catheter, and derived cardiac output was used to compute the gain constant (α=conductance cardiac output/thermodilution cardiac output). The measurements were repeated during dobutamine infusion (5 and 10 μg·kg⁻¹·min⁻¹). The response to dobutamine infusion was deemed to be at steady state after ≥10 minutes or when the HR had reached a new plateau.

**Data Analysis**

Pressure-volume loops recorded during preload reduction were analyzed offline to derive 2 load-independent indexes of contractility, the end-systolic pressure-volume relation (ESPVR) and preload recruitable stroke work index (PRSW). Similarly, a load-independent diastolic index was derived from the linear function of the end-diastolic pressure-volume relation (EDPVR). An index of VA coupling was calculated as the ratio between effective arterial elastance (Ea) and end-systolic elastance (Ees). In addition, the time constant of isovolumic relaxation (τ) was measured from a mono-exponential fit to the pressure decay curve. The peak diastolic ventricular filling rate was obtained by the first differential of the volume-time signal averaged over ≥5 steady-state cardiac cycles.

**Statistical Analysis**

Repeated 1-way ANOVA was used to test the effect of dobutamine infusion on hemodynamic indexes, with the null hypothesis rejected if P<0.05.

**Results**

All data presented below are expressed for the entire group. There were no obvious trends toward a relationship between

---

**Exercise**

**Dobutamine**

---

**Figure 2.** Hemodynamic response. Top, Response to exercise; bottom, response to dobutamine infusion.
demographics, operative data, previous interventions, and functional results, although clearly a formal subset analysis was not possible.

Exercise
All subjects exercised to a satisfactory end point. This was defined by arbitrary criteria of maximal aerobic capacity (respiratory quotient \( >1.1 \)). Median\( \pm \)SD maximum workload was \( 70 \pm 10.4 \text{ W/m}^2 \), with only 1 subject falling short of predicted workload. However, maximum oxygen consumption was impaired (30.5\( \pm \)7.6 mL\( \cdot \)min\(^{-1}\)\( \cdot \)kg\(^{-1} \); mean, 77\% of predicted for age and sex\(^{17} \); \( P<0.02 \)).

During exercise, HR increased by 103\( \pm \)12 bpm (\( P<0.0001 \)) to a maximum predicted HR of 62.8\% to 92\% (mean, 82.7\%; \( P<0.005 \)). Cardiac index increased by 6700\( \pm \)1600 mL/min (\( P<0.005 \); Figure 2). After an early rise in stroke volume index of a mean of 13.8\( \pm \)18 mL\( \cdot \)min\(^{-1}\)\( \cdot \)m\(^{-2} \), all patients showed a progressive fall by 18.5\( \pm \)8.46 mL/m\(^2 \) as workload increased.

Dobutamine Infusion
A similar response was observed during dobutamine infusion. There was a progressive increase in HR of 47\( \pm \)20 bpm (\( P<0.001 \)) and an increase in cardiac index of 920\( \pm \)681 mL\( \cdot \)min\(^{-1}\)\( \cdot \)m\(^{-2} \) (\( P<0.001 \)). However, dobutamine infusion was associated with a progressive fall in stroke volume of 7.4\( \pm \)10.6 mL\( \cdot \)min\(^{-1}\)\( \cdot \)m\(^{-2} \) (\( P<0.05 \)) as HR increased.

Despite the reduction in stroke volume index during dobutamine infusion, RV contractility was augmented. Figure 3 shows typical examples of the hemodynamic responses. This was manifest (Figure 4) by increases in ESPVR of \( 2.03 \pm 0.88 \text{ mm Hg/mL} \) (\( P<0.0001 \)) and PRSW of 64.85\( \pm \)52.3 erg/mL\( \cdot \)10\(^{-3} \) (\( P<0.001 \)). Furthermore, the ratio of Ea to Ees was reduced from 3.47\( \pm \)0.48 to 1.40\( \pm \)0.23 (\( P<0.0001 \)), suggesting improved VA coupling. The rate of isovolumic relaxation was enhanced by dobutamine infusion so that \( \tau \) was reduced by 23.28\( \pm \)6.91 s\(^{-1} \) (\( P<0.0001 \)), and there was no change in the slope of the EDPVR. However, the ventricular filling rate, dV/dt, failed to increase.

There were no differences in dobutamine responses when the subset of 7 patients who underwent exercise testing was compared with the rest of the group; furthermore, no relationships were found between indexes of RV function and exercise performance.

Discussion
The almost universal finding of a dilated RV with reduced ejection fraction has been taken as a manifestation of the inadequacy of the RV to perform as the systemic ventricle after the Mustard operation. Furthermore, this dysfunction has been implicated in the similarly universal finding of reduced exercise capacity in these often asymptomatic patients. There can be no doubt that RV function may be “abnormal,” but the impact of the RV dilatation and reduced myocardial shortening on functional performance is far from clear. These features may merely reflect a “normal” response
of the systemic RV to its afterload, and it is no surprise that there is little\textsuperscript{7} or no\textsuperscript{18} direct relationship between these indexes and exercise performance. In this study, we confirmed a failure to maintain an increased stroke volume as the primary hemodynamic abnormality at peak exercise at a time when it would be expected to be \( \sim 40\% \) higher than resting values.\textsuperscript{19} Although cardiac output rose, the HR response was disproportionate, leading to a progressive fall in stroke volume during exercise-induced tachycardia.

A similar response was seen during dobutamine infusion. The expected \( 33\% \) increase in stroke volume during infusion of 10 \( \mu \text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \) was not seen in our patients. Indeed, there was a fall in stroke volume index of \( 19\% \) at maximum stimulation. Although representing a different cardiovascular stress compared with exercise (when for example increased preload is expected), the similarity in response, with a fall in stroke volume at higher HRs, is compelling.

Our study is unique in measuring load-independent indexes of RV performance and confirms that abnormal myocardial mechanics cannot be invoked as a mechanism for these abnormal stroke volume responses.

Load-independent indexes of systolic contraction (ESPVR, PRSW) showed an appropriate increase with higher dobutamine doses, suggesting that there was an appropriate RV myocardial contractile reserve.

Effective arterial compliance incorporates the principal elements of vascular load, including peripheral resistance, vascular compliance, characteristic impedance, and systolic and diastolic time intervals. The ratio of \( E_a \) to \( E_{es} \) describes the efficiency of power transfer during ejection from ventricle to aorta. This ratio, which in optimum conditions would equal unity,\textsuperscript{21} showed an appropriate fall toward this value, suggesting that dobutamine, in addition to enhancing RV contractile performance, also improved coupling.

Similarly, there is little evidence of abnormalities of myocardial mechanical performance during diastole. Isovolumic relaxation was enhanced, as shown by the steep fall in \( \tau \), and the magnitude of this change is comparable to previously reported values at this dobutamine dose.\textsuperscript{22} Furthermore, the slope of EDPVR, a load-independent index describing the inherent elastic and distensible properties of the RV, did not change during the study period, confirming that there were no changes in compliance of the ventricle.

The most obvious abnormality, however, was the lack of change in ventricular filling rate, \( dV/dt \). The doses of dobutamine used in this study have been shown to cause a 30\% increase in ventricular filling rate\textsuperscript{22} in normal human hearts. Therefore, it is not surprising that stroke volume falls under the circumstances of reduced diastolic filling time and constant filling rate. The mechanism for failure of augmentation of filling rate must remain speculative, but in the absence of other abnormalities of diastolic function, it is likely that the capacitance and conduit function of the abnormal, often calcified, intra-atrial pathways may be responsible even in our patients proven to have no evidence of stenosis at rest. If correct, then the implications for those with truly stenotic pathways, coexisting left ventricular or RV systolic or diastolic abnormalities, or pathological tachyarrhythmia are clear. Further studies are re-
quired to assess the impact of this physiology during, for example, atrial flutter, but it is easy to construct a hypothesis to support the potential malignant effect of inappropriate tachycardia on stroke volume, cardiac output, and ultimately the incidence of sudden death.

**Study Limitations**
Our data use conductance catheter to derive load-independent indexes of ventricular function. Although not specifically validated for use in the systemic RV, the method is relatively independent of ventricular morphology and geometry and has been validated and refined by our group and others in a variety of pathological morphological and physiological states. There are several alternative techniques enabling measurement of load-independent indexes of ventricular function. Ultrasonic sonomicrometry is inapplicable outside the operating theater. Quantitative echocardiographic analyses, including wall stress analysis, involve geometric assumptions that are suspect in congenital heart disease. The presence of incoordinate contraction or hypertrophy serves to increase potential errors of these noninvasive techniques. The conductance catheter technique overcomes these considerations by measuring chamber volume as time-varying conductance of the blood pool contained within the chamber. Measurements were diligently calibrated with measurements of blood resistivity and parallel conductance. In addition, the dimensionless gain constant (α) relating conductance-derived volumes to a reference method was applied to account for electric field inhomogeneity resulting from changes in ventricular size and geometry. Thus, errors in measurement were minimized and internally constant.

The subjects of this study were all survivors of the Mustard operation. During this operation, pericardial, dural, or Dacron baffles were created within the atrial chamber to redirect venous return. The Senning operation, although introduced earlier than the Mustard operation, was slow to find acceptance in many centers. However, the Senning procedure uses native atrial tissue to create intra-atrial baffles with a minimum of foreign material and is less susceptible to the development of baffle stenosis. It is possible that the pathways created in the Senning operation will prove to be less restrictive to a higher demand for blood flow, and this clearly requires further study.

**Conclusions**
These data suggest that the major factor limiting the increase in cardiac output and stroke volume in response to exercise and pharmacological stress late after the Mustard operation is most likely to be impaired AV transport. This presumably reflects anatomical and functional abnormalities of the AV pathways, which may be amplified by coexisting baffle stenosis or ventricular disease. There may also be implications for the cardiovascular responses of patients during pathological tachycardia, because it is likely that ventricular filling is even more compromised above a critical HR.

**Acknowledgments**
We would like to thank the British Heart Foundation for their generous research support. Dr Derrick is supported by a British Heart Foundation Project Grant (PG 98176).

**References**
Failure of Stroke Volume Augmentation During Exercise and Dobutamine Stress Is Unrelated to Load-Independent Indexes of Right Ventricular Performance After the Mustard Operation
Graham P. Derrick, Indra Narang, Paul A. White, Andrea Kelleher, Andrew Bush, Daniel J. Penny and Andrew N. Redington

_Circulation_. 2000;102:Iii-154-Iii-159
doi: 10.1161/01.CIR.102.suppl_3.III-154
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2000 American Heart Association, Inc. All rights reserved.
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:
http://circ.ahajournals.org/content/102/suppl_3/Iii-154

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/