A randomized study of the effects of exercise training on patients with atrial fibrillation

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Background Exercise training is beneficial in ischemic and congestive heart disease. However, the effect on atrial fibrillation (AF) is unknown.

Methods Forty-nine patients with permanent AF (age [mean ± SD], 70.2 ± 7.8 years; male-to-female ratio, 0.75; body mass index [mean ± SD], 29.7 ± 4.3 kg/m²) were randomized to 12-week aerobic exercise training or a control group. Exercise capacity, 6-minute walk test (6MWT), cardiac output, quality of life, and natriuretic peptides were measured. Cardiac output was measured at rest and during ergometer testing, and atrial natriuretic peptide and N-terminal pro–B-type natriuretic peptide were measured before and after the training period. Quality of life was evaluated using the Short-Form 36 and Minnesota Living With Heart Failure (MLHF-Q) questionnaires.

Results Improved exercise capacity and 6MWT were observed in the active patients (P < .001), and at study end, there was a significant difference between the active patients and the controls (P = .002). Resting pulse decreased in the active patients (94.8 ± 22.4 to 86.3 ± 22.5 beats/min, P = .049) but remained unchanged in the controls. Cardiac output was unchanged from baseline to end-of-study period. The MLHF-Q score improved in the active group (21.1 ± 18.0 vs 15.4 ± 17.5, P = .03). Active patients showed progress in 3 of the 8 Short-Form 36 subscales: physical functioning (P = .02), general health perceptions (P = .001), and vitality (P = .02). Natriuretic peptides were unchanged.

Conclusion Twelve weeks of exercise training increased exercise capacity and 6MWT and decreased resting pulse rate significantly in patients with AF. Overall quality of life increased significantly as measured by the cardiology-related MLHF-Q. Cardiac output and natriuretic peptides were unchanged in both groups. (Am Heart J 2011;162:1080-7.)

Materials and methods

Patient population

From medical records from the department of cardiology's consecutive list of patients with a diagnosis of AF (diagnostic code 148.9), eligible patients were identified and contacted (Figure 1). Written informed consent was obtained. Inclusion criteria were as follows: adults with permanent AF who were willing to participate in a training program and able to give informed consent to participation. Exclusion criteria are as follows: severe CHF (New York Heart Association classes III-IV), severe refractory hypertension, previous heart valve surgery, moderate-to-severe pulmonary disease, low life expectancy, and lack of ability to exercise. The regional medical ethics committee approved the study (committee approval nos. KF-13577 and KF-13675).
At enrollment, an electrocardiogram was recorded to document heart rhythm, and a standard clinical examination was carried out to rule out CHF and pulmonary disease. Echocardiography was performed to exclude severe valvulopathy and heart failure. The echocardiographic studies were performed in the supine resting position, according to the standard procedure.

Exercise training

Subjects were randomized in 1:1 ratio to either exercise training or a control group of patients who did not receive any exercise training. The training schedule was similar to the ETICA trial. Training was carried out in groups of 5 with aerobic exercises, supervised by a physiotherapist, and included ergometer cycling, walking on stairs, running, fitness training on physioballs, and interval training. Sessions included warm-up and cool-down periods to avoid rapid changes in pulse and blood pressure. Training intensity was managed based on a Borg scale score corresponding to 70% of maximal exercise capacity (Borg scale scores 14-16). Total exercise duration was 60 minutes 3 times weekly for 12 weeks, of which minimum 30 minutes was at 70% of maximal exercise capacity.

Patients randomized to training were encouraged to do light exercise for 30 minutes daily. The control patients were advised to continue a habitual physical activity.

The patients were evaluated at baseline and after the training period.

Ergometer test

Ergometer testing was carried out based on a prespecified protocol to standardize the procedure and motivational encouragements to do maximal efforts.

Tests were performed on a cycle ergometer in accordance with the American College of Cardiology/American Heart Association guidelines starting at 25 W and increasing by 25 W every 2 minutes.

A physician and a research assistant blinded to the group allocation status of the patients were present. However, remarks were sometimes made by the patient hinting to their trial status.

Six-minute walk test

To test the patients' functional exercise capacity, a self-paced standardized 6-minute walk test (6MWT) was performed by a physiotherapist blinded to the patients' trial status.

