Age-related effects of exercise training on diastolic function in heart failure with reduced ejection fraction: The Leipzig Exercise Intervention in Chronic Heart Failure and Aging (LEICA) Diastolic Dysfunction Study

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Aims
Diastolic dysfunction (DD) was identified as a predictor of adverse prognosis in heart failure with reduced ejection fraction (HFREF). It is, however, unknown if DD is improved by exercise training, which is known to induce reverse remodelling, and if the training effect is attenuated in elderly HFREF patients. We therefore assessed DD in a cohort of referent controls (RCs) and HFREF patients and studied the response of DD to endurance exercise in two age groups (≤55 years and ≥65 years).

Methods and results
Sixty RC (30 ≤ 55 years, mean age 50 ± 5 years; 30 ≥ 65 years, 72 ± 4 years) and 60 HFREF patients (30 ≤ 55 years, 46 ± 5 years; 30 ≥ 65 years, 72 ± 5 years, EF 28 ± 5%) were randomized to 4 weeks of supervised endurance training or to a control group. Exercise training was effective in reducing LV isovolumetric relaxation time by 29% in young and by 26% in old HFREF patients (P < 0.05 for both). As assessed by tissue Doppler, septal E′ increased by 37% in young and by 39% among old HFREF patients (P < 0.005 for both) resulting in a significant decrease in the E/E′ ratio from 13 ± 1 to 10 ± 1 in young and 14 ± 1 to 11 ± 1 in old HFREF patients (P < 0.05 for both). Serum levels of N-terminal pro brain natriuretic peptide were significantly reduced after endurance training in HFREF patients of all ages.

Conclusion
In HFREF, diastolic function is significantly impaired in all age groups. Endurance training is highly effective in improving left ventricular diastolic function in HFREF patients regardless of age. This study is registered at ClinicalTrials.gov (number: NCT00176319).

Keywords
Ageing • Diastolic function • Exercise • Aerobic endurance • Heart failure • Systolic

Introduction
It is increasingly recognized that diastolic dysfunction (DD) is highly prevalent among patients with heart failure with reduced ejection fraction (HFREF) affecting up to 78% of all patients with reduced LV ejection fraction.¹–³ In the clinical context of HFREF, DD has been identified as an important predictor of increased mortality and reduced exercise capacity; a number of studies have documented the prognostic relevance of Doppler-derived diastolic parameters (E-wave velocity, E/A ratio) in HFREF patients.⁴–⁹ These findings were recently corroborated using tissue Doppler-derived measures, such as reduced E′ and elevated E/E′ ratio.¹⁰–¹⁴

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The prevalence of diastolic left ventricular dysfunction is influenced by a number of clinical factors: among those age, hypertension, obesity, and diabetes are clinically most relevant.\(^{15,16}\) The impact of ageing on diastolic function was documented in elderly individuals, who show a prolonged isovolumetric relaxation time (IVRT) and deceleration time (DT), a reduced early diastolic filling rate (E), and an augmentation of the atrial component of LV filling (A) resulting in a reduced E/A ratio.\(^{17}\) These observations were corroborated by state-of-the-art tissue Doppler measurements in the Umeå Heart Study where a marked decrease in early diastolic velocities was recorded with age (from 16 cm/s at 30 years to 9 cm/s at 80 years) accompanied by a corresponding significant increase in late diastolic velocities (from 10 to 16 cm/s).\(^{18}\)

Up to now, no therapeutic strategies to improve diastolic function in HFREF have been established. Based on randomized clinical studies confirming a training-induced reverse remodelling in HFREF patients after 3–6 months of aerobic exercise training\(^{19,20}\) and a smaller previous conventional Doppler study indicating that improvement in diastolic function can be achieved by endurance training in HFREF over 2 months,\(^{21}\) we hypothesized that a high-intensity 4-week endurance training program may effectively improve diastolic left ventricular dysfunction as measured by state-of-the-art echocardiographic assessment, including tissue Doppler.

The LEICA study research protocol was approved by the University of Leipzig Ethics Committee and all patients provided written informed consent before entry into the study. To achieve a difference in mean age of \(\sim20\) years between the young and old cohort RC and patients aged \(\leq55\) years and \(\geq65\) years were included.

### Exclusion criteria

Exclusion criteria for both RCs and patients with reduced EF were significant valvular heart disease (\(>\) grade II), uncontrolled hypertension, insulin-dependent diabetes mellitus, history of LV tachycardia/fibrillation without implanted cardioverter defibrillator (ICD), peripheral vascular disease, pulmonary disease, or orthopaedic comorbidities precluding exercise training. Given the high prevalence of atrial fibrillation in HFREF patients, it would have been unrealistic to exclude patients with sinus rhythm. In recent years, the application of tissue Doppler-derived parameters such as E’ has extended the reliability of assessments of diastolic function to patients on AF.\(^{22}\) For patients with atrial fibrillation, only E wave velocity, IVRT, DT, and E’ were reported. The prevalence of atrial fibrillation did not change during the study period.

The LEICA study research protocol was approved by the University of Leipzig Ethics Committee and all patients provided written informed consent before entry into the study.

### Training intervention

Patients were randomly assigned to either a training group or an inactive control group by drawing a sealed envelope with intervention assignment enclosed. Four baskets of envelopes (\(n=30\) each) were prepared for each of the four cohorts: RC \(\leq55\) years, RC \(\geq65\) years, HFREF patients \(\leq55\) years, and HFREF patients \(\geq65\) years. Cardiopulmonary exercise testing, echocardiography, and venous blood samples were obtained at baseline and after the training intervention.

