**Controlled Trial of Physical Training in Chronic Heart Failure**

**Exercise Performance, Hemodynamics, Ventilation, and Autonomic Function**

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**Background.** Many secondary abnormalities in chronic heart failure (CHF) may reflect physical deconditioning. There has been no prospective, controlled study of the effects of physical training on hemodynamics and autonomic function in CHF.

**Methods and Results.** In a controlled crossover trial of 8 weeks of exercise training, 17 men with stable moderate to severe CHF (age, 61.8±1.5 years; left ventricular ejection fraction, 19.6±2.3%), increased exercise tolerance (13.9±1.0 to 16.5±1.0 minutes, p<0.001), and peak oxygen uptake (13.2±0.9 to 15.6±1.0 ml/kg/min, p<0.01) significantly compared with controls. Training increased cardiac output at submaximal (5.9–6.7 l/min, p<0.05) and peak exercise (6.3–7.1 l/min, p<0.05), with a significant reduction in systemic vascular resistance. Training reduced minute ventilation and the slope relating minute ventilation to carbon dioxide production (−10.5%, p<0.05). Sympathovagal balance was altered by physical training when assessed by three methods: 1) RR variability (+19.2%, p<0.05); 2) autoregressive power spectral analysis of the resting ECG divided into low-frequency (−21.2%, p<0.01) and high-frequency (+51.3%, p<0.05) components; and 3) whole-body radiolabeled norepinephrine spillover (−16%, p<0.05). These measurements all showed a significant shift away from sympathetic toward enhanced vagal activity after training.

**Conclusions.** Carefully selected patients with moderate to severe CHF can achieve significant, worthwhile improvements with exercise training. Physical deconditioning may be partly responsible for some of the associated abnormalities and exercise limitation of CHF, including abnormalities in autonomic balance. (Circulation 1992;85:2119–2131)

**KEY WORDS** • heart failure • exercise training • hemodynamics • power spectral analysis • heart rate • norepinephrine

Physical training increases exercise tolerance in normal subjects and in patients with ischemic heart disease. Training has been shown to improve exercise hemodynamics, blood lipid profiles, susceptibility to ventricular arrhythmias, and psychological status, all of which would be of considerable benefit in chronic heart failure (CHF) if such patients could safely perform enough exercise to train. Patients with moderate to severe heart failure in whom exercise intolerance interferes most with daily life would have the most to gain from increased fitness, yet these patients have often been routinely excluded from exercise programs.

We designed a controlled crossover trial comparing home-based exercise training with activity restriction to look at the effects of exercise training in stable CHF. In addition to conventional hemodynamic, exercise, ventilatory, and symptom measures, we used three methods of assessing sympathovagal balance (heart rate variability, power spectral analysis of the ECG, and norepinephrine [NE] spillover) to critically assess whether short-term physical training could modify the abnormalities of autonomic control seen in moderate to severe CHF. The present trial was designed to answer the following questions. 1) Can patients with moderate to severe CHF achieve a training effect with regular exercise? 2) Compared with a control period of normal activity, does training improve exercise duration and maximal oxygen consumption? 3) Are there associated...
improvements in other known abnormalities of CHF including autonomic imbalance? The training protocol and exercise performance results of the first 11 patients have been published in an interim report, but other than this preliminary report, this is the first controlled, prospective study of physical training in CHF.

Methods

Study Design

The study, which was approved by the Central Oxford Research Ethics Committee, was a randomized crossover comparison of 8 weeks of exercise training against 8 weeks of restricted activity (rest). Two to three baseline laboratory visits were used to familiarize the patients to the exercise tests and other laboratory procedures. The physician conducting the tests was unaware of the training status of the patients. Habituation to test procedures was avoided by the patients not attending the hospital during the 8 weeks of either phase of the study.

Study Population

All subjects gave informed consent for this trial. Inclusion criteria were stable New York Heart Association class II–III heart failure of at least 3 months' duration; ischemic etiology (as evidenced by documented myocardial infarction and/or coronary arteriography and coronary bypass surgery); stable sinus rhythm; limitation of exercise by symptoms of dyspnea or fatigue only and ability to reach a respiratory exchange ratio of at least unity; absence of Holter monitoring evidence of sustained ventricular tachycardia or other serious arrhythmias; and absence of symptomatic angina or ECG evidence of ischemia limiting exercise. Radionuclide ventriculography was performed at baseline, but the results did not constitute part of the entry criteria. This test was not repeated during the study and did not constitute one of the tests of efficacy. This was decided because the trial was a crossover design requiring at least three assessment points, and it was not felt justified to ask the subjects to undergo three scans for this trial; therefore, no information is available on the effects of physical training on ejection fraction.

Training Program

The patients were instructed on the use of a training bicycle (Tunturi Professional Ergometer, Tunturi, Finland) that they kept for their use at home for 8 weeks. They were instructed to exercise at 50 rpm for 20 minutes 5 days per week and to keep the resistance setting of the bicycle so that their continuously monitored heart rate (Micro Sports Lab Computer, Triadcolour, London) was kept in the range of 60–80% of their previously determined maximum heart rate. Compliance was assessed as the percentage of expected bicycle wheel revolutions achieved over the training period.

Control Rest Phase

The patients were asked to avoid exercise above their normal prestudy routine and specifically to avoid exercise that would lead to feelings of dyspnea or exhaustion. No formal compliance assessment was made. The patients did not have the exercise bicycle in their houses during this phase of the trial.