Impedance cardiography

A CardioScreen apparatus version 3.1 (Medis, Ingelheim, Germany) was used to measure CO. Measurements were done by electrical currents applied to pairs of electrodes on the neck.
Table I. Baseline characteristic of patients with AF (n = 47)

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Active, baseline (mean ± SD)</th>
<th>Controls, baseline (mean ± SD)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>69.5 ± 7.3</td>
<td>70.9 ± 8.3</td>
<td>.55</td>
</tr>
<tr>
<td>M:F ratio</td>
<td>0.75 ± 0.44</td>
<td>0.74 ± 0.45</td>
<td>.93</td>
</tr>
<tr>
<td>Body height (cm)</td>
<td>177 ± 10</td>
<td>175 ± 8</td>
<td>.54</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>92.9 ± 17.4</td>
<td>90.5 ± 12.9</td>
<td>.59</td>
</tr>
<tr>
<td>Body mass index (kg/m)</td>
<td>29.6 ± 3.8</td>
<td>29.7 ± 4.8</td>
<td>.95</td>
</tr>
<tr>
<td>Ergometer cycle test (W),</td>
<td>160 ± 59</td>
<td>135 ± 38</td>
<td>.10</td>
</tr>
<tr>
<td>maximal performance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ventricular ejection fraction ≥0.55 &amp;</td>
<td>0.55 NS</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

There were no significant differences between the groups.

and flanks. Pulsations in the blood flow cause current fluctuations, and changes in the current waveform were used to calculate CO using the Sramek-Bernstein formula.13

Natriuretic peptides

Atrial natriuretic peptide (ANP) and N-terminal (NT) pro-B-type natriuretic peptide (BNP) were measured as described previously.14 Venous blood samples were drawn in the supine resting position after 10 minutes of rest upon enrollment and after the training period.

Quality of life assessment

Health-related QoL was self-assessed using the SF-36 and the Minnesota Living With Heart Failure (MLHF-Q) questionnaires. Both questionnaires consist of multiple physical and mental scales. The SF-36 is divided into 8 domains, from which summation of data into physical and mental domains can be made. The MLHF-Q is a questionnaire that covers physical, socioeconomic, and psychological functions. The total score can be divided into 2 subscales for measuring physical and mental well-being. The MLHF-Q has been developed specifically for patients with heart failure and is more related to symptoms of cardiac disease compared with SF-36, which is used to measure the general QoL.15,16 The questionnaires are validated for use in patients with AF,15,16 Reliability, validity, and internal consistency of both questionnaires and subscales have been confirmed with satisfactory results.17

Blinding of the patients’ trial status

In an exercise study, it is not possible to keep the study double blinded. Obviously, the patients knew which group they belonged to, but we have tried to maintain blinding as far as possible for the examiner.

Statistical analysis

Sample size calculations showed that a difference between active patients and controls of 20% can be found with an α value of 5% and a power of 80%, if 17 patients are included in each group. Because of the risk of dropouts, we planned to recruit 24 patients for each group.

The Student t test and Mann-Whitney rank sum test were performed where appropriate. Results are reported as mean ± SD. P < .05 was considered statistically significant. All analyses were done using standard SAS statistical software version 9.2 (SAS, Cary, NC) and SigmaStat 3.1 (SigmaStat, San Jose, CA).

The study was supported by grants from Danish Medical Association Research Foundation, Hvidovre Hospital Research Foundation, and Lundbeck Foundation.

Results

Patients

From 400 patient records coded for AF, we identified 157 patients who fulfilled the inclusion criteria and none who fulfilled the exclusion criteria. Eighty-five patients declined to participate in the study. Twenty-three patients were excluded because of sinus rhythm (12 patients), atrial flutter,1 CHF with left ventricular ejection fraction less than 40%,3 aortic stenosis,4 low lung capacity with force expiratory volume in 1 second less than 80% of the expected volume,5 and inability to ride bicycle.1 Randomization was carried out by envelopes containing either the text “control” or “active,” as generated by a random list.

Twenty-five patients were randomized to active treatment and 24 to control group. Two patients dropped out from the study, 1 because of influenza and 1 because of the need for surgery.

Demographic characteristics are shown in Table I. Medical history, physical activity, and medication are summarized in Table II. Medication was unchanged throughout the study.