The exercise intervention consisted of four supervised training sessions per weekday each for 20 min (excluding 5 min of warming-up and cooling-down) using a bicycle ergometer (ErgoFit Inc., Pirmasens, Germany) interrupted by recreation intervals of at least 60 min after each session. Workloads were adjusted to heart rate so that 70% of the symptom-limited maximum oxygen uptake was reached. Due to the short training period and the up-titrated beta-blockade in HFREF patients, we did not adjust training heart rate during the course of the 4-week training program. Subjects of the training groups attended group training session consisting of walking, calisthenics, and ball games once per week. No further education with regards to lifestyle modification or patient initiated disease management was offered. As a result of the supervised design of the training intervention, an adherence to the assigned training program of 100% was achieved.

Patients assigned to the control group received usual clinical care by their physicians. All examinations including exercise testing were repeated at 4-week follow-up. Patients and RC continued on their individually tailored medication. Medication included chronic use of angiotensin converting enzyme inhibitors and beta-blockers in adequate dosages in all HFREF patients. Patients with LV-EF < 30% or in NYHA functional class III were maintained on stable
spironolactone/eplerenone medication for a minimum of 3 months prior to study enrolment and throughout the study period.

Assessments

Cardiopulmonary exercise testing

Exercise testing was performed on a calibrated, electronically braked bicycle (ZAN600, ZAN, Bad Hall, Austria) in an upright position. Workload was increased progressively every 3 min in steps of 25 W beginning at 25 W. Respiratory gas exchange data were determined continuously. Exercise was terminated when patients were physically exhausted (as indicated by a RER >1.1) or developed severe dyspnoea/dizziness or peripheral muscle fatigue.

Measurement of N-terminal pro brain natriuretic peptide

N-terminal pro brain natriuretic peptide (NT-proBNP) was determined by ElectroChemiLuminescence ImmunoAssay (ECLIA, Roche Diagnostics, Mannheim, Germany) with an analytic sensitivity of 5 pg/mL (0.6 pmol/L) on a COBAS 6000 analyzer (Roche Diagnostics, Mannheim, Germany).

Echocardiography

The echocardiographic studies were performed according to current echocardiography guidelines at baseline and at the end of the study by an experienced echocardiographer blinded to patient status and group assignment. Ninety percent of all echocardiograms were performed by a single experienced cardiologist (S.G.). Intraobserver variabilities of key parameters were below 5%, and interobserver variabilities were below 10%. Assessment was performed under standardized conditions in a temperature and humidity controlled room after 15 min of supine rest. Examinations were stored/videotaped with a long apical four-chamber view sequence for final analysis. End-systolic and end-LV diastolic diameters were determined in the parasternal long axis. Three consecutive cardiac cycles were analysed on a GE Vivid 7 echocardiography system (Software: EchoPAC™, Dimension '06, GE Healthcare, Chalfont St Giles, UK) and averaged for each patient in sinus rhythm. In patients with atrial fibrillation, five beats were averaged for each parameter. Left ventricular volume and ejection fraction (LVEF) were calculated in the apical four-chamber view using the Simpson method-of-disk. The following flow-derived parameters of diastolic LV function were measured in all patients and RC: mitral E/A ratio, mitral E-wave DT and IVRT. Tissue-Doppler imaging was performed to obtain septal and lateral diastolic myocardial annular tissue velocities (E’, A’). For this purpose, the pulsed-Doppler sample volumes were positioned within 1 cm of the septal and lateral insertion sites of the mitral valve leaflets. The severity of DD was classified according to the current recommendations.

Statistical analysis

Based on the study by Belardinelli, the change in the E/A ratio was used as the primary endpoint for the purpose of sample size calculation. A difference in the treatment effect between the groups of 0.3 was assumed with an estimate of the standard deviation of 0.2. With an a error of 0.05 and a b error of 0.10 (power 90%), minimal group size was estimated to be 15 patients in each group. Kolmogorov–Smirnov tests for all continuous variables revealed no significant deviations from normal distribution. Comparisons over time were done by paired t-tests. The complex study design was adequately reflected by general linear models and all main significant findings, regarding the differences training group vs. control, remained significant after Bonferroni correction. Contrasts were estimated and used for intergroup comparisons with Fisher LSD method. χ²-tests were performed to compare groups on categorical variables. All tests were performed as two-sided at a significance level of 0.05. A P-value of less than 0.05 was considered statistically significant. The correlation analysis with the Pearson’s linear correlation coefficient was used to determine the relationship between changes in exercise capacity, LV-ejection fraction, and changes in E/E’. SPSS version 14.0 (IBM Germany GmbH, Munich, Germany) was used for statistical analysis.

Results

Baseline characteristics

From September 2005 to August 2008, a total of 60 RCs and 60 HFREF patients were enrolled into the study. In both cohorts, 30 patients/subjects were ≤55 and >65 years, respectively (Figure 1).

As expected, hypertension, non insulin-dependent diabetes, and dyslipidaemia were more prevalent at baseline among elderly RCs when compared with younger RCs (Table 1).

At baseline, younger and older heart failure patient cohorts in the training and the control groups did not differ with respect to aetiology or duration of HFREF, ejection fraction, or the rate of ICDs. Medical therapy was similar in both groups and remained unchanged during the study period. All HFREF patients were on guideline-orientated optimal medical therapy, including ACE-inhibitors, β-blockers, aldosterone-antagonists, and diuretics as indicated (Table 1). As a result of the age stratification, an age difference of more than 20 years was found between the younger and the older groups (Table 1).

Within the 4 weeks of the study period, no serious adverse events, including cardiac decompensations, hospitalizations due to worsening of heart failure, revascularization procedures, acute myocardial infarction, or life-threatening ventricular arrhythmias occurred. There were no significant changes in body weight in all study cohorts. As a result of the supervised design of the training intervention, an adherence to the assigned training program of nearly 100% was reached.