Exercise Testing

At each visit, after overnight fasting and before administration of medication, the patients performed an incremental (4-minute, 25-W stages) upright bicycle exercise test to exhaustion, with 1-minute average measurements of respiratory gas exchange. Inspiratory flow (Harvard Instruments Dry Gas Meter) and expiratory oxygen and carbon dioxide concentrations (Servomex 570A and PA404 meters, Servomex, Crowborough, Sussex, England) were measured, and oxygen consumption and carbon dioxide production were calculated by standard formulas. The gas meters were calibrated against gases of known concentrations before each test.

Hemodynamic Measurements

On the same day after 1 hour's rest, a second exercise test was performed (supine posture) during which hemodynamic measurements were made. Measurements were made at rest and at the end of each 4-minute, 25-W incremental stage of the supine bicycle exercise test (Elema-Schönander, AM 368, Stockholm). Pulsed-wave Doppler ultrasonic measurements of ascending aortic blood velocity from the suprasternal approach were made using a Pedof Doppler ultrasound generator (Vingmed, Norway) and our own laboratory-made, computer-based, fast Fourier transform spectral analyzer. We used the intensity-weighted mean frequency in each 5-msec time bin (the integral of velocity and time for the ejection period) to calculate stroke distance. We used standard formulas and an echocardiographic measurement of aortic cross-sectional area (leading edge to leading edge, immediately distal to the sinus of Val-salva) to calculate stroke volume. Measurements of volume flow by this method in our laboratory have been validated in a flow rig and in humans against thermodilution and electromagnetic catheter measurements and found to be accurate (standard deviation of differences between methods in estimate of stroke volume, 8.7%). The accuracy of the Doppler cardiac output may be less during exercise because of the effects of body motion and increased respiratory excursion, but this is probably also a feature of other methods of measuring cardiac output. Dr. Coats reviewed the available validation studies of Doppler-derived cardiac output during exercise and concluded that the standard deviations of differences between Doppler-derived measurement and other techniques averaged 22%, significantly worse than at rest but still an acceptable level of accuracy for measurement during this difficult state. Blood pressure was measured by a previously validated automatic sphygmomanometer (Copal UA 251, Takeda Medical, Tokyo). Peripheral vascular resistance was calculated by the approximation of mean blood pressure divided by cardiac output.

ECG Recordings

During exercise. Heart rate was recorded at the end of each stage of a bicycle exercise test and was derived from the average of 20 beats. A three-lead ECG was recorded throughout exercise.
Twenty-four-hour Holter monitoring. Twenty-four-hour ECG monitoring was performed using a two-channel (modified V_1 and V_3 leads) recorder (Oxford Medilog II, Oxford Medical Instruments). Qualitative and quantitative ECG analysis was performed using a computerized nontriggered template system consisting of a Z80A preprocessor and DEC-LSI master, which was developed and validated in our laboratory. Analysis of the recordings was performed blind to the current training status.

Tapes were analyzed to obtain the mean and standard deviation of all RR intervals that had normal morphology and cycle lengths within 80% and 120% of the preceding cycle duration. Results are presented separately for the whole 24 hours and separately for daytime (14-20 hours) and nighttime (0-6 hours). These 6-hour periods were chosen as being unaffected by the trip to the hospital and most likely to represent daytime and sleeping states. They are not, however, full summaries of waking and sleeping heart rate behavior.

Resting ECG recording in the laboratory. During supine rest in a quiet, darkened room, 640 consecutive heartbeats were recorded on a Store 4 Racal-Thermionic FM tape recorder (Southampton, UK) at a tape speed of 15/16 in./sec. Lead V_3 was used for this recording. These recordings were used to perform power spectral analysis of variations in RR interval. No special attempts were made to control or alter the patient’s respiratory pattern during this recording, but special care was taken that the patient was relaxed, stable, and undisturbed.

Power Spectral Analysis of RR Interval Variability

The tape-recorded resting ECG signal from the laboratory recording period was digitized off-line by a 12-bit analog-to-digital converter (NB-MIO-16 board, National Instruments, Austin, Tex.) at a sampling rate of 500 samples per second. The converter was connected to a Macintosh IIcx computer (Apple Inc., Cupertino, Calif.) equipped with a 5-Mb random access memory and a 60-Mb hard disk. A “C” language program identified all the QRS complexes in each sequence and located the peak of each R wave. From these data, the RR intervals were obtained. For each sequence, 256 heartbeats were analyzed. Trends were removed from each sequence by subtraction of that same sequence after a 124-lag window smoothing procedure, following a previously described algorithm. Premature beats were interactively identified and corrected by linear interpolation with the previous and following beats.

Power spectral analysis of the RR interval signal was by an autoregressive model. Model coefficients were evaluated according to a modification of the Burg algorithm. Model order was assessed by Akaike criteria. In most cases, a model order between 9 and 13 was found to be adequate. Spectral components were obtained by a previously described decomposition method. This method was used to measure the area below each spectral peak.

We expressed the variation in Hertz rather than in cycles per beat, assuming that the RR interval changes were small with respect to the mean RR interval and considering the sampling time equal to the mean RR interval. The power spectrum shows two separate peaks: a higher-frequency peak related to respiration and a low-frequency peak unrelated to any respiratory event. Occasionally, the low-frequency peak is further subdivided into a low- and a very-low-frequency peak, but this was not done in this study because the very-low-frequency peak can be difficult to differentiate from low-frequency noise unless the recording period is very prolonged.