Maximal exercise capacity

Maximal exercise capacity increased significantly in the active patients but not in the controls. Both groups
showed significant changes at baseline—the active group increased their maximal exercise capacity, whereas the controls decreased their maximal exercise capacity (Table III and Figure 2).

Walking capacity
Six-minute walk test was similar at baseline in the active and control groups. The active patients increased significantly in walking distance. No change was observed in the controls (Table III and Figure 3).

Natriuretic peptides
No significant changes in ANP and NT-pro-BNP were observed from baseline until after the training period. There were no significant differences between the active and the control patients (Table III).

Cardiac output
Cardiac output at rest and at maximal exercise was unchanged from baseline until after the training period (Table III and Figure 4).

Heart rate and blood pressure
Resting heart rate decreased significantly in the active group (P = .049) but not in the controls. There were no changes in maximal heart rate (Table III).

There were no significant differences in systolic blood pressure before and after the exercise training period (active group: 131 ± 15 vs 132 ± 13 mm Hg, not significant; control group: 129 ± 10 vs 128 ± 11 mm Hg, not significant).

Quality of life
For Qol measured using the MLHF-Q, the total score and the 2 subscales regarding physical and emotional well-being were significantly different from baseline until after the training period (P = .022, P = .039, and P = .045, respectively) in the active patients but not in the controls (Table IV).

For Qol measured by SF-36, there was no significant difference between the groups at baseline. The active patients showed significant progress in Qol in 3 of the 8 scales after exercise: physical functioning (P = .021), general health perceptions (P = .001), and vitality (P = .023) (Table IV).

Adverse effects and safety
No adverse effects or safety issues were encountered.

Discussion
This study shows that short-term exercise training positively affects exercise capacity, resting heart rate, and Qol in patients with AF. This confirms previous findings18,19 and corresponds to effects seen in randomized clinical studies of exercise training programs for patients with ischemic heart disease and CHF.4-9

General effects of exercise training
Adaptations to exercise training include bradycardia, increased end-diastolic dimension, and maximal stroke volume. These effects may be caused by increased vagal tone.

Chronic exercise makes the myocardium less susceptible to acute ischemia and can prevent and/or reverse cardiac malfunction occurring with hypertension, myocardial infarction, and advancing age.20

Exercise training is an established treatment in patients with ischemic heart disease and CHF.4-9 In AF, few studies of exercise training have been carried out.18,19,21,22 The present study has the highest number of patients and...
There is good agreement between the results of the various studies, despite differences in outcome variables and measurements.

**Hemodynamics**

In the active group, maximal exercise capacity increased, whereas in the control groups, maximal exercise capacity decreased. This finding strongly supports that a 12-week physical exercise training program improves the fitness of patients with AF, despite of inherent hemodynamic disabilities associated with AF.

Regarding the slight decrease in exercise capacity of the control group, there is no indication for a systematic error; it may have appeared purely by chance.

It is possible that the enrolled patients favored exercise and would therefore be disappointed if allocated to the control group. However, it seems unlikely that such disappointment would be reflected in a test carried out 3 months after enrollment.

A well-known effect of training in subjects with sinus rhythm is the reduction of heart rate at rest and at a given submaximal workload caused by increased parasympathetic and decreased sympathetic stimulation. In a study by Vanhees et al, significant reductions in heart rate and rate pressure product at rest were observed not only in patients with sinus rhythm but also in patients with AF. The study of Vanhees et al demonstrated that a training-induced lowering effect in resting heart rate can be achieved in patients with chronic AF. These findings are confirmed in the present study.

In our study, myocardial oxygen consumption was not measured. As far as we know, the only studies on exercise training in patients with AF that have measured oxygen consumption was the 2 nonrandomized studies by Mertens and Kavanagh and Vanhees et al. Mertens and Kavanagh found that maximal oxygen consumption and exercise capacity increased equally.

It is therefore likely that measurements of maximal oxygen consumption in our study would show changes corresponding to the change in exercise capacity.

We considered estimating maximal oxygen consumption based on exercise capacity and weight, but such estimates have not been validated in patients with AF.

