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

Philip Samuel Osbak, MD, [a] **Malene Mourier, PT,** [a] **Andreas Kjaer, MD, DMSc,** [b] **Jens Henrik Henriksen, MD, DMSc,** [c] **Klaus Fuglsang Kofoed, MD, PhD, DMSc,** [a] **and Gorm Boje Jensen, MD, DMSc** [a] ***Copenhagen, Denmark***

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/m^2) 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.)

Patients with atrial fibrillation (AF) often report clinical symptoms such as fatigue, decreased exercise tolerance, dyspnea, and palpitations. This leads to decreased quality of life (Qol).[1] In patients with uncontrolled symptomatic AF showed reduced Qol in all 8 Short-Form 36 (SF-36) subscales.[2]

Decreased Qol is reversible when sinus rhythm is restored.[2,3] However, in a large proportion of patients, restoration of sinus rhythm is not possible.

Exercise training is beneficial for patients with ischemic heart disease and patients with congestive heart failure (CHF),[4-9] but the effect of training on patients with AF is not well known.

In the present study, we therefore conducted a randomized study of exercise training in patients with permanent AF to test if 12 weeks of exercise can increase patients' well-being and Qol and influence hemodynamic parameters such as cardiac output (CO), blood pressure, heart rate, and resting levels of natriuretic peptides.

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 I48.9), 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-13377 and KF-13675).

From the [a]*Department of Cardiology, Hvidovre Hospital, Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark,* [b]*Department of Clinical Physiology, Nuclear Medicine and PET and Cluster for Molecular Imaging, Rigshospitalet, Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark, and* [c]*Department of Clinical Physiology and Nuclear Medicine, Hvidovre Hospital, Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark.*

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Reprint requests: Philip Osbak, MD, Hospital Hvidovre, Department 253, Kettegaard Allé 30, DK-2650 Hvidovre, Denmark.
E-mail: philiposbak@yahoo.dk

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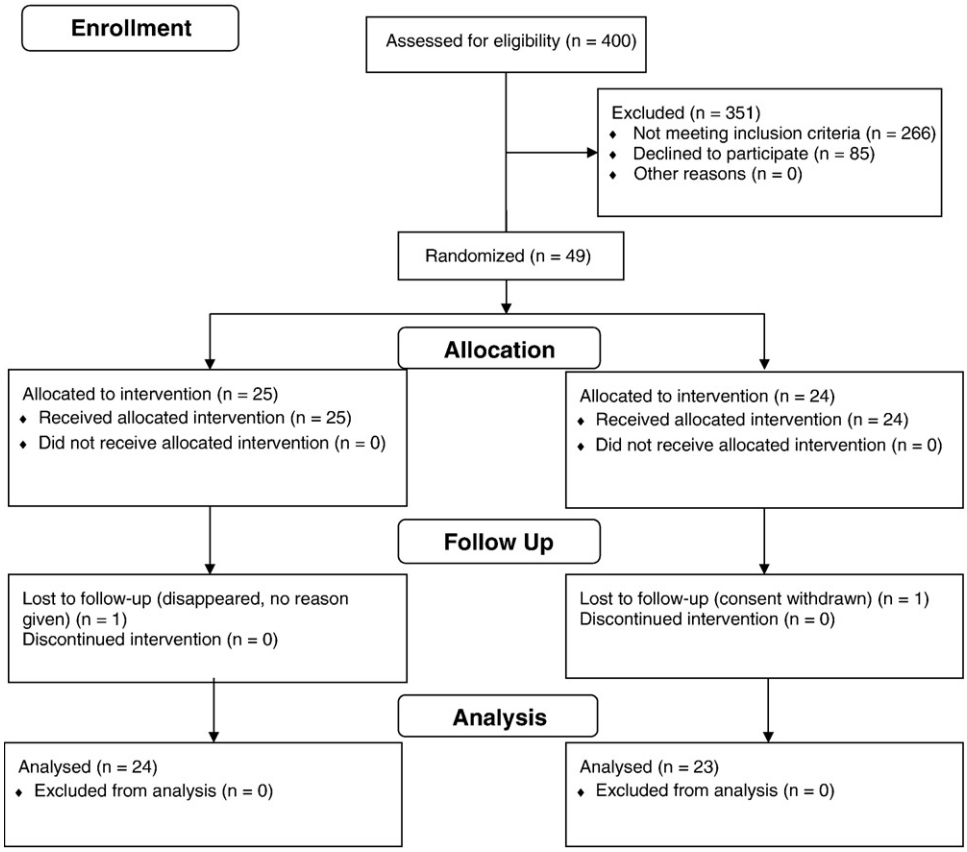
Figure 1



CONSORT diagram.