Power spectral analysis is a relatively new technique, and some explanation of its capabilities and limitations may be helpful. Spectral analysis is a mathematical technique in which variations in heart rate are analyzed in the frequency domain. In other words, this analysis can tell us how much of the variability of RR intervals occurs in a regular rhythmic fashion and how much of it occurs at different frequencies. From experiments on parasympathetic and β-blockade in dogs and humans, it appears that the high-frequency rhythm is entrained by the respiratory frequency and, apart from a small residual (probably mechanical) respiratory component seen after cardiac transplantation, is carried almost entirely by vagal activity. The low-frequency rhythm is mediated jointly by the vagus and the sympathetics but predominantly by the latter.

We evaluated the power of the harmonic components in the region between 0.03 and 0.14 Hz (low-frequency component, LF) and those in the range between 0.18 and 0.40 Hz (high-frequency component, HF).

To simplify comparison between spectra, we considered the relative percentage of each spectral component compared with the total oscillatory power and expressed it as normalized units (nu). In addition, we evaluated the absolute value of the HF area as an expression of respiratory sinus arrhythmia (RSA).

The relative amount of HF and the absolute amount of RSA have been considered as indexes of parasympathetic activity, whereas the relative amount of LF has been considered as an index of sympathetic activity. It must be stressed, however, that power spectral measurements are not strictly quantitative, because it is impossible to assess absolute measurements of oscillatory power in different frequency ranges without taking into account differences in heart rate variability. It has not been shown that power within a certain frequency band can be used to quantify differences in sympathetic or parasympathetic tone between individuals. Mostly, the ratio between high- and low-frequency power is used, and this ratio does not lend itself to simple quantitative analysis. No gold standard measure of autonomic balance exists. The power spectral technique gives qualitative and semiquantitative information, which, when combined with other autonomic measures, can help describe autonomic nervous control of the intact circulation.

NE Kinetics

NE kinetics were measured according to the techniques of Esler et al in seven subjects. [1-2,5,6-3H]norepinephrine (New England Nuclear) was given intravenously as a bolus (12 μCi, 0.44 MBq) followed by constant infusion (0.7 μCi, 0.026 MBq min⁻¹ m⁻²) for up to 60 minutes. Blood samples were collected at rest and at submaximal (50-W) supine bicycle exercise in both training and detraining phases of the study. Plasma NE
was measured by using high-performance liquid chromatography. The normal range in our laboratory is 120–300 pg/ml. Plasma [3H]NE was measured by liquid scintillation counting of alumina extracts with correction for recovery of a nonradioactive internal standard (dihydroxybenzylamine). NE plasma clearance and whole-body NE spillover were measured according to the following relations, which hold under steady-state conditions.

\[
\text{Whole-body NE clearance} = \frac{\text{Infusion rate (dpm/min)}}{\text{Plasma [3H]NE (dpm/ml)}}
\]

\[
\text{Whole-body NE spillover} = \frac{\text{Infusion rate (dpm/min)}}{\text{Specific activity of [NE] (dpm/pg)}}
\]

**Symptom Assessment**

Patients' completed scores from a modified Likert symptom questionnaire were used to assess severity of symptoms relevant to CHF at the end of each phase of the trial. Questions were asked on breathlessness, fatigue, chest pain, daily activity, and ease of daily activities, and the patients were asked to grade each on a scale of 1–7. Three questions were ordered with improvement being indicated by a higher score and two by a lower score to lessen bias, but for simplicity of presentation in the “Results” section, the scores were corrected so that for all questions, an improvement in symptoms is indicated by a higher score.

**Statistical Analysis**

The trial was analyzed according to the recommendations of Hills and Armitage25 for crossover trials and analyzed for the presence of period or carry-over effects, none of which were found. Analysis of variance followed by Student’s t test was used for normally distributed parameters, and Wilcoxon signed rank test was used for nonnormally distributed parameters. Significance at the 5% level or lower is reported and corrected where appropriate for multiple comparison testing by the Scheffe procedure. Data are presented as mean±SEM.

**Results**

**Patients**

Nineteen patients entered the trial, and two failed to complete the program. Both dropouts occurred in the first phase, which in both was the rest phase; in one, death followed progressive worsening of cardiac failure and the second underwent cardiac transplantation after an admission with severe cardiac failure. The remaining 17 patients completed the trial without adverse events and with no change in drug therapy. Patient characteristics are shown in Table 1 subdivided by the randomization order of treatments. Individual patient details of drug therapy are given in Table 2.

Patients were aged 61.8±1.5 years (range, 47–74 years). All had documented myocardial infarction (anterior alone in 12, anterior and inferior in two, inferior alone in two, and inferolateral in one); six had undergone coronary artery bypass grafting, and none had limiting angina pectoris. All subjects were taking diuretics (average furosemide dose, 77.6±10.0 mg), and 15 of

<table>
<thead>
<tr>
<th>TABLE 1. Patient Characteristics at Baseline</th>
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<tr>
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<tr>
<td>Training first</td>
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<tr>
<td>(n=8)</td>
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<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>LVEF</td>
</tr>
<tr>
<td>NYHA class II/III</td>
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<tr>
<td>Peak VO₂ (ml/min/kg)</td>
</tr>
<tr>
<td>Exercise time (minutes)</td>
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<tr>
<td>Height (cm)</td>
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<tr>
<td>Weight (kg)</td>
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</table>

Results are expressed as mean±SEM. LVEF, radionuclide left ventricular ejection fraction; NYHA, New York Heart Association.

17 were on ACE inhibitors. Mean radionuclide left ventriculographic ejection fraction was 19.6±2.3%. There was random allocation to rest or training first, and no significant differences were found in any of the baseline variables between those allocated to exercise first and those to rest first.

**General Training Results**

Overall compliance to the training program was good, with a mean (range) compliance of 77.3% (26–116%)

In one patient, the revolution counter broke during the training phase, so compliance data were available in only 16 subjects. There were no adverse training-related side effects reported by the subjects other than mild fatigue after exercise. Pharmacological treatment remained stable for 3 months before the study and for the duration of the study in all 17 completed subjects. There was no consistent weight change produced by training.