An alternative approach is estimating maximal oxygen uptake ml/kg body mass/min (VO2max) from 6MWT using the formula proposed by Ross et al: mean VO2max (mL kg⁻¹ min⁻¹) = 4.948 + 0.023 * mean 6MWT (distance in meters). The formula is based on a pooled analysis of 1083 patients with cardiopulmonary disease (predominantly CHF). This approach was used in our study; the mean VO2max (mL kg⁻¹ min⁻¹) increased in the active patients from 16.6 ± 6.9 to 18.1 ± 7.1 mL kg⁻¹ min⁻¹, a 9% increase (P = .001). No change was observed in the controls.

The measurements of CO showed marked variations, and we were unable to demonstrate a difference between the groups at rest or during exercise. That the variation was too large to detect a real difference or that CO is not a factor neither explains the improved exercise capacity.

**Six-minute walk test**

The 6MWT is responsive to changes in patients with CHF and can be used as a reliable independent predictor of worsening in heart failure.
The present study shows that exercise training improves 6MWT performance by a mean of 13%. This corresponds well to a study of patients with CHF participating in a 52-week exercise training trial, in which gains of cardiorespiratory function plateaued at 16 to 26 weeks, with 10% to 15% improvement in 6MWT, maximal exercise capacity, and reduction in resting heart rate.\textsuperscript{27}

A placebo effect cannot be ruled out but is less likely, considering that the effect is consistent with others findings.\textsuperscript{7}

### Table IV. Quality of life measured by the MLHF-Q and SF-36

<table>
<thead>
<tr>
<th>QoL questionnaire</th>
<th>Active baseline, mean ± SD</th>
<th>Active posttraining, mean ± SD</th>
<th>Active baseline–posttraining, P values</th>
<th>Control baseline, mean ± SD</th>
<th>Control posttraining, P values</th>
<th>Control baseline–posttraining, P values</th>
<th>Posttraining, active vs control, P values</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MLHF-Q</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total potential range (0-105)</td>
<td>21 ± 18</td>
<td>15 ± 17</td>
<td>.02</td>
<td>.76</td>
<td>20 ± 20</td>
<td>23 ± 21</td>
<td>.225</td>
</tr>
<tr>
<td>Physical potential range (0-40)</td>
<td>8 ± 7</td>
<td>6 ± 7</td>
<td>.04</td>
<td>.67</td>
<td>8 ± 9</td>
<td>9 ± 9</td>
<td>.375</td>
</tr>
<tr>
<td>Emotional potential range (0-25)</td>
<td>5 ± 4</td>
<td>4 ± 4</td>
<td>.05</td>
<td>.47</td>
<td>4 ± 5</td>
<td>5 ± 6</td>
<td>.303</td>
</tr>
<tr>
<td><strong>SF-36</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical functioning</td>
<td>72 ± 18</td>
<td>77 ± 16</td>
<td>.02</td>
<td>.797</td>
<td>70 ± 28</td>
<td>68 ± 27</td>
<td>.54</td>
</tr>
<tr>
<td>Physical role functioning</td>
<td>49 ± 45</td>
<td>62 ± 44</td>
<td>.11</td>
<td>.059</td>
<td>74 ± 39</td>
<td>66 ± 42</td>
<td>.098</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>73 ± 23</td>
<td>76 ± 24</td>
<td>.30</td>
<td>.087</td>
<td>83 ± 26</td>
<td>79 ± 27</td>
<td>.375</td>
</tr>
<tr>
<td>General health perceptions</td>
<td>57 ± 19</td>
<td>69 ± 19</td>
<td>.001</td>
<td>.378</td>
<td>62 ± 20</td>
<td>60 ± 19</td>
<td>.415</td>
</tr>
<tr>
<td>Vitality</td>
<td>60 ± 23</td>
<td>69 ± 21</td>
<td>.02</td>
<td>.579</td>
<td>65 ± 25</td>
<td>59 ± 26</td>
<td>.049</td>
</tr>
<tr>
<td>Social role function</td>
<td>87 ± 19</td>
<td>92 ± 15</td>
<td>.15</td>
<td>.932</td>
<td>88 ± 21</td>
<td>85 ± 18</td>
<td>.497</td>
</tr>
<tr>
<td>Emotional role functioning</td>
<td>64 ± 44</td>
<td>77 ± 37</td>
<td>.06</td>
<td>.405</td>
<td>77 ± 35</td>
<td>62 ± 42</td>
<td>.064</td>
</tr>
<tr>
<td>Mental health</td>
<td>82 ± 17</td>
<td>83 ± 17</td>
<td>.68</td>
<td>.684</td>
<td>80 ± 20</td>
<td>78 ± 22</td>
<td>.20</td>
</tr>
</tbody>
</table>

MLHF-Q: total score and the subscales regarding physical and emotional well-being were significantly different from baseline until after the training period. There were no statistically significant changes between the groups or within the control group. SF-36: there were no statistically significant changes between the groups from baseline until after the training period, except for the category “vitality”, where the controls were statistically significantly more vital than the active patients. The active patients showed statistically significant progress in QoL in 3 of the 8 scales: physical functioning (P = .02), general health perceptions (P < .001), and vitality (P = .02).