Cardiopulmonary exercise testing

Baseline characteristics

Referent control

As expected, elderly RC achieved a significantly lower maximal workload and maximum oxygen uptake when compared with younger RC (Table 2).

Heart failure with reduced ejection fraction

In both younger and older patients with HFREF, maximal exercise capacity (in Watts) and maximum oxygen uptake were significantly reduced when compared with that of RC (Table 2).

Training effects

Referent control

After 4 weeks of supervised endurance training, maximal exercise capacity increased by 30% from 129 ± 3 to 152 ± 4 W (P = 0.003) in the younger and by 31% from 91 ± 4 to 119 ± 3 W (P = 0.001) in the older RC group. Maximal oxygen uptake increased by 14% from 23.9 ± 2.1 to 27.9 ± 2.9 mL/kg/min (P = 0.01) in the younger and by 19% from 21.1 ± 1.7 to 26.1 ± 2.2 mL/kg/min in the older training group (P = 0.004; Table 2). There were no detectable age-dependent...
differences in the training response with regards to the assessed parameters \( P = 0.84 \) for change of maximal workload (\( \Delta P_{max} \)) and \( P = 0.62 \) for \( \Delta V\text{O}_2\text{max} \).

Heart failure with reduced ejection fraction

All HFREF patients randomized to exercise training increased their maximal exercise capacity (younger HFREF by 31\% from 66 ± 3 to 86 ± 2 W; \( P = 0.02 \); older HFREF by 37\% from 60 ± 2 to 82 ± 2 W; \( P = 0.0001 \); Table 2) and their maximal oxygen uptake (young by 26\% from 13.3 ± 1.6 to 18.1 ± 1.5 mL/kg*min; \( P = 0.01 \); old by 27\% from 12.9 ± 1.4 to 17.1 ± 1.1 mL/kg*min; \( P = 0.008 \); Table 2). We detected no age-related differences between younger and older training patients with respect to the change in exercise test parameters (young vs. old training patients \( P = 0.1 \) for \( \Delta P_{max} \) and \( P = 0.74 \) for \( \Delta V\text{O}_2\text{max} \)).

In all control groups, no significant changes in exercise capacity or \( V\text{O}_2\text{max} \) were observed.

Left ventricular dimensions and systolic left ventricular function

Baseline characteristics

Referent control

Left atrial size was slightly increased among older RC (42 ± 2 vs. 46 ± 2 mm; \( P = 0.04 \); Table 3).

Heart failure with reduced ejection fraction

Both younger and older patients with HFREF had severely reduced LVEF and increased left atrial and LV diameters (Table 3).

Training effects

Referent control

Four weeks of exercise training did not affect LVEF or left ventricular diameters in either young or old RCs when compared with controls. There was a statistical trend toward a reduction in left atrial size among older RCs assigned to the training intervention (from 46 ± 3 to 42 ± 2 mm; \( P = 0.06 \) vs. control; \( P = 0.09 \) vs. baseline; Table 3). No age-dependent attenuation of the training effects was noted.

Diastolic left ventricular function

Baseline characteristics

Referent control

Older RC exhibited reduced E/A ratio, increased mitral DT, and increased IVRT. Septal and lateral E' and A' velocities were
pseudonormal transmitral filling pattern or by E

Twenty-seven of the 30 younger (90%) and 28/30 older HFREF patients (93%) had DD as defined by impaired relaxation, a

Heart failure with reduced ejection fraction

Twenty-seven of the 30 younger (90%) and 28/30 older HFREF patients (93%) had DD as defined by impaired relaxation, a pseudonormal transmitral filling pattern or by E<8 cm/s. Isovolumetric relaxation time and DT were prolonged when compared with younger RCs and E' and A' velocities were significantly reduced. As a result, the E/E' ratio was increased indicating elevated left ventricular end-diastolic filling pressure (Table 3).

Table 1  Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>HFREF ≤55 years</th>
<th>Control (n = 15)</th>
<th>HFREF ≥65 years</th>
<th>Control (n = 15)</th>
<th>Referent controls ≤55 years</th>
<th>Control (n = 15)</th>
<th>HFREF &gt;65 years</th>
<th>Control (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>50 ± 5</td>
<td>49 ± 5</td>
<td>72 ± 4**</td>
<td>72 ± 3**</td>
<td>46 ± 4</td>
<td>47 ± 6</td>
<td>72 ± 5**</td>
<td>72 ± 4**</td>
</tr>
<tr>
<td>Female gender, n (%)</td>
<td>3 (20)</td>
<td>2 (13)</td>
<td>3 (20)</td>
<td>3 (20)</td>
<td>2 (13)</td>
<td>4 (27)</td>
<td>3 (20)</td>
<td>3 (20)</td>
</tr>
<tr>
<td>BMI</td>
<td>29 ± 2</td>
<td>30 ± 3</td>
<td>28 ± 3</td>
<td>28 ± 2</td>
<td>26 ± 1</td>
<td>26 ± 2</td>
<td>28 ± 2</td>
<td>28 ± 1</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>14 (93)</td>
<td>15 (100)</td>
<td>13 (87)</td>
<td>14 (93)</td>
<td>5 (33)</td>
<td>4 (27)</td>
<td>13 (87)**</td>
<td>12 (80)**</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>6 (40)</td>
<td>4 (27)</td>
<td>7 (46)</td>
<td>9 (60)</td>
<td>0</td>
<td>0</td>
<td>5 (33)**</td>
<td>4 (27)**</td>
</tr>
<tr>
<td>Dyslipidaemia, n (%)</td>
<td>12 (80)</td>
<td>11 (73)</td>
<td>13 (87)</td>
<td>11 (73)</td>
<td>4 (27)</td>
<td>3 (20)</td>
<td>8 (53)**</td>
<td>10 (75)**</td>
</tr>
</tbody>
</table>