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.[10] 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.[11]

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)[12] 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)

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

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.

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).

Table II. Medical history, physical activity, and medication

	Active (n = 240), mean ± SD	Controls (n = 23), mean ± SD	*P*
AF duration (y)	5.3 ± 6.4	7.4 ± 9.6	.41
Admitted for AF (fraction)	0.86 ± 0.35	0.86 ± 0.35	.99
No. of admissions for AF	2.0 ± 1.0	2.5 ± 1.8	.28
Hypertension (fraction)	0.82 ± 0.4	0.65 ± 0.5	.34
Physically active weekly (fraction)	0.65 ± 0.49	0.52 ± 0.51	.38
Physical activity (h/wk)	4.2 ± 2.1	5.5 ± 4.9	.42
β-Blocker treatment (fraction)	0.67 ± 0.48	0.57 ± 0.51	.49
Metoprolol (mg), range	50-200	50-200	
Digitalis glycoside treatment (fraction)	0.38 ± 0.50	0.39 ± 0.50	.91
Digoxin (μg), range	125-187.5	125-187.5	
ACE-I and ATIIA treatment (fraction)	0.54 ± 0.51	0.44 ± 0.51	.48
Diuretic treatment (fraction)	0.29 ± 0.46	0.17 ± 0.39	.35
Furosemide (mg), range	40-80	40-80	
Bendroflumethiazide (mg), range	2.5	2.5	
Statin treatment (fraction)	0.21 ± 0.42	0.17 ± 0.39	.77
Warfarin treatment (fraction)	0.88 ± 0.34	0.78 ± 0.42	.41

Medication was unchanged during the intervention. *ACE-1*, Angiotensin-converting enzyme inhibitors; *ATIIA*, angiotensin II receptor antagonists.

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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 reclined to participate in the study. Twenty-three patients were excluded because of sinus rhythm (12 patients), atrial flutter,[4] CHF with left ventricular ejection fraction less than 40%,[4] aortic stenosis,[3] low lung capacity with force expiratory volume in 1 second less that 80% of the expected volume,[3] 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

Table III. Cardiac output, heart rate, heart rate reserve, natriuretic peptides, and 6MWT

	Baseline			After training period		
	Active, mean ± SD	Control, mean ± SD	*P*	Active, mean ± SD	Control, mean ± SD	*P*
Resting CO (L/min)	5.93 ± 2.26	5.97 ± 2.14	.95	6.05 ± 1.88	5.69 ± 1.50	.48
Maximal CO (L/min)	14.3 ± 11.0	14.0 ± 6.0	.91	14.9 ± 5.6	12.7 ± 7.6	.28
Resting heart rate (beats/min)	94.8 ± 22.4	91.4 ± 16.6	.57	86.3 ± 22.5*	94.0 ± 11.8	.21
Maximal heart rate (breaths/min)	152.3 ± 33.7	143.7 ± 25.7	.33	151.1 ± 29.2	138.4 ± 30.7	.15
Maximal power (W)	160 ± 59	135 ± 38	.10	174 ± 56†	127 ± 37‡	.002
Heart rate reserve (beats/min)	57.4 ± 29.3	52.3 ± 22.7	.51	64.8 ± 29.3§	44.3 ± 29.8‖	.03
ANP (nmol/L)	5.30 ± 1.79	5.18 ± 1.17	.79	5.19 ± 1.34	5.08 ± 1.15	.80
NT-pro-BNP (pg/mL)	161 ± 253	114 ± 64	.40	124 ± 63	108 ± 65	.37
6MWT (m)	504.4 ± 85.1	453.1 ± 100.1	.064	569.9 ± 92.6¶	454.1 ± 95.7#	.001

Natriuretic peptides did not change significantly from baseline until after the training period in either active or control patients.
* Significantly different from baseline, $P = .049$.
† Significantly different from baseline, $P < .001$.
‡ Significantly different from baseline, $P < .004$. All others showed no statistically significant change from baseline until after the training period.
§ Active heart rate reserve before and after, $P = .123$.
‖ Control heart rate reserve before and after, $P = .024$.
¶ Six-minute walk test: a significant difference was seen in the active patients, $P < .001$.
# Six-minute walk test: no significant difference was seen in the controls, $P = .88$.

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 findings[18,19] and corresponds to effects seen in randomized clinical studies of exercise training programs for patients with ischemic heart disease and CHF.[4-9]

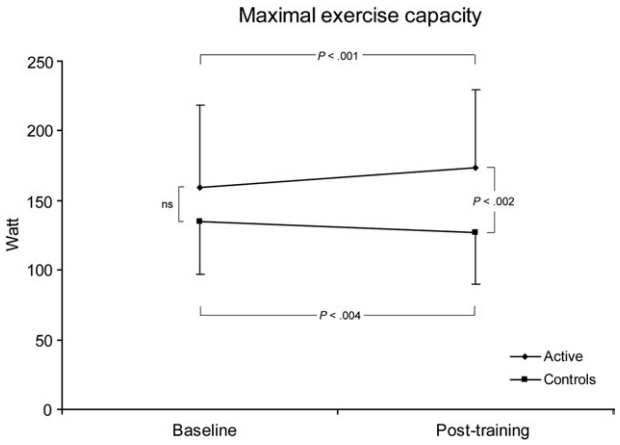
General effects of exercise training

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]

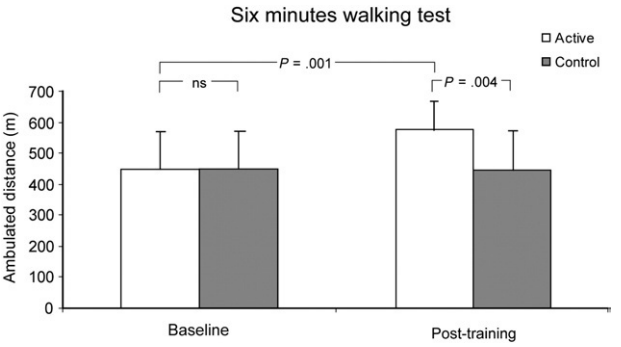
Exercise training is an established treatment in patients with ischemic heart disease and CHF.[4-9] In AF, few studies of exercise training have been carried out.[18,19,21,22] The present study has the highest number of patients and

Figure 2



Ergometer testing at baseline and after training. The active group improved significantly ($P < .001$). The opposite was the case for controls, where maximum exercise capacity decreased after the training period ($P < .004$). After the study period, there was a significant difference between the groups ($P < .002$). Heart rate reserve (heart rate at maximal exercise – heart rate at rest) was significantly different in the active and controls after the training period ($P = .026$; not shown).

Figure 3



Six-minute walking test at baseline and after training. The active group significantly increased their walking distance after the training period ($P < .001$), and after the training period, there were significant differences between the groups ($P = .001$). Apart from these differences, there were no statistically significant changes from baseline until after the training period or between the groups.

effect variables (Table V). 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.[23] In a study by Vanhees et al,[21] 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[22] and Vanhees et al.[21] 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.

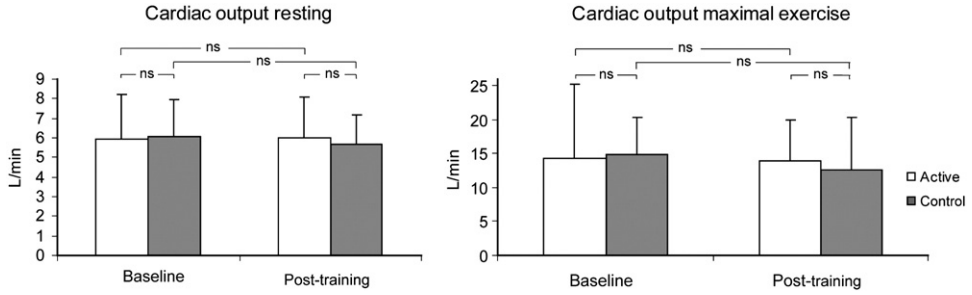
An alternative approach is estimating maximal oxygen uptake ml/kg body mass/min (Vo_{2max}) from 6MWT using the formula proposed by Ross et al[24]: mean Vo_{2max} (mL kg^{-1} min^{-1}) = 4.948 + 0.023 * mean 6MWT (distance in meters). The formula is based on a pooled analysis of 1083 patients with cardiopulmonary disease (predominantly CHF). This approach was used in our study; the mean Vo_{2max} (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.[25]

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.[26]

Figure 4



Left panel: resting CO at baseline and after training. There were no significant changes from baseline until after the training period or between the groups. Right panel: maximal CO at baseline and after training. There were no significant changes from baseline until after the training period or between the groups.

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

QoI questionnaire	Active baseline, mean ± SD	Active posttraining, mean ± SD	Active baseline–posttraining, *P* values	Baseline, active vs control, *P* values	Control baseline, mean ± SD	Control posttraining, mean ± SD	Control baseline-posttraining, *P* values	Posttraining, active vs control, *P* values
MLHF-Q								
Total potential range (0-105)	21 ± 18	15 ± 17	.02	.76	20 ± 20	23 ± 21	.225	.13
Physical potential range (0-40)	8 ± 7	6 ± 7	.04	.67	8 ± 9	9 ± 9	.375	.21
Emotional potential range (0-25)	5 ± 4	4 ± 4	.05	.47	4 ± 5	5 ± 6	.303	.35
SF-36								
Physical functioning	72 ± 18	77 ± 16	.02	.797	70 ± 28	68 ± 27	.54	.21
Physical role functioning	49 ± 45	62 ± 44	.11	.059	74 ± 39	66 ± 42	.098	.73
Bodily pain	73 ± 23	76 ± 24	.30	.087	83 ± 26	79 ± 27	.375	.63
General health perceptions	57 ± 19	69 ± 19	<.001	.378	62 ± 20	60 ± 19	.415	.14
Vitality	60 ± 23	69 ± 21	.02	.579	65 ± 25	59 ± 26	.049	.15
Social role function	87 ± 19	92 ± 15	.15	.932	88 ± 21	85 ± 18	.497	.15
Emotional role functioning	64 ± 44	77 ± 37	.06	.405	77 ± 35	62 ± 42	.064	.22
Mental health	82 ± 17	83 ± 17	.68	.684	80 ± 20	78 ± 22	.20	.35

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 QoI 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.[27]

A placebo effect cannot be ruled out but is less likely, considering that the effect is consistent with others findings.[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[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.

Table V. Published studies of exercise training in patients with AF

Studies of exercise training in patients with AF	No. of patients	Exercise intervention	Effect variables
Hegbom et al,[18,19] randomized design	15 active patients 15 controls	2 mo 24 sessions Exercise training program	QoL* Resting heart rate* Exercise capacity* Heart rate variability*
Mertens and Kavanagh,[22] no randomization	20 patients, no controls	1 y 5 times weekly Walking program	VO_{2max}* Exercise capacity*
Vanhees et al,[21] no randomization	19 patients with AF 44 controls with sinus rhythm	3 mo 3 times weekly Exercise training program	VO_{2max}* Resting heart rate*
Present study, randomized design	25 active 24 controls	12 wk 3 times weekly Exercise training program	QoL* Resting heart rate* Exercise capacity* Heart rate* Heart rate reserve* 6MWT* CO Blood pressure Natriuretic peptides

* Significant effect.

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.[29] 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.[30] 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.[22]

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 50 000 individuals have AF[31] (roughly 1% of the total population). With 34% being suitable for exercise training, as many as 17 000 patients may benefit from exercise training. In parallel, about 10 000 to 15 000 patients are offered physical rehabilitation annually for ischemic heart disease.

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

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Disclosures

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