The present study shows that exercise training improves 6MWT performance by a mean of 13%. This corresponds well to a study of patients with CHF participating in a 52-week exercise training trial, in which gains of cardiorespiratory function plateaued at 16 to 26 weeks, with 10% to 15% improvement in 6MWT, maximal exercise capacity, and reduction in resting heart rate.\textsuperscript{27}

A placebo effect cannot be ruled out but is less likely, considering that the effect is consistent with others findings.\textsuperscript{7}

### Natriuretic peptides

Atrial natriuretic peptide and BNP were increased in our patients. Although the mean NT-pro-BNP was lower after the training period than at baseline in the active group and no change was seen in the control group, the difference was not statistically significant. Nilsson et al\textsuperscript{28} also observed that no significant changes in NT-pro-BNP levels took place after the interval training in patients with chronic heart failure, despite significant improvement of functional capacity.
Quality of life

In the within-group analysis of all MLHF-Q categories and 3 of 8 subscales of the SF-36, there were statistically significant improvements. The within-group analysis has more power than a between-group comparison. The active patients had improvements in these categories, whereas the mean values for the controls all seemed to deteriorate (higher MLHF-Q means and lower SF-36 means), although this deterioration was only statistically significant for 1 SF-36 subscale.

Quality of life in the patients with AF is reduced compared with healthy volunteers. Our study shows that this reduction can be reverted with exercise training.

Maximal exercise capacity, 6MWT, and resting heart rate improved by around 10%. We think that improvements of that magnitude after only 12-week intervention are promising.

Strengths and limitations

The study was designed to find a 20% difference between the groups, with α values of 5% and 80% power. Because of the large variation seen in some categories, for example, natriuretic peptides, it is possible that a real difference was overlooked.

In the active patients, there may be self-bias toward reporting positive effect of the intervention. However, owing to the 12-week-long interval between filling out the questionnaires, it is unlikely that the patients remembered their initial answers.

It is important to enroll potential responders. We may have enrolled patients with too little discomfort due to AF to show significant changes with exercise training. The relatively low MLHF-Q scores at baseline indicate that this was the case.

The safety of exercise programs for patients with AF has been evaluated with favorable outcome. Patients with permanent AF can safely participate in exercise training programs and achieve significant functional gains despite poor initial fitness levels.

Both the active and control patients were asked to answer the SF-36 form under the same conditions. A possibility to decrease bias due to group allocation could be “sham-exercise training” at low intensity, or maybe, we could have had a control group of patients who met 3 times weekly for 1 hour to play cards. This may have reduced bias because of a better sociopsychological status of being in a trial unrelated to the physiological effect of exercise training.

Because of exclusion criteria, a large percentage of potential candidates were excluded. Many suitable candidates declined to participate. Therefore, the results of the study do not necessarily reflect the results of all patients with permanent AF.

Perspective/conclusion

This study can provide the background for offering exercise programs as a part of rehabilitation to patients with AF.

From the screened records, 34% of the patients were suitable candidates for participating in the study. It cannot be assumed that all patients with AF necessarily are amenable to exercise training. It is likely that patients who were excluded can also undergo exercise training. Further studies should be made to prove or disproved if other strata of patients with AF may benefit from exercise training.

It is an important finding that 96% of the participants were able to complete the training program.
In Denmark more than 50000 individuals have AF (roughly 1% of the total population). With 34% being suitable for exercise training, as many as 17000 patients may benefit from exercise training. In parallel, about 10000 to 15000 patients are offered physical rehabilitation annually for ischemic heart disease.

The effect of exercise training on cardiovascular endpoints is unknown but should be studied in suitable trials with sufficient power.

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Disclosures

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References