Characterization of HFREF

<table>
<thead>
<tr>
<th>NYHA class I/II/III/IV</th>
<th>HFREF ≤55 years</th>
<th>Control (n = 15)</th>
<th>HFREF ≥65 years</th>
<th>Control (n = 15)</th>
<th>Referent controls ≤55 years</th>
<th>Control (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0/0/6/0</td>
<td>0/1/0/0</td>
<td>0/1/0/0</td>
<td>0/0/4/0</td>
<td>0/0/6/0</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>Ischaemic, n (%)</td>
<td>8 (53)</td>
<td>9 (60)</td>
<td>10 (67)</td>
<td>11 (73)</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>Dilated, n (%)</td>
<td>7 (46)</td>
<td>6 (40)</td>
<td>5 (33)</td>
<td>4 (27)</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>Time since first diagnose of HFREF (months)</td>
<td>24 ± 18</td>
<td>28 ± 14</td>
<td>30 ± 15</td>
<td>25 ± 11</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
</tbody>
</table>

LVEF (%)               | 27 ± 6*         | 28 ± 5*          | 29 ± 6*         | 28 ± 6*          | 63 ± 5                     | 62 ± 5           | 62 ± 4          | 62 ± 5           |

LVEDP (mmHg)            | 22 ± 4          | 23 ± 5           | 25 ± 4          | 23 ± 3           | 9 ± 1                      | 10 ± 1           | 15 ± 2          | 16 ± 3           |

Sinus rhythm, n (%)     | 10 (67)*        | 11 (73)*         | 9 (60)*         | 10 (67)*         | 15 (100)                   | 15 (100)         | 15 (100)        | 15 (100)         |

Atrial fibrillation, n (%) | 5 (33)* | 4 (27)*           | 6 (40)*         | 5 (33)*          | 0                          | 0               | 0              | 0               |

ICD 1-chamber/2-chamber/CRT (n) | 4/6/3 | 3/7/2           | 2/8/1           | 3/7/1           | n.a.                       | n.a.             |

Medication, n (%)       |                 |                  |                 |                  |                            |                  |

Aspirin                | 14 (93)*        | 13 (87)*         | 15 (100)*       | 13 (87)*         | 0                         | 0               | 6 (40)         | 5 (33)           |

Vitamin-K-antagonists   | 5 (33)*         | 4 (27)*          | 5 (33)*         | 5 (33)*          | 0                         | 0               | 0              | 0               |

Beta-blocker            | 15 (100)*       | 15 (100)*        | 15 (100)*       | 15 (100)*        | 3 (20)                     | 3 (20)           | 12 (80)        | 11 (73)          |

ACE-inhibitor           | 11 (73)*        | 12 (80)*         | 14 (93)*        | 13 (87)*         | 3 (20)                     | 4 (27)           | 8 (53)         | 9 (60)           |

ARB                    | 4 (27)*         | 3 (20)*          | 1 (7)*          | 2 (13)*          | 1 (7)                      | 1 (7)            | 3 (20)         | 3 (20)           |

Diuretics              | 13 (87)*        | 11 (73)*         | 12 (80)*        | 14 (93)*         | 0                         | 0               | 2 (13)         | 3 (20)           |

Spironolactone          | 6 (40)*         | 8 (53)*          | 7 (47)*         | 7 (47)*          | 0                         | 0               | 0              | 0               |

Data as mean ± SEM.
LV, left-ventricular; LVEDP, left ventricular end-diastolic pressure; VO2max, maximal oxygen consumption; ICD, implantable cardioverter defibrillator; ACE inhibitor, angiotensin converting enzyme inhibitor; ARB, angiotensin II subtype I receptor blocker.

*P < 0.05 vs. referent controls in the same age group.

**P < 0.05 vs. <55 years.

reduced in older when compared with younger RC. As a consequence, the E/E' ratio was significantly increased in older RC (Table 3).

Heart failure with reduced ejection fraction

As expected, training did not affect diastolic LV function in young RC without DD at baseline (Table 3; Figure 2A). In elderly RC, a significant increase in the E/A ratio (by +36% from 0.9 ± 0.1 to 1.4 ± 0.1; P = 0.0002), a significant reduction in MV-DT (by −17% from 248 ± 5 to 228 ± 3 ms, P = 0.005; and IVRT (by −21% from 147 ± 4 to 116 ± 4 ms; P = 0.001) and an increase in septal and lateral E'-wave velocities (septal by 39% from 147 to 21% ± 8 cm/s; lateral by 48% from 15 ± 1 to 10 ± 1 cm/s; P = 0.0001) were observed after training. These changes were accompanied by a reduction in the E/E' ratio (septal by −30% from 12 ± 1 to 10 ± 1, P = 0.008; lateral by −34% from 13 ± 1 to 9 ± 1, P = 0.0004; Table 3; Figure 2A). The lateral ΔE/E' ratio correlated inversely with ΔVO2max in the older
Age-related effects of exercise training on diastolic function in HFREF

Table 2: Exercise test

<table>
<thead>
<tr>
<th></th>
<th>≤5 years Training</th>
<th>≤5 years Control</th>
<th>&gt;6 years Training</th>
<th>&gt;6 years Control</th>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>4 weeks</td>
<td>Baseline</td>
<td>4 weeks</td>
</tr>
<tr>
<td>VO2max (mL/kg/min)</td>
<td>23.9 ± 2.1</td>
<td>27.9 ± 2.9*</td>
<td>23.7 ± 1.6</td>
<td>23.4 ± 2.7</td>
</tr>
<tr>
<td>VO2VT (mL/kg/min)</td>
<td>18.5 ± 1.9</td>
<td>21.7 ± 1.4*</td>
<td>18.7 ± 2.0</td>
<td>18.5 ± 1.6</td>
</tr>
<tr>
<td>Pmax (W)</td>
<td>129 ± 3</td>
<td>152 ± 4*</td>
<td>130 ± 4</td>
<td>129 ± 5</td>
</tr>
<tr>
<td>Exercise duration (s)</td>
<td>698 ± 37</td>
<td>803 ± 40*</td>
<td>705 ± 39</td>
<td>710 ± 32</td>
</tr>
<tr>
<td>HR at rest (bpm)</td>
<td>68 ± 2</td>
<td>66 ± 2</td>
<td>69 ± 2</td>
<td>68 ± 1</td>
</tr>
<tr>
<td>Sys BP at rest (mmHg)</td>
<td>122 ± 3</td>
<td>125 ± 3</td>
<td>123 ± 3</td>
<td>127 ± 3</td>
</tr>
<tr>
<td>Dia BP at rest (mmHg)</td>
<td>68 ± 2</td>
<td>69 ± 2</td>
<td>66 ± 3</td>
<td>70 ± 2</td>
</tr>
<tr>
<td>Sys BP at peak exercise (mmHg)</td>
<td>189 ± 9</td>
<td>193 ± 8</td>
<td>184 ± 9</td>
<td>186 ± 8</td>
</tr>
<tr>
<td>Dia BP at peak exercise (mmHg)</td>
<td>98 ± 6</td>
<td>101 ± 7</td>
<td>100 ± 5</td>
<td>102 ± 5</td>
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</tbody>
</table>

HFREF patients

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>4 weeks</th>
<th>Baseline</th>
<th>4 weeks</th>
<th>Baseline</th>
<th>4 weeks</th>
<th>Baseline</th>
<th>4 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO2max (mL/kg/min)</td>
<td>13.3 ± 1.6***</td>
<td>18.1 ± 1.5*</td>
<td>13.6 ± 1.3***</td>
<td>13.4 ± 1.2</td>
<td>12.9 ± 1.4***</td>
<td>17.1 ± 1.1*</td>
<td>13.1 ± 1.5***</td>
<td>13.3 ± 1.2</td>
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<tr>
<td>VO2VT (mL/kg/min)</td>
<td>10.3 ± 1.4***</td>
<td>13.2 ± 1.6*</td>
<td>10.6 ± 1.1***</td>
<td>9.8 ± 1.7</td>
<td>10.3 ± 2.0***</td>
<td>13.5 ± 1.4*</td>
<td>10.8 ± 1.6***</td>
<td>10.2 ± 1.5</td>
</tr>
<tr>
<td>Pmax (W)</td>
<td>66 ± 3***</td>
<td>86 ± 2</td>
<td>67 ± 2***</td>
<td>66 ± 1</td>
<td>60 ± 2***</td>
<td>82 ± 2*</td>
<td>62 ± 2***</td>
<td>61 ± 2</td>
</tr>
<tr>
<td>Exercise duration (s)</td>
<td>559 ± 22***</td>
<td>689 ± 31*</td>
<td>569 ± 27***</td>
<td>553 ± 20</td>
<td>542 ± 19***</td>
<td>650 ± 21*</td>
<td>552 ± 27***</td>
<td>539 ± 31</td>
</tr>
<tr>
<td>HR at rest (bpm)</td>
<td>65 ± 2</td>
<td>66 ± 2</td>
<td>67 ± 2</td>
<td>68 ± 3</td>
<td>66 ± 2</td>
<td>69 ± 2</td>
<td>66 ± 2</td>
<td>69 ± 2</td>
</tr>
<tr>
<td>Sys BP at rest (mmHg)</td>
<td>118 ± 3</td>
<td>119 ± 3</td>
<td>116 ± 3</td>
<td>116 ± 2</td>
<td>113 ± 3</td>
<td>115 ± 3</td>
<td>113 ± 3</td>
<td>114 ± 2</td>
</tr>
<tr>
<td>Dia BP at rest (mmHg)</td>
<td>66 ± 2</td>
<td>67 ± 2</td>
<td>71 ± 3</td>
<td>70 ± 2</td>
<td>65 ± 2</td>
<td>69 ± 2</td>
<td>66 ± 2</td>
<td>67 ± 2</td>
</tr>
<tr>
<td>Sys BP at peak exercise (mmHg)</td>
<td>179 ± 10</td>
<td>182 ± 8</td>
<td>182 ± 9</td>
<td>180 ± 7</td>
<td>175 ± 7</td>
<td>180 ± 7</td>
<td>179 ± 8</td>
<td>177 ± 9</td>
</tr>
<tr>
<td>Dia BP at peak exercise (mmHg)</td>
<td>102 ± 4</td>
<td>98 ± 6</td>
<td>96 ± 7</td>
<td>95 ± 4</td>
<td>99 ± 3</td>
<td>98 ± 7</td>
<td>97 ± 4</td>
<td>100 ± 5</td>
</tr>
</tbody>
</table>

Data as mean ± SEM.

Pmax, maximal work load; VO2max, maximal oxygen consumption; VO2VT, oxygen consumption at ventilatory threshold; HR, heart rate; Sys, systolic; Dia, diastolic; BP, blood pressure.

*P < 0.05 vs. baseline.

**P < 0.05 vs. subjects ≤55 years at baseline.

***P < 0.05 vs. referent controls in the same age group.

healthy training cohort (R² = 0.69; r = −0.83; P = 0.0001). No changes were observed in the control groups.

Heart failure with reduced ejection fraction

After the training intervention, the E/A ratio was increased among HFREF patients (young by +38% from 0.7 ± 0.1 to 1.1 ± 0.1; P = 0.002; old by 35% from 0.8 ± 0.1 to 1.2 ± 0.1; P = 0.001). In addition, significant reductions in DT (young by −20% from 274 ± 9 to 231 ± 8 ms; P = 0.03; old by −15% from 282 ± 6 to 245 ± 4 ms; P = 0.02) and IVRT (young by −29% from 158 ± 5 to 123 ± 4 ms; P = 0.002; old by −26% from 163 ± 6 to 130 ± 4 ms; P = 0.002) were observed. Septal and lateral E’ velocities were significantly increased after 4 weeks of exercise training (young: septal E’ by +37% from 4.6 ± 0.4 to 7.1 ± 0.2 cm/s, P = 0.004; lateral E’ by +57% from 3.8 ± 0.2 to 9.1 ± 0.4; P = 0.03; old: septal E’ by +39% from 4.4 ± 0.4 to 7.1 ± 0.4 cm/s, P = 0.002; lateral E’ by +51% from 4.3 ± 0.3 to 9.2 ± 0.1 cm/s, P = 0.02; Table 3). Accordingly, E/E’ ratios were significantly reduced as a result of the exercise intervention (Table 3; Figure 2A). The training effect on diastolic function was not influenced by age. Furthermore, a significant inverse correlation between ΔE/E’ ratio and ΔVO2max could be detected in the training groups (young: r² = 0.58; r = −0.76; P = 0.0009 and old: r² = 0.42; r = −0.64; P = 0.01).

N-terminal pro brain natriuretic peptide

Baseline characteristics

Referent control

Serum levels of NT-ProBNP were not elevated in younger and older RCs at baseline (Table 3).

Heart failure with reduced ejection fraction

Among younger and older patients with HFREF, levels of NT-proBNP were significantly elevated at baseline (Table 3).

Training effects

Referent control

NT-proBNP levels in healthy individuals were not affected by the intervention (Table 3).
Exercise training led to a significant reduction in NT-proBNP levels, as shown in Table 3. The data are presented as mean ± SEM.

<table>
<thead>
<tr>
<th>Echocardiographic parameters</th>
<th>≤55 years</th>
<th>≥65 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Training</td>
<td>Control</td>
</tr>
<tr>
<td></td>
<td>Baseline</td>
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<td>LA (mm)</td>
<td>43 ± 2</td>
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<td>LVEDD (mm)</td>
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<td>LVESD (mm)</td>
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<tr>
<td>LVEF (%)</td>
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<td>64 ± 1</td>
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<tr>
<td>Septum (mm)</td>
<td>12 ± 2</td>
<td>11 ± 3</td>
</tr>
<tr>
<td>LVMi (g/m²)</td>
<td>107 ± 10</td>
<td>111 ± 12</td>
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<tr>
<td>E/A ratio</td>
<td>1.7 ± 0.1</td>
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</tr>
<tr>
<td>DT (ms)</td>
<td>190 ± 4</td>
<td>188 ± 4</td>
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<tr>
<td>IVRT (ms)</td>
<td>90 ± 3</td>
<td>91 ± 3</td>
</tr>
<tr>
<td>E' septal (cm/s)</td>
<td>17.4 ± 0.9</td>
<td>17.2 ± 0.8</td>
</tr>
<tr>
<td>E' lateral (cm/s)</td>
<td>18.3 ± 1.4</td>
<td>18.4 ± 1.2</td>
</tr>
<tr>
<td>Sm septal (cm/s)</td>
<td>4.2 ± 0.9</td>
<td>4.4 ± 1.2</td>
</tr>
<tr>
<td>Sm lateral (cm/s)</td>
<td>7.5 ± 1.0</td>
<td>8.2 ± 0.9</td>
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<td>Grade of diastolic dysfunction (0/I/II/III)</td>
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<td>15/10/5/0</td>
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<tr>
<td>NT-proBNP (pg/mL)</td>
<td>73 ± 6</td>
<td>68 ± 4</td>
</tr>
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</table>

HFREF patients

<table>
<thead>
<tr>
<th>Echocardiographic parameters</th>
<th>≤55 years</th>
<th>≥65 years</th>
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</thead>
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<tr>
<td></td>
<td>Training</td>
<td>Control</td>
</tr>
<tr>
<td></td>
<td>Baseline</td>
<td>4 weeks</td>
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<tr>
<td>LA (mm)</td>
<td>53 ± 4</td>
<td>51 ± 5</td>
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<tr>
<td>LVEDD (mm)</td>
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<tr>
<td>LVESD (mm)</td>
<td>53 ± 2</td>
<td>51 ± 2</td>
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<tr>
<td>LVEF (%)</td>
<td>27 ± 2</td>
<td>34 ± 2</td>
</tr>
<tr>
<td>Septum (mm)</td>
<td>14 ± 1</td>
<td>13 ± 1</td>
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<tr>
<td>LVMi (g/m²)</td>
<td>163 ± 12</td>
<td>169 ± 16</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>0.7 ± 0.1</td>
<td>1.1 ± 0.1</td>
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<tr>
<td>DT (ms)</td>
<td>274 ± 9</td>
<td>231 ± 8</td>
</tr>
<tr>
<td>IVRT (ms)</td>
<td>158 ± 5</td>
<td>123 ± 4</td>
</tr>
<tr>
<td>E' septal (cm/s)</td>
<td>4.2 ± 1</td>
<td>7.3 ± 1.2</td>
</tr>
<tr>
<td>E' lateral (cm/s)</td>
<td>5.3 ± 1.5</td>
<td>9.4 ± 1.7</td>
</tr>
<tr>
<td>Sm septal (cm/s)</td>
<td>2.3 ± 0.6</td>
<td>3.6 ± 0.9</td>
</tr>
<tr>
<td>Sm lateral (cm/s)</td>
<td>3.5 ± 0.7</td>
<td>4.4 ± 0.5</td>
</tr>
<tr>
<td>Grade of diastolic dysfunction (0/I/II/III)</td>
<td>0/1/1/0</td>
<td>10 ± 1/0/1/10</td>
</tr>
<tr>
<td>NT-proBNP (pg/mL)</td>
<td>1675 ± 354</td>
<td>965 ± 133</td>
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</table>

Table 3 Echocardiographic parameters

Data as mean ± SEM.
LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVEDD, left ventricular end-diastolic diameter; LVMi, left ventricular mass index; DT, mitral E-wave deceleration time; IVRT, isovolumetric relaxation time.

**P < 0.05 vs. baseline.
***P < 0.05 vs. referent controls ≤55 years.
****P < 0.05 vs. referent controls in the same age group.

**Heart failure with reduced ejection fraction**

Exercise training led to a significant reduction in NT-proBNP levels (young from 1675 ± 354 to 965 ± 133 pg/mL, P < 0.05 and old 1301 ± 261 to 712 ± 68 pg/mL, P < 0.05, Table 3) in young and older patients with HFREF.

**Discussion**

In this first age-stratified randomized prospective trial of aerobic exercise training inpatients with HFREF and in RCs, we studied the effects of a 4-week endurance training intervention on global physical fitness.
exercise capacity and left ventricular diastolic function. The primary and secondary hypotheses were answered as follows:

- The primary hypothesis was confirmed: a short-term endurance training program of 4 weeks resulted in a significant improvement of LV diastolic function as assessed by state-of-the-art Doppler and tissue Doppler echocardiography.

- The secondary hypothesis was falsified: the training effects on exercise capacity and the relative improvement in diastolic LV function were not attenuated in older patients aged ≥65.

The LEICA Diastolic Dysfunction study provides first-time evidence of a significant improvement of diastolic function and a reverse remodelling in HFREF patients of all age groups. The key finding

**Figure 2** (A) Individual changes of the E/E′ ratio in referent controls. P-values: *P < 0.05 from begin to 4-week follow-up; ‡P < 0.05 vs. control. Data as mean ± SEM. (B) Individual changes of the E/E′ ratio in HFREF-patients. P-values: *P < 0.05 from begin to 4-week follow-up; ‡P < 0.05 vs. control. Data as mean ± SEM. Lateral E′ measurements were used to calculate the E/E′ ratio for (A) and (B).
that the beneficial effects of endurance training on whole-body exercise capacity and left ventricular systolic and diastolic function are not attenuated in elderly patients with significant implications for the current practice of rehabilitation medicine in HFREF where the age group with the highest HFREF prevalence is clearly underrepresented.

Additionally, the study corroborates the safety of endurance training interventions in HFREF patients in regard to the systolic LV function. Contrary to initial fears that the extra workload imposed on the left ventricle by exercise training may further reduce contractile function, a number of randomized clinical studies have documented small but significant increases in LVEF associated with a reduction in cardiomegaly.\(^{19,20}\) In line with these studies, we found an absolute improvement of LVEF of +7% in HFREF patients ≤55 years and +7% in HFREF patients ≥65 years. It is noteworthy, however, that the present study is the first to document that the reverse remodelling induced by the training intervention is detectable as early as 4 weeks after the initiation of exercise training and is not attenuated by age.

**Interaction between ageing and diastolic function in referent control subjects**

In two longitudinal population-based studies, the Baltimore Longitudinal Study of Aging and the Framingham Study, an age-related decline in early diastolic LV filling and an increased atrial contribution to LV filling measured by Doppler echocardiography resulting in a reduction in the E/A ratio were observed.\(^ {17,26}\) These changes in LV filling are accompanied by an age-dependent increase in pulmonary artery pressure.\(^ {27}\) Data from animal experiments on ageing support these findings: Choi et al. observed an increased end-diastolic pressure–volume relation in 25-month-old Fisher rats when compared with young (6 weeks) animals. The degree of LV DD was related to the extent of myocardial collagen deposition among older rats.\(^ {28}\)

Although this was not the focus of the current study, the age-dependent decline in the E/A in RCs is consistent with the data derived from the Baltimore Longitudinal Study on Aging and the Framingham Study.\(^ {17,26}\) Tissue Doppler measurements documented a reduced E′ velocity and a higher E/E′ ratio in subjects older than 65 years, a finding that confirms previous results.\(^ {29}\)

**Improvement in diastolic left ventricular function by exercise**

**Referent control**

In a landmark study on the effects of life-long physical activity on diastolic LV compliance, Arbab-Zadeh et al.\(^ {30}\) invasively measured the LV pressure–volume relation in healthy sedentary seniors, elderly master athletes, and young inactive controls. Sedentary seniors had significantly reduced LV compliance, whereas master athletes had pressure–volume curves not different from those of young sedentary RCs. In an uncontrolled observational clinical trial, Levy et al.\(^ {31}\) observed an augmented diastolic filling as measured by echocardiographic strain analysis at rest and during exercise after a 6-month endurance training program in a mixed age group of healthy individuals involving younger (24 to 32 years) and older subjects (60 to 82 years).

In the current study, exercise training did not affect diastolic function in the absence of any baseline DD among the subgroup of young healthy individuals. In the older healthy training cohort, IVRT as a parameter for LV relaxation and E′ as an indicator for LV compliance were significantly improved after 4 weeks. Additionally, ΔE/E′ was closely related to the improvement in exercise capacity.

**Heart failure with reduced ejection fraction**

In the first prospective randomized endurance training study (the Leipzig Heart Failure Training Trial) in HFREF patients with both invasive and non-invasive assessment of LV systolic function, we were able to demonstrate that endurance training reduced LV end-diastolic diameters and improved LVEF after 6 months of training from 30 ± 8 to 35 ± 9%, indicating the possibility of a reverse remodelling.\(^ {19}\) Exercise testing with simultaneous right heart catheterization revealed a significant decrease in pulmonary artery resistance and total peripheral resistance especially at peak exercise accompanied by a decline in mean pulmonary artery pressures.

The present study now offers a mechanistic concept for the reductions in PA pressures previously observed: endurance training interventions in HFREF patients lead to a significant improvement in diastolic LV function with improved LV filling—both in early and late diastole—with a parallel reduction in LV mean diastolic filling pressures as assessed by the E/E′ ratio. These results strengthen the idea of a training-induced reverse remodelling in HFREF, a concept also supported by the close correlation between E/E′ reduction and the improvement of LVEF.

Alternatively, the observed changes in diastolic function could also be influenced by changes in venous capacitance, which is reduced in HFREF.\(^ {22}\) Training studies in HFREF using venous occlusion plethysmography reported reduced peripheral vascular resistance resulting in increased venous capacitance; however, the relation to cardiac function was not shown in these studies.\(^ {33}\)

Apart from the present study, data on the effects of physical activity on diastolic function are rare: in 1995, Belardinelli et al.\(^ {21}\) were the first to describe improved left ventricular diastolic filling patterns with the increased transmitral E/A ratio in 55 consecutive (mean age, 55 ± 7 years) patients with HFREF after 2 months of exercise training. The clinical relevance and validity of the study is, however, limited by the lack of a normal age-matched control group of RCs, the exclusion of patients with atrial fibrillation, the young mean patient age, and the technical limitations of Doppler-derived flow parameters to assess diastolic function, which are known to be affected by changes in preload conditions and heart rate.

In a small observational non-randomized study, Smart et al.\(^ {34}\) compared the relation between training-induced changes in diastolic function with the gain in exercise capacity in 22 patients with systolic HF and 18 patients with diastolic HF. He found a similar increase in peak VO₂\(_{\text{max}}\) in systolic HF and diastolic HF after exercise training, but in contrast to the present study this did not correlate with improved diastolic parameters.\(^ {34}\) However, the reliability of this study is limited by the uncontrolled observational design and the small patient number.

In a recently published echocardiographic substudy of the HF-ACTION trial in 2331 HFREF patients randomized to 1 year
on moderate duration endurance training, Gardin et al. showed significant bivariate correlations between baseline E/E' ratio/E/A ratio and peak oxygen uptake/VE/CO₂ slope. The HF-ACTION study group did not report any data on training-induced changes in diastolic function.

In summary, evidence is accumulating that endurance training may have beneficial effects on diastolic LV function in different clinical settings with DD at baseline.

Training effects on N-terminal pro brain natriuretic peptide

Four weeks of endurance training were associated with a significant decline in serum NT-proBNP in HFREF patients, which ranged between −42% in patients ≤55 years and −45% in patients ≥65 years. This decrease in NT-proBNP is well in line with the reduced E/E' ratio as an estimate of LV filling pressures and of improved LVEF. The NT-proBNP values in the HFREF cohort of the LEICA study were higher when compared with the HF-ACTION trial, which may be related to differences in methodology (serum vs. plasma measurements), and the higher prevalence of diabetes with presumably more reduced renal function in the LEICA study. It has nicely been shown that NT-proBNP increases 9% when eGFR decreases 10%.35

Limitations

As a result of the study design and mode of patient recruitment, the following limitations of the current study need to be considered.

Patients with HFREF were recruited based on ejection fraction, clinical symptoms, and clinical stability from consecutive heart failure patients referred to a single centre. As a consequence of the limited sample size and the single centre nature of the study, patients in the current study may not be representative of the entire HFREF population so that reliable statements about the relation between age, baseline clinical status, and baseline VO₂_max within the HFREF cohort cannot be made. In contrast to the HF-ACTION study, we did not observe an age-related decline in exercise capacity among HFREF patients.37

Because the study protocol demanded an invasive exclusion of patients with atypical chest pain referred to rule out CAD. This recruitment mode implies the risk of a referral bias, leading to the inclusion of control subjects with a higher prevalence of cardiovascular risk factors when compared with the age-matched general population. Cardiovascular risk factors might confound the prevalence and severity of DD in elderly RC subjects. As a consequence of diagnosed hypertension, a number of RC subjects >65 years were on anti-hypertensive medication that potentially influenced myocardial diastolic function. However, a stable medication was required for at least 3 months and medical therapy was kept unchanged during the entire study period. It is therefore unlikely that the study results in RC subjects were influenced by medication. Nonetheless, the mean baseline septal wall thickness of 13–14 mm and the increased left ventricular mass index indicate the presence of hypertensive heart disease in a substantial proportion of the elderly RC subjects (compare Table 3). As a consequence, changes truly attributable to age cannot be inferred from the current study among RC subjects.

As a methodological limitation, the current study purely relied on non-invasive echocardiographic measurements of diastolic functional parameters. We did not use invasive conductance catheter measurements to confirm the non-invasive data.

Conclusion

In patients with HFREF, active left ventricular relaxation and passive left ventricular compliance were both improved by aerobic exercise training. The positive effects of training were not attenuated among older HFREF patients underscoring the potential for rehabilitation interventions in age groups with the highest prevalence of HFREF.

Acknowledgement

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References