**Exercise Testing and Ventilatory Function**

Compared with the rest phase, training significantly increased upright bicycle exercise time (13.9±1.0 to 16.5±1.0 minutes, p<0.001) and increased peak oxygen uptake (13.2±0.9 to 15.6±1.0 ml/min/kg, p<0.01). Individual patient data on the change in exercise time are shown in Figure 1. There was no significant difference between the baseline and rest periods. Upright bicycle exercise was performed after training with lower heart rates at comparable work loads. After training, there were significant reductions in submaximal heart rate at

![Figure 1. Graph of individual and mean±SEM patient upright exercise durations for baseline, training, and detraining periods. Order has been sorted. ***p<0.001 for comparison between training and detraining periods, n=17.](image-url)
25-W and 50-W exercise with no change in peak heart rate (see Figure 2). Resting heart rate was reduced nonsignificantly from 84.6±3.5 to 81.0±4.2 (p=0.09), 25-W heart rate from 101.0±3.9 to 92.4±4.1 (p<0.05), 50-W heart rate from 111.1±4.1 to 103.2±4.6 (p<0.05), and peak heart rate unchanged (135.9±4.7 to 133.4±6.1, p=NS). The submaximal work load (50 W) rate-pressure product (−11.8%, p<0.01) was also significantly reduced by training, indicating a more efficient exercise performance with respect to myocardial oxygen requirement.

Submaximal exercise performance was also improved by training. Taking the point during exercise at which the respiratory exchange ratio equaled unity as an approximate marker of when anaerobic muscular metabolism is starting, this was achieved later in the exercise protocol after training (+1.8 minutes, p<0.01) and occurred at a higher oxygen uptake (13.7±0.7 compared with 11.9±0.8 ml/kg/min, p<0.001).

To study the control of ventilation during exercise, we looked at the relation between minute ventilation and the rate of carbon dioxide production (V/VCO₂ slope), which has been shown to parallel the severity of CHF. The V/VCO₂ slope was significantly reduced by physical training (0.038±0.004 to 0.034±0.003, p<0.05). An example in a single subject is shown in Figure 3. Overall, there was no significant change in the intercept of this slope nor in peak ventilation achieved, but minute ventilation was significantly reduced at submaximal work loads by training. The relation between ventilation and work load in Figure 4 shows a significant reduction in

TABLE 2. Individual Patient Data

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Diuretics</th>
<th>ACE inhibitor (duration)</th>
<th>Other agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>47</td>
<td>F 80, A 10</td>
<td>C 100 (10 months)</td>
<td>Aspirin</td>
</tr>
<tr>
<td>2</td>
<td>63</td>
<td>F 40, A 5</td>
<td>C 75 (12 months)</td>
<td>Aspirin</td>
</tr>
<tr>
<td>3</td>
<td>63</td>
<td>F 40, A 5</td>
<td>C 75 (12 months)</td>
<td>Aspirin, amiodarone</td>
</tr>
<tr>
<td>4</td>
<td>66</td>
<td>B 2</td>
<td>E 10 (5 months)</td>
<td>Aspirin, slow K</td>
</tr>
<tr>
<td>5</td>
<td>65</td>
<td>F 40</td>
<td>C 75 (2 years)</td>
<td>Fenbufen</td>
</tr>
<tr>
<td>6</td>
<td>59</td>
<td>F 120, A 15</td>
<td>L 10 (18 months)</td>
<td>Aspirin</td>
</tr>
<tr>
<td>7</td>
<td>64</td>
<td>F 40</td>
<td>C 75 (12 months)</td>
<td>Aspirin</td>
</tr>
<tr>
<td>8</td>
<td>62</td>
<td>B 1</td>
<td>C 75 (16 months)</td>
<td>Aspirin, digoxin, ISDN</td>
</tr>
<tr>
<td>9</td>
<td>53</td>
<td>B 4, A 10</td>
<td>E 10 (18 months)</td>
<td>Warfarin, ranitidine</td>
</tr>
<tr>
<td>10</td>
<td>68</td>
<td>B 2</td>
<td>C 75 (7 months)</td>
<td>Warfarin, slow K</td>
</tr>
<tr>
<td>11</td>
<td>58</td>
<td>B 2, A 20</td>
<td></td>
<td>Warfarin, digoxin</td>
</tr>
<tr>
<td>12</td>
<td>73</td>
<td>F 40, A 5</td>
<td>C 37.5 (20 months)</td>
<td>Diltiazem, dipyridamole</td>
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<tr>
<td>13</td>
<td>74</td>
<td>F 240</td>
<td>C 37.5 (12 months)</td>
<td>Warfarin</td>
</tr>
<tr>
<td>14</td>
<td>60</td>
<td>F 160, S 100</td>
<td>C 37.5 (8 months)</td>
<td>Warfarin</td>
</tr>
<tr>
<td>15</td>
<td>64</td>
<td>F 80, A 10</td>
<td>E 10 (9 months)</td>
<td>Aspirin</td>
</tr>
<tr>
<td>16</td>
<td>67</td>
<td>F 160, A 10, S 50</td>
<td>C 50 (6 months)</td>
<td>Aspirin, amiodarone</td>
</tr>
<tr>
<td>17</td>
<td>59</td>
<td>F 40</td>
<td>L 10 (7 months)</td>
<td>Aspirin</td>
</tr>
</tbody>
</table>

F, furosemide; A, amiloride; S, spironolactone; B, bumetanide; C, captopril; E, enalapril; L, lisinopril; ISDN, isosorbide dinitrate. All figures after drugs refer to daily dose in milligrams. All drugs were stable for 3 months before entering the trial and for the duration of the trial. For the ACE inhibitors, the duration of stable therapy before trial entry is given in parentheses.
submaximal minute ventilation at 25-W and 50-W exercise with no difference in resting or peak ventilation.

Hemodynamic Assessment During Supine Exercise

Hemodynamic measurements were obtained at the end of each 4-minute stage of a supine bicycle ergometer test as described in "Methods." In one of the 17 subjects, the Doppler recordings during the training phase were corrupted by electrical interference and were not usable. The exercise duration was increased by training from 10.7±0.7 to 12.3±0.7 minutes (p<0.001). The hemodynamic responses are shown in Figure 5. There was a significant systemic vasodilatation produced by training at rest, submaximal (25-W), and peak exercise. This was associated with an increase in cardiac output at submaximal (25-W) and peak exercise, with no significant change in mean blood pressure. The increased cardiac output was largely due to increased stroke volume at submaximal exercise with no change in heart rate, whereas at peak exercise there was also an increase in peak heart rate.

ECG Recordings

Twenty-four-hour Holter monitoring. Training produced significant reductions in 24-hour mean heart rate (79.1±3.0 to 77.0±2.7 beats per minute, p<0.05) as well as separately for both daytime and nighttime heart rate averages (see Table 3). No serious or complex ventricular arrhythmias were detected on any of the recordings, but there was a significant excess of ventricular ectopic beats during the training phase (rest phase, 29.4±8.6; training, 60.7±24.5 hour⁻¹, p<0.05), which may have been related to the slower heart rate unmasking ventricular automaticity. There was no significant change in the rate of early premature ventricular beats.

Twenty-four-hour heart rate variability, indicated by the standard deviation of normal morphology RR intervals, was significantly higher after training (125.6±9.0 versus 109.3±8.3 msec; n=14, p<0.05). As shown for individual subjects in Figure 6 (left panel), nocturnal heart rate variability was also higher after training (96.4±9.3 versus 82.4±7.5, p<0.05), but the daytime heart rate variability was not significantly different (101.0±11.0 versus 90.5±7.5 NS) possibly because of the effects of different levels of physical activity between the two phases of the trial.

Resting ECG recording in the laboratory. During supine rest in a quiet, darkened room, 640 consecutive heartbeat records were recorded as described in "Methods." Only normal morphology complexes with RR intervals between 80% and 120% of the preceding RR interval were included in the calculation of heart rate variability.
to exclude an effect of increased ectopics on the measure of heart rate variability. Resting heart rate variability (standard deviation of all 640 consecutive beats) was significantly higher after training (40.9±6.1 versus 34.3±6.5, p<0.05). An individual example of the effects of physical training is shown by use of an RR interval frequency histogram in Figure 7. Overall patient results are shown in Figure 6, right panel.

**Power Spectral Analysis**

An example of a 256-beat RR interval tachogram and spectral display is shown in Figure 8 for a single subject. The power of the LF heart rate variability component, expressed in normalized units (see "Methods"), indicative of sympathetic activity, was reduced after training (49.7±6.9 versus 63.1±5.1; n=15, p=0.012). Two patients of 17 had too many ventricular ectopic beats to enable power spectral analysis of these recordings. In the other 15, a period of ECG recording with few or no ectopics was chosen for analysis, and when no completely ectopic-free period of 256 beats could be found, ectopic beats were deleted and the two RR intervals affected by this editing were corrected by linear interpolation with the previous and following RR intervals (see "Methods").

In 10 of 15 patients, there was considerable reduction in the LF measure of sympathetic drive after training, whereas the remaining five showed no change or a slight increase (Figure 9, left panel). The greater degree of variability in this response compared with mean 24-hour rate or heart rate variability may reflect a greater degree of inherent variability in this measurement, or alternatively, a poorer relation to fitness effects. The relative amount (in normalized units) of the HF component increased after training (40.4±6.9 versus 26.7±4.9; n=15, p<0.05), as did an absolute measure (in milliseconds squared) of respiratory sinus arrhythmia (343.9±201.3 versus 192.7±146.0 msec²; n=15, p<0.05). Both can be considered indexes of vagal tone. As expected, the same 10 out of 15 patients showed an augmented HF component (parasympathetic) after training (Figure 9, right panel) as showed a decrease in the LF component. The 10 autonomic responders could not be distinguished from the nonresponders on the basis of disease severity, drug usage, or history of coronary surgery.

**NE Kinetics**

Whole-body NE spillover at rest was 381±51 ng/min/m²; this decreased to 321±49 ng/min/m² (p<0.05) after physical training. Resting whole-body NE clearance was not changed (1,199±92 versus 1,157±110 ng/min/m², p=NS). During submaximal supine bicycle exercise (50 W), whole-body NE spillover tended to be lower after physical training, although the difference did not reach statistical significance (592±152 versus 648±102 ng/min/m², p=NS).

**FIGURE 6.** Graphs show effects of physical training on nocturnal (0–6 AM) heart rate variability (left panel, n=14) and heart rate variability of 640 consecutive beats (right panel; laboratory recordings, n=15). For method of calculation, see text. *p<0.05 for comparison rest versus training. SD, standard deviation.

**FIGURE 7.** Schematic demonstration (frequency histogram) of the effect of training on resting heart rate variability expressed as standard deviation (SD) of the RR intervals of 640 consecutive beats recorded in the laboratory at rest in a single subject. Left panel is after the rest phase; right panel is after physical training.
**Symptom Assessment**

There were significant improvements (higher scores better) after training in patient-scored symptoms of breathlessness (2.5±0.3 to 3.9±0.4, \( p < 0.01 \)) and fatigue (2.4±0.4 to 4.6±0.4, \( p < 0.001 \)) but no change in the perception of chest pain. Significant improvements with training were also noted in the daily activity scores (1.4±0.5 to 4.6±0.4, \( p < 0.01 \)) and in the ease of these activities (2.6±0.3 to 4.0±0.4, \( p < 0.01 \)).

**Correlates of Improved Exercise Performance**

To elucidate the factors most likely to predict the improvement in exercise capacity, simple and multiple linear regression analysis was performed for baseline parameters against the percentage improvement in upright exercise time or maximal oxygen uptake; these two were very highly correlated, as expected, and either could substitute in the regression equations. None of the baseline characteristics significantly predicted improvement; in particular, there was no evidence for the more severely affected patients with lower initial left ventricular ejection fractions or lower peak oxygen uptakes having a different response to training. There was, however, a strong correlation between improvement and the independently measured compliance to the program \( (r=0.74, p<0.01) \); this relation is shown in

**Figure 8.** Tracings show effect of physical training on the RR interval tachogram (display of individual RR intervals) for 256 consecutive beats (upper panels) and on the low- (0.08 Hz) and high-frequency (0.25 Hz) spectral components after power spectral analysis of RR variability (lower panels) in an individual patient. Note the higher variability after training and its more predominant high-frequency pattern. This individual subject trained first and then entered the resting (detraining) phase.

**Figure 9.** Graphs show effects of physical training on low-frequency (left panel) and high-frequency (right panel) oscillatory components. Normalized units (nu), percentage of each spectral component of the total oscillatory power, both \( n=15 \). Individual subjects are identified by number.
Figure 10. Graph shows relation between percentage increment in exercise tolerance against compliance to the training program; n=16.

Figure 10. There was no significant correlation between the severity of heart failure (measured by either ejection fraction or peak oxygen uptake) and compliance to the program.

We investigated whether other patient characteristics were related to the extent of training-induced changes in the measures of autonomic function. There was no significant effect on these changes (either absolute or percentage change) of the site of prior myocardial infarction, the history of coronary bypass grafting, the duration of heart failure symptoms, or the taking of or duration of any particular cardiovascular medication. There were only two subjects taking digoxin, only one on a calcium antagonist, and only two not taking an ACE inhibitor; therefore, these numbers were too small to determine whether these medications significantly affected the training response.

We determined which training-induced change was best correlated with the improvement in exercise performance as measured by the percentage increase in exercise duration. The percentage increase in heart rate variability was the best correlate of improvement in exercise performance ($r=0.79$, $p<0.01$). The correlation between the increase in supine exercise tolerance and the percentage reduction in NE spillover was also strong ($r=-0.72$, $p<0.01$).

Using the increase in peak oxygen uptake as the dependent variable instead of exercise duration, very similar correlations were found. The percentage reduction in submaximal exercise heart rate and the percentage increase in nocturnal heart rate variability were the strongest correlates of improvement ($r=-0.70$ and $r=0.82$, respectively). Other changes were not significant at the 1% level.

Correlations Between Baseline Measurements of Autonomic Balance

At baseline, the different methods of estimating autonomic balance correlated poorly and nonsignificantly with each other, with the exception of the expected inverse correlation between LF and HF components of heart rate variability ($r=-0.92$, $p<0.001$). All methods, however, showed an improvement in sympathovagal balance after training, and as described in the previous section, the changes in each method produced by training were well correlated with improved exercise tolerance.

Discussion

There are many similarities between the abnormalities associated with CHF and those seen in physical deconditioning. Both conditions are associated with exercise intolerance, sympathetic activation, reduced heart rate variability, wasted skeletal muscle, and depleted skeletal muscle oxidative enzymes. In CHF, acute pharmacologically or transplant-induced improvements in hemodynamics are not associated with immediate improvements in exercise performance, because the increased exercise tolerance often takes several weeks to develop. This may be due to the need for increased activity to reverse some of the secondary abnormalities of CHF, which may themselves have actually become the limiting factors to exercise. This study gives some insight into whether exercise training alone can partially reverse the features of deconditioning seen in CHF and thereby improve symptoms and exercise performance.

General Conclusions

The results show conclusively that in carefully selected patients with ischemic heart failure of moderate to severe degree, an exercise training program at home improves exercise performance, hemodynamics, ventilation, autonomic function, and symptomatic status. This has been shown in the first prospective, controlled trial of training in this patient group and questions the commonly held belief that avoidance of exercise is required in all forms and stages of heart failure. The degree of improvement shown here in a controlled trial is similar to that reported by Sullivan and colleagues in retrospective, uncontrolled reports of rehabilitation in slightly less severely affected patients and also in early reports of training in patients with left ventricular dysfunction.

Comparison With Training in Normal Subjects

The percentage increase in exercise time or peak oxygen consumption is similar to that seen in training programs in normal subjects and patients with ischemic heart disease without heart failure. The features of the training response seen here are mostly consistent with a normal response to regular exercise training, including reductions in 24-hour heart rate and blood pressure and a reduction in exercise heart rate and rate–pressure product. Two features are, however, not typical of the training response described in normal subjects. First, the reduction in heart rate during exercise seen in the upright posture is not duplicated in the supine exercise test, and second, the increase in cardiac output we found at submaximal work loads is not usually seen in normal subjects after training. The explanation of these differences may be due to the fact that the supine posture was used in this study for exercise with hemodynamic measurements. A similar differential posture-dependent effect of training on heart rate has been seen in studies that have looked at supine versus upright exercise performance after bed rest and training.
cance. This is probably due to chance, because day, night, and 24-hour average heart rates all showed significant reductions, as did the 256-beat period of ECG recording taken for the power spectral analysis. It may be that anticipation of exercise causes an increased heart rate, which masks the training-induced bradycardia.

The increased stroke volume we found after training is consistent with the training response in normal subjects,3 the mechanism of which is not established. It may represent enhanced diastolic recoil and/or a true increase in left ventricular mass and contractile performance. We have no data from our studies to determine which of these or other factors are operative, nor can we tell whether the increased stroke volume response was due to an increased end-diastolic volume, a decreased end-systolic volume, or both. Athletes have been shown to use both mechanisms to increase stroke volume during exercise,42 a feature erroneously considered to indicate left ventricular dysfunction because it leads to a reduced ejection fraction despite enhanced cardiac performance.42

This study cannot tell us the precise mechanisms of the training-induced improvements in exercise capacity, but as the changes in ventilation, heart rate, and NE spillover would allow the same work load to be achieved at a lower sympathetic drive, heart rate, myocardial oxygen requirement, and minute ventilation, it is then plausible that reserve exercise capacity could be enhanced. It is not known whether these are direct effects or whether they reflect reflex adaptations to enhanced skeletal muscle performance.

**Training Effects on Autonomic Balance**

Abnormalities in the autonomic control of the circulation have been frequently described as part of the syndrome of CHF.28,43 Little is known of the mechanism of these changes in autonomic balance. Chronic activation of the adrenergic system, decreased vagal activity, and impaired arterial baroreflex activity have all been described in CHF.43,44 Furthermore, these may be prognostically important abnormalities, as reduced heart rate variability and baroreflex sensitivity and increased plasma NE levels have all been shown to be independent predictors of increased mortality in CHF.45–47 Nonpharmacological approaches to reducing sympathetic activity (such as exercise training) could, therefore, be of considerable importance, given the other improvements in risk factors that regular exercise can produce.

Exercise training has been shown to enhance heart rate variability and baroreflex gain and reduce catecholamines in subjects with normal left ventricular function.27,29 Recent preliminary reports have suggested a restoration of the baroreflex gain and heart rate variability after pharmacological treatment48 or transplantation,40 but the beneficial effects may take many weeks to develop, raising the possibility that physical conditioning may be contributing to the improvements described after these interventions. Nothing previously has been published on the effects of physical training on the abnormalities of autonomic control of the circulation in CHF. In this study, physical training produced significant reductions in 24-hour, daytime, and nighttime heart rate as well as increased heart rate variability in both waking and sleep states. These findings may reflect beneficial changes in central autonomic drive and/or baroreflex and cardiopulmonary reflex gains29,49 and are in agreement with the increased vagal tone described after endurance exercise training in sedentary hypertensive men.29,50 The significant correlations between improved exercise performance after training and the changes in various measures of autonomic tone suggest that there may be a beneficial feedback between improvement in cardiovascular function and shifts in autonomic balance from sympathetic to vagal predominance.

A number of studies have been conducted51–53 using power spectral analysis of heart rate variability as a noninvasive means of assessing “tonic” autonomic input to the heart. This method has, however, been little used to assess the autonomic balance in a controlled intervention trial in CHF. A reduced sympathetic activity after training suggested by the changes in power spectral components was confirmed in this study by a significant reduction in whole-body NE spillover. Even this method is not a direct measure of sympathetic activity, as it cannot differentiate between different causes for the measured increase in the rate at which NE spills over from the nerve terminals. This could be due to increased presynaptic release of NE, decreased uptake of NE by uptake1, or a combination of mechanisms. We have no information in this study on the mechanisms of the apparently reduced sympathetic activity.

An increase in vagal tone was suggested by the increase in both the relative and absolute oscillatory powers of the HF power spectral component and the relative bradycardia both during exercise and on 24-hour ECG monitoring.

We found no evidence for any differences in the autonomic effects of training when the patients were subdivided on the basis of disease severity and duration, pharmacological treatment, or history of coronary bypass grafting. All except two of the patients were taking ACE inhibitors (known to affect parasympathetic tone), so we can conclude that training has effects additive to ACE inhibition, but we cannot determine whether there is any significant interaction between training and ACE inhibition. This is the subject of a blinded trial currently underway.

The lack of significant intermethod correlations between the individual autonomic techniques at baseline in our patients may indicate that in CHF, individual measures of autonomic balance reflect different aspects of circulatory control, and a comprehensive description necessitates more than one method. These results suggest that single techniques for estimating autonomic balance may be inadequate to describe autonomic function in CHF.

**Significance of Training Effects**

Cardiac failure is associated with enhanced vasoconstrictor activity caused by activation of the sympathetic nervous, renin–angiotensin, and arginine–vasopressin systems.54 This endogenous release of vasoconstrictor neurohormones may eventually play a deleterious role in the development of CHF, increasing the loading conditions of the failing ventricle and favoring the development of complex ventricular arrhythmias. Rest-
ing supine plasma NE is a significant independent predictor of mortality among patients with moderate to severe CHF. The results of this trial suggest that physical training may not only improve exercise tolerance but may also improve prognosis because of reductions in adverse prognostic features (e.g., increased NE spillover, reduced heart rate variability).

Training in ischemic heart disease without heart failure has been suggested to have a beneficial effect on prognosis.

Comparison With Other Therapeutic Approaches

Previous reports have shown that the reduced heart rate variability in heart failure is partially corrected by cardiac transplantation. Our values of heart rate variability in the baseline phase are similar to those described by Smith et al before transplantation. The change in heart rate variability produced by training seen in our study is of similar magnitude to the increased variability described after transplantation. Increased physical activity and training effects after transplantation may explain a large part of the improved heart rate variability described by Smith and colleagues and may also explain the delay in improvement seen after cardiac transplantation. Similar delays are described after ACE inhibitor treatment and may similarly reflect the need to undo some of the effects of physical deconditioning.

Physical Deconditioning as a Complication of CHF

Prolonged inactivity is common in advanced heart failure. This will lead to deconditioning of the skeletal muscle and cardiovascular system, which may be partly responsible for the abnormalities of autonomic control of heart rate described in heart failure. Future studies should control for conditioning status when assessing autonomic function in heart failure in either cross-sectional or intervention studies.

The training-induced increase in cardiac output and reduced peripheral resistance may be primarily a peripheral adaptation either with reduced vasoconstrictor influences or with enhanced skeletal muscle bulk increasing effective limb vasodilatory capacity via an increased muscle vascular network. It is known that there is a profound wasting of skeletal muscles in CHF (N. Buller and P. Poole-Wilson, personal communication), and this may be partially reversed by exercise training of the leg muscles. In addition, there may be an improvement in left ventricular pumping capacity, perhaps resulting from a true positive inotropic effect of training as seen in animals. Thus, the increased submaximal and peak cardiac output produced by training could be due to changes in the peripheral circulation, preload and afterload changes, or direct positive inotropic changes in ventricular muscle such as that described in athletes.

Changes that have been proposed as important limitations to exercise in CHF such as skeletal muscle histological and metabolic changes may also be partly attributable to muscle wasting secondary to prolonged inactivity. Further prospective trials early in the evolution of heart failure would be necessary to show whether the secondary changes could be ameliorated by avoidance of physical deconditioning.

Ventilatory Effects

Beneficial reductions are seen in minute ventilation during exercise. The slope of the ventilation–to–carbon dioxide production relation has been used as a marker of the severity of CHF, and this has been significantly improved by physical training. These findings may help explain the reduced sensation of breathlessness observed in this trial and may allow a greater respiratory reserve during endurance exercise. Whether this beneficial effect on ventilation reflects more efficient muscular performance, reduced pulmonary capillary wedge pressures, or an improved matching of ventilation to perfusion in the lung cannot be answered by this study but could provide an interesting insight into the poorly understood basis for the excessive ventilation seen in CHF.

Limitations

Limitations to the extension of this trial into treatment of a wider patient group include the very strict entry criteria and the selection of a homogeneous patient population. Only patients with an ischemic etiology were entered into this trial, and it remains a possibility that some of the idiopathic cardiomyopathies may have an adverse response to the repetitive sympathetic stimulation of exercise (despite perhaps a reduction in sympathetic activity throughout the rest of the day) or may not show the same benefits in exercise tolerance and autonomic balance. No patients with limiting angina were recruited into this trial, but with the known benefits of exercise training on angina thresholds and collateral development, it is likely that training would be of benefit in the patients with mixed heart failure and angina. It may seem surprising that patients with an ischemic etiology did not have ECG evidence of myocardial ischemia, but some had had bypass grafting and all were highly selected so that reversible myocardial ischemia was not a cause of exercise limitation. In addition, no patients with serious ventricular arrhythmias (e.g., ventricular tachycardia) were recruited; hence, it may be argued that these patients are for both these reasons not truly representative of a general CHF population. The results remain valid for this specific group, and similar studies in different groups of heart failure patients would clearly be worthwhile.

The methods for assessing autonomic function have not been rigidly validated in CHF because no gold standard exists that can be used in intact humans. Differences in \( \beta \)-receptor responsiveness will affect nerve traffic measures (e.g., NE spillover) differently to end-organ response measures (e.g., heart rate and power spectral measures). No data exist on the effect of physical training on \( \beta \)-receptor function in CHF. The wide range of autonomic functional measures used here, all showing a similar trend, go some way to overcoming the lack of a truly representative and quantitative measure of sympathetic and vagal control of the circulation.

Safety and prognosis cannot be addressed in a small, intensive study of this nature, but an overview of rehabilitation programs suggests an overall improvement in prognosis in ischemic heart disease. The incidence of potentially fatal exercise-induced arrhyth-
mias in rehabilitation programs or exercise testing in heart failure is very low and would add a negligible extra risk, given the extremely poor prognosis of these patients. One hundred minutes of exercise per week would add very little to their risk of death based on the incidences of arrhythmias seen in rehabilitation programs and in maximal exercise testing in heart failure trials. There is also the possibility of improving prognosis by reducing the susceptibility to ventricular arrhythmias and improving heart rate variability and perhaps other cardiovascular risk factors including blood lipids and sympathetic activation.

At what stage heart failure patients should be advised to train cannot be definitively answered in this study. Training is beneficial after the early healing phase of myocardial infarction; provided that the patient is stable with no evidence of exercise-induced ventricular arrhythmia and provided that diuretic treatment is optimized, training should be recommended down to the severity of patients in this report, i.e., the ability to perform at least 50-W bicycle exercise for 3–4 minutes. The intensity of training should, however, be customized for each patient and only recommended after detailed cardiac and cardiopulmonary evaluation.

Conclusions

Training can improve the symptoms, exercise performance, hemodynamics, ventilation, autonomic function, and symptoms in stable moderate to severe heart failure patients. The possibility that exercise could lessen or reverse some of the secondary abnormalities of CHF is raised, and recommendations of the use of training in CHF are proposed.

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