Combined endurance-resistance training vs. endurance training in patients with chronic heart failure: a prospective randomized study

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Aims
This study was designed to compare the effects of combined endurance-resistance training (CT) with endurance training (ET) only on submaximal and maximal exercise capacity, ventilatory prognostic parameters, safety issues, and quality of life in patients with chronic heart failure (CHF).

Methods and results
Fifty-eight CHF patients (NYHA class II–III) were randomized either to 6 months CT \( n = 28, \) 58 years, left ventricular ejection fraction (LVEF) 26%, \( \text{VO}_2\text{peak} 18.1\ \text{mL/kg/min} \) or ET \( n = 30, \) 59 years, LVEF 23%, \( \text{VO}_2\text{peak} 21.3\ \text{mL/kg/min} \). The increase in steady-state workload \( (P = 0.007) \) and the decrease in heart rate at SSW \( (P = 0.002) \) were significantly larger in CT- compared with ET-trained patients. Maximal exercise capacity (i.e. \( \text{VO}_2\text{peak} \), maximal workload) and work-economy (Wattmax/\( \text{VO}_2\text{peak} \)) evolved similarly. \( \text{VO}_2\text{peak} \) halftime was reduced following CT \( (P = 0.001) \). Maximal strength in upper limbs increased significantly \( (P < 0.001) \) in favour of the CT group. CT also had a beneficial effect on health-related quality of life, i.e. 60% of CT-trained patients vs. 28% of ET-trained patients reported a decrease in cardiac symptoms \( (\text{OR} = 3.86, 95\% \text{CI} 1.11–12.46, P = 0.03) \). There were no differences with regard to improved LVEF, evolution of left ventricular dimensions, nor outcome data (mortality and cardiovascular hospital admissions during follow-up).

Conclusion
In CHF patients, CT had a more pronounced effect on submaximal exercise capacity, muscle strength, and quality of life. The absence of unfavourable effects on left ventricular remodelling and outcome parameters is reassuring and might facilitate further implementation of this particular training modality.

Keywords
Exercise training • Chronic heart failure • Cardiac rehabilitation • Resistance training • Endurance training

Introduction
Despite major progress in pharmacological and device therapy, patients with chronic heart failure (CHF) are left with reduced exercise performance and poor quality of life. In recent years, physical training has gained acceptance as a highly effective means to improve physical capacity and to reduce morbidity. Meta-analyses of published trials also suggest a significant effect in terms of mortality,1 but the results of larger multi-centre randomized trials are awaited to conclude on this issue.2

Randomized trials have almost exclusively focused on endurance training (ET) (aerobic) in this particular patient group. The aim to increase aerobic capacity is a direct consequence of the prognostic power attributed to peak oxygen uptake (\( \text{VO}_2\text{peak} \)) in healthy subjects and in cardiovascular patients.3 Due to skeletal muscle atrophy, CHF patients will also likely benefit from resistance exercise training.4,5 To a large extent, quality of life in these disabled patients depends on engagement in daily life activity, which does not demand peak aerobic performance. Simple tasks such as pulling, pushing, and lifting require skeletal muscle mass and the strength of both upper and lower limbs. Concerns about safