Tetralogy of Fallot: Postoperative Delayed Recovery of Left Ventricular Stroke Volume after Physical Exercise—Assessment with Fast MR Imaging

In six asymptomatic patients with corrected tetralogy of Fallot and nine healthy control subjects, the authors assessed left ventricular (LV) function during recovery from supine bicycle exercise by performing fast magnetic resonance (MR) flow mapping in the ascending aorta. Abnormal recovery of LV function after exercise was observed in the patients. MR flow mapping allows assessment of cardiac recovery after exercise.

After surgical repair of tetralogy of Fallot with the aim of closure of the ventricular septal defect and relief of the right ventricular outflow tract obstruction by means of resection or patch placement, most patients are in good physical and clinical condition (1). However, some of the patients have decreased exercise tolerance (2). Substantial pulmonary regurgitation or residual pulmonary stenosis limit exercise capacity and increase the risk of sudden cardiac death due to ventricular arrhythmia (3–5). Furthermore, an enlarged right ventricle due to pulmonary regurgitation after repair of tetralogy of Fallot contributes to left ventricular (LV) dysfunction at rest (6) and during exercise (7). Moreover, abnormalities in pulmonary function at rest and during exercise are exercise-limiting factors in these patients (8).

Cardiovascular recovery after supine physical exercise has been studied previously in healthy control subjects (9–11) and patients with ischemic heart disease (12). The rate of decline in heart rate after the cessation of exercise is a direct predictor of mortality (13) and indicates the importance of evaluating exercise recovery.

Findings in a previous study show that recovery kinetics of heart rate and oxygen uptake after exercise are abnormal in pediatric patients after the Fontan procedure (14). Abnormal recovery kinetics may contribute to reduced physical activity in these patients because prolonged duration of recovery may lead to a longer interval between exercise sessions and, consequently, an overall reduction in physical activity (14). To our knowledge, recovery of cardiac function after exercise has not yet been evaluated in patients after surgical repair of tetralogy of Fallot.

Magnetic resonance (MR) velocity mapping is a noninvasive accurate technique with which to evaluate cardiac function in patients with various cardiac diseases. The introduction of high-power gradient systems and fast echo-planar MR imaging (15) allows reliable assessment of flow maps in the great vessels in 3–4 seconds (16), which provides the possibility of studying the hemodynamic response to physical exercise by performing MR imaging (17–19). The use of exercise MR imaging to study hemodynamics during and after physical exercise in patients after correction of tetralogy of Fallot may help detection of ventricular dysfunction that is not apparent at rest (20) and may be useful in the timing of pulmonary valve replacement.

The purpose of this study was to elucidate the kinetics of LV stroke volume during recovery from submaximum ergometer exercise in patients after correc-
tion of tetralogy of Fallot by performing fast MR flow mapping.

1 Materials and Methods

The study population included six patients who were asymptomatic after correction of tetralogy of Fallot and were scheduled consecutively to undergo cardiac MR imaging at rest for clinical follow-up of pulmonary regurgitation and biventricular function. Patients who did not have contraindications for MR imaging examination (for a pacemaker, arrhythmias, claustrophobia) or bicycle exercise. Nine healthy control subjects were also included. The control subjects had normal findings at clinical examination and a normal electrocardiography tracing at rest and during exercise; they did not have a history of cardiovascular disease or any symptoms. The groups were similar in terms of age, height, body weight, and body surface area.

The mean age of the control subjects (five women and four men) was 17.3 years ± 2.6 (mean ± SD), and the mean age of the patients (two women and four men) was 17.3 years ± 2.7 ($P = .95$). There was no difference in height, weight, or body surface area between the control subjects and patients (height: control subjects 171 cm ± 4, patients 173 cm ± 3, $P = .78$; weight: control subjects 61.6 kg ± 5.3, patients 66.0 kg ± 5.2, $P = .58$; body surface area: control subjects 1.74 m$^2$ ± 0.09, patients 1.77 m$^2$ ± 0.09, $P = .83$).

Mean age at correction of tetralogy of Fallot was 1.5 years ± 0.3, and mean follow-up time was 15.8 years ± 1.1. No patients were receiving any medication. No patients had a history of arrhythmias, and no arrhythmias were observed during the examinations. All patients and control subjects gave their written informed consent to take part in the study, which was performed with the approval of the local ethics committee.

Exercise Testing Procedure

On a day prior to the MR examination, maximum levels of oxygen consumption and carbon dioxide output after exercise were determined in all participants by means of a 10 W/min incremental maximum ramp exercise test performed with an MR-compatible programmable bicycle ergometer (model BV; Lode, Groningen, the Netherlands). The maximum levels were normalized for body weight. Ventilatory equivalents (ie, the ratio of minute ventilation to oxygen uptake or carbon dioxide output) at peak exercise were calculated on the basis of nonnormalized data. The maximum heart rate and workload were also assessed.

MR Imaging Protocol

The participants underwent MR imaging with a 1.5-T whole-body MR system (Gyroscan ACS/NT; Philips Medical Systems, Best, the Netherlands) equipped with a PT6000 gradient system (23 mT/m amplitude and 105 mT/m/msec slew rate) and dedicated cardiac research software (CPR6). Exercise was performed by using the ergometer, which allows supine physical exercise during an MR examination. Participants were positioned in the supine position on a modified tabletop that was fitted with the ergometer. Pulmonary valve function was assessed by performing MR flow mapping perpendicular to the pulmonary trunk between the pulmonary valve and the pulmonary bifurcation (21). LV ejection fraction was assessed by acquiring 10 consecutive sections in the short-axis direction of the LV during a breath hold at end expiration with a turbo field-echo echo-planar MR sequence (19).

Flow in the ascending aorta was assessed by means of quantitative phase-contrast measurement perpendicular to the ascending aorta at the level of the pulmonary trunk with through-plane flow encoding, which represents LV stroke volume. The fast flow mapping technique consisted of an electrocardiographically triggered turbo field-echo echo-planar phase-contrast MR sequence that combined k-space segmentation and echo-planar imaging. Two signals were acquired within one heart-phase interval, and each signal was followed with five echo-planar MR imaging readouts. The following parameters were used: 13.9/4.6 (repetition time msec/echo time msec), field of view of 330 × 165 mm, matrix size of 128 × 40, final reconstructed image resolution of 2.6 × 2.6 mm, section thickness of 10 mm, constant flip angle of 30°, and velocity-encoding range of 200 cm/sec. The temporal resolution was 29 msec per cardiac phase. Acquisition time for a complete flow map was eight heartbeats.

For each participant, 21 flow measurements were obtained throughout the entire study (Fig 1). The first flow measurement was acquired at rest at the beginning of the examination. The participants then performed exercise at an individual workload that corresponded to 60% of maximum oxygen consumption. The second measurement was achieved at the steady-state exercise level. A period of 4½ minutes during passive recovery after exercise was covered with 19 flow measurements in 15-second intervals. Acquisition time for a complete flow map was eight heartbeats.
Table 1: Exercise Testing Results

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control Subjects</th>
<th>Patients with Tetralogy of Fallot</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO2max (mL/kg/min)</td>
<td>40.3 ± 1.8</td>
<td>40.8 ± 2.5</td>
</tr>
<tr>
<td>VCO2max (mL/kg/min)</td>
<td>32.8 ± 3.7</td>
<td>34.9 ± 4.3</td>
</tr>
<tr>
<td>Vrmax (L/min)</td>
<td>77.6 ± 8.8</td>
<td>93.9 ± 9.3</td>
</tr>
<tr>
<td>Vrmax/VrO2max</td>
<td>30.9 ± 1.1</td>
<td>35.5 ± 1.11</td>
</tr>
<tr>
<td>Vrmax/VrCO2max</td>
<td>26.6 ± 0.7</td>
<td>30.9 ± 1.11</td>
</tr>
<tr>
<td>HRmax (bpm)</td>
<td>176 ± 4</td>
<td>173 ± 5</td>
</tr>
<tr>
<td>WLmax (W)</td>
<td>201 ± 21</td>
<td>213 ± 21</td>
</tr>
</tbody>
</table>

Note.—Data are means ± standard errors of the mean.
* Significantly different from the respective data at rest.
† Significantly different from the respective data in control subjects.

Table 2: Overview of Cardiac Exercise Response

<table>
<thead>
<tr>
<th>Group and Parameter</th>
<th>Rest</th>
<th>Exercise*</th>
<th>Percentage Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control subjects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>73 ± 3</td>
<td>130 ± 4</td>
<td>79 ± 7</td>
</tr>
<tr>
<td>Stroke volume (mL)</td>
<td>96 ± 8</td>
<td>106 ± 10</td>
<td>11 ± 4</td>
</tr>
<tr>
<td>Cardiac output (L/min)</td>
<td>6.9 ± 0.4</td>
<td>13.7 ± 1.1</td>
<td>96 ± 5</td>
</tr>
<tr>
<td>Peak flow (mL/sec)</td>
<td>483 ± 43</td>
<td>741 ± 83</td>
<td>51 ± 4</td>
</tr>
<tr>
<td>Patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>68 ± 2</td>
<td>125 ± 3</td>
<td>85 ± 8</td>
</tr>
<tr>
<td>Stroke volume (mL)</td>
<td>84 ± 7</td>
<td>92 ± 9</td>
<td>10 ± 4</td>
</tr>
<tr>
<td>Cardiac output (L/min)</td>
<td>5.7 ± 0.4</td>
<td>11.5 ± 1.2</td>
<td>103 ± 17</td>
</tr>
<tr>
<td>Peak flow (mL/sec)</td>
<td>420 ± 34</td>
<td>643 ± 62</td>
<td>52 ± 3</td>
</tr>
</tbody>
</table>

Note.—Data are means ± standard errors of the mean. Differences in all parameters were not significant between control subjects and patients. * Significantly different from the respective data at rest (P < .05, paired t test).

Data Analysis

All images were analyzed quantitatively with analytic software (FLOW; Medis, Leiden, the Netherlands) (22) that allowed calculation of stroke volume by multiplying vessel area and spatial average flow velocity during systole within the vessel and cardiac output (stroke volume × heart rate) for all flow measurements. Values obtained at exercise and during the recovery period were expressed as a percentage of the resting values.

Heart rate recovery data were assumed to be a single-exponential decay, as previously described (14). The data were fitted to the following equation:

$$HR(t) = a + b \cdot e^{-t/t},$$

where HR is heart rate, $t$ is time after exercise, $a$ is the heart rate for $t = \infty$, $b$ is the difference in heart rate between peak exercise and rest, $t$ is the half-time period of the exponential ($e$) heart rate decay during recovery, and $a + b$ is the heart rate at the beginning of the recovery period ($t = 0$).

Differences between groups in the changes in stroke volume and cardiac output during the 4½-minute recovery period were tested with a mixed-model analysis of variance with a random patient factor.

Mean values and standard errors of the mean were calculated for all parameters for all participants. Parameters obtained at rest and with exercise were compared by means of a paired Student $t$ test. Differences between patients and control subjects were analyzed by means of the two-tailed unpaired Student $t$ test. A $P$ value of less than .05 was considered to indicate a statistically significant difference.

I Results

Exercise Testing Procedure

Table 1 gives an overview of the parameters obtained during the ergometer exercise test. No significant differences between the patients and the control subjects were found in peak oxygen consumption, peak carbon dioxide output, peak ventilation, maximum heart rate, and maximum workload. The ventilatory equivalent at peak exercise for oxygen uptake (patients 35.5 ± 1.1 vs control subjects 30.9 ± 1.1, $P = .004$) and carbon dioxide output (patients 30.9 ± 1.1 vs control subjects 26.6 ± 0.7, $P = .007$) were significantly higher for the patients compared with the control subjects.

Cardiac Response to Exercise

All patients had pulmonary regurgitation (right ventricular stroke volume: 27 mL ± 6, percentage 25% ± 5). None of the patients presented with marked pulmonary stenosis. At rest, the LV ejection fraction of patients (56% ± 3) was significantly lower than that of control subjects (64% ± 2) ($P = .04$). All participants were able to fulfill the exercise protocol at individually determined workloads. On the basis of findings at the lung function examination, a mean work load of 114 W ± 14 for the control subjects and 121 W ± 13 for the patients was selected as the exercise level for the MR examination. Differences in workload between the two groups were not significant ($P = .744$).

Table 2 is an overview of the cardiovascular response to submaximum exercise as assessed with MR flow mapping. A statistically significant increase ($P < .05$) from rest to exercise was found in heart rate, stroke volume, cardiac output, and peak flow in both control subjects and patients.

Recovery after Exercise

After cessation of exercise, heart rate recovered exponentially during the 4½-minute period to 14.88% ± 4.8 higher than the resting heart rate in the control subjects and to 13.2% ± 5.3 of that in the patients ($P = .476$). A half-time period of the exponential heart rate decay of 29.0 seconds ± 5.6 was found in control subjects compared with 22.2 seconds ± 3.5 in patients ($P = .386$). No difference was found in heart rate recovery between patients and control subjects during the entire period. Figure 2 shows the changes in heart rate during the 4½-minute recovery period.

Assessment of flow in the ascending aorta during recovery after exercise was possible in all participants. In each control subject, 19 flow maps were obtained after exercise. Figure 3 shows modulus and phase images acquired during exer-
cise and 4 minutes after termination of exercise. Figure 4 shows flow volume curves and the corresponding stroke volumes for a control subject and a patient during the entire protocol at rest, during exercise, and during the recovery period. The example shows the increase in stroke volume in response to physical exercise. Moreover, a shortening of the systolic flow peak and an increase in the peak flow volume were observed. Table 3 shows an overview of the hemodynamic data in control subjects and patients during recovery. All participants showed an initial increase in stroke volume after termination of exercise (Fig 5). However, the increase in maximum stroke volume during recovery was significantly larger than that at rest in patients (37% ± 13) and control subjects (10% ± 6) \( (P = .033) \).

Although stroke volume in control subjects (−5% ± 4) decreased linearly to the resting level by 3 minutes after exercise termination, that in patients (18% ± 12) remained significantly greater than the resting level during 4 minutes \( (P = .035) \). Differences in the changes in stroke volume during the 4½-minute recovery period were significant between the patients and control subjects \( (P < .01, \text{mixed-model analysis of variance}) \). The difference in stroke volume recovery was manifest in the changes in cardiac output during 4½-minute recovery period (Fig 6). Cardiac output decreased significantly more slowly in patients compared with that in control subjects \( (P < .01) \). Four minutes after termination of exercise, cardiac output compared with that at rest was significantly larger in patients (32% ± 13) than that in control subjects (7% ± 5) \( (P = .03) \).

**Discussion**

The results of the present study indicate that it is feasible to assess recovery of LV stroke volume after supine physical exercise by performing fast MR flow mapping in the ascending aorta. In patients with corrected tetralogy of Fallot, cardiac output recovery was prolonged compared with that for control subjects. This abnormal recovery was the result of an "overshoot" of LV stroke volume during recovery rather than heart rate.

As part of this observational study, we speculated about the possible mechanisms that underlay the abnormal recovery of LV stroke volume in patients.

**Fast MR Flow Mapping**

It has been shown previously that fast MR flow mapping is a valuable tool with which to study aortic flow at rest (16) and during exercise (17,18). In the present study, we applied a turbo field-echo echoplanar phase-contrast flow-mapping MR sequence that was validated by Pedersen and co-workers (18). They proved the feasibility of the sequence in the study of abdominal aortic flow at controlled levels of exercise. Owing to the use of multiple short echo-planar imaging readouts, the echo time was kept low, and fast image acquisition was possible. The sequence applied in the present study allowed sampling with improved temporal resolution.
compared with that reported earlier (17,18). While the duration of the systolic peak immediately after exercise may be reduced to 230 msec (17), the short heart phase interval used in the present study allowed accurate sampling of the ejection period during systolic flow with a minimum of six data points for all stages of exercise and recovery.

According to Hofman et al (23), a minimum of 3 pixels per vessel is required to allow accurate evaluation of blood volume flow rates. With the turbo field-echo echo-planar MR sequence used in the present study, the minimum diameter of the ascending aorta that was necessary to perform accurate measurements of volume flow through it was 12 mm, which is well below the lower limit of normal ascending aortic diameters of 23 mm (24).

The turbo field-echo echo-planar MR sequence used in the present study allowed assessment of flow events in the cardiovascular system that are subject to rapid dynamic alterations. This allowed MR imaging evaluation of the dynamic process of cardiovascular recovery after exercise.

**Table 3**

<table>
<thead>
<tr>
<th>Hemodynamic Data during Recovery</th>
</tr>
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<tbody>
<tr>
<td><strong>Recovery Time (min)</strong></td>
</tr>
<tr>
<td><strong>Group and Parameter</strong></td>
</tr>
<tr>
<td>Heart rate</td>
</tr>
<tr>
<td>Stroke volume</td>
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<tr>
<td>Cardiac output</td>
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<td>Peak flow</td>
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<tr>
<td>Cardiac output</td>
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<tr>
<td>Peak flow</td>
</tr>
</tbody>
</table>

Note.—Data (mean ± standard error of the mean) are percentage change from values at rest.

* Differences from respective data in control subjects were significant (P < .05, unpaired t test).

LV Stroke Volume Recovery

A number of investigators have evaluated cardiac function at rest and during exercise in patients after correction of tetralogy of Fallot (7,21). However, changes in LV function during recovery after exercise have not been studied, to our knowledge. An initial increase in LV stroke volume during recovery after exercise was found in all participants in the present study. Elevation of the stroke volume, or a so-called overshoot in cardiac function during recovery from physical exercise, has been described previously in healthy subjects (25,26) and in patients with coronary artery disease (29). The increase in stroke volume during recovery is ascribed to an afterload reduction (10) coupled with a relatively slow decrease in sympathetic stimulation (26,29). The afterload reduction is a result of a buildup of metabolites that sustain vasodilation. At the same time, the resistance offered by the contracting muscles is decreased (10). The combination of the latter two factors causes an abrupt reduction in the peripheral resistance (10).

Furthermore, levels of nitric oxide and norepinephrine play a role in modulation of cardiac function during recovery (29). In the present study, an increased elevation in the LV stroke volume during initial recovery and a prolonged period during which the stroke volume was increased after exercise were observed in the patients compared with those in control subjects. This resulted in a prolonged recovery of the cardiac output in the pa-
patients. The period and extent of increased stroke volume during recovery depend on the metabolic demand accumulated during exercise, the changes in myocardial function with exercise, and the extent of venous return during active (ie, loadless pedaling after exercise) recovery (25,30). The control subjects in our study stopped pedaling during the recovery from supine exercise; therefore, they accumulated metabolic demand during exercise. Changes in myocardial function during exercise seem to be the prime mechanisms underlying the overshoot of stroke volume after exercise.

Early onset of anaerobic metabolism during exercise can be caused by ventilatory abnormalities (34,35). A significantly increased ventilatory equivalent at peak exercise for oxygen uptake and carbon dioxide output was observed in the patients compared with that in the control subjects in our study, which suggests a maldistribution of ventilation and pulmonary blood flow (34). The inability to deliver oxygen normally during exercise may lead to an increased oxygen deficit and early onset of anaerobic metabolism (36). Therefore, the increased elevation of LV stroke volume and prolonged recovery in the patients in our study may be a result of the early onset of anaerobic metabolism and a higher oxygen debt with exercise. This may represent a mechanism to repay an oxygen deficit that is higher than that in control subjects with a normal heart rate recovery (25,31).

In patients with coronary artery disease, however, the only predictor of the rate of cardiac recovery is the degree of exercise-induced regional myocardial asynergy of the LV (30). In patients in our study with moderate to severe pulmonary regurgitation, LV function at rest was significantly impaired, but the response to exercise was similar compared with that in the control subjects. The results of Kondo et al (7) suggest that right ventricular volume overload alters LV function at rest and during exercise. Moreover, Pearlman et al (37) concluded that impairment of contractile reserve due to myocardial damage in the septum may be a cause of LV dysfunction during exercise after repair of tetralogy of Fallot.

The parameters evaluated in the present study do not allow a final conclusion about the status of LV function during exercise in patients with corrected tetralogy of Fallot. We speculate that LV function in response to exercise may play a minor role in the increased elevation of LV stroke volume and prolonged recovery.

The data obtained in the present study also do not allow a final conclusion about the apparent second increase in stroke volume that occurred during recovery in the patients. We ascribe the first increase to afterload reduction (peripheral resistance is reduced abruptly as a result of cessation of intense contraction of the leg muscles) coupled with a relatively slow decrease in sympathetic stimulation (26,29). Furthermore, levels of nitric oxide and norepinephrine play a role in modulation of cardiac function during recovery (29). We hypothesize that the second increase may be induced by an abnormal decrease in sympathetic stimulation (26) or abnormalities in the levels of nitric oxide and norepinephrine (29).

Limitations

Data for gas exchange were not obtained during MR assessment because of the lack of MR-compatible gas analysis equipment. The differences in cardiac function between patients and control subjects during recovery may indicate disturbed gas exchange in the patients; therefore, application of an MR-compatible gas analyzer is essential in any subsequent studies.

In the present study, we used an adjusted MR examination protocol that was focused on the application of MR flow mapping at rest, with exercise, and during recovery. Therefore, valuable information about pulmonary regurgitation and biventricular function with exercise was not available. Furthermore, a limited number of patients with tetralogy of Fallot were studied, but the sample size was sufficiently large to show statistically significant differences between control subjects and patients. However, we cannot rule out type II errors in the parameters that did not show significant differences.

In conclusion, findings in this study demonstrate the feasibility of assessing LV stroke volume during recovery from physical exercise by performing fast MR flow mapping. In the long term after correction of tetralogy of Fallot, we observed a delayed recovery of LV stroke volume. This abnormal recovery may reflect an altered metabolic response to exercise or dysfunction of the LV during exercise. Further investigation is warranted to
study the exact mechanism of abnormal cardiac recovery in patients after correction of tetralogy of Fallot.

Fast MR flow mapping allows assessment of cardiac function at rest, with exercise, and during recovery after exercise and may help evaluation of cardiac function in other patient groups, such as those with ischemic heart disease.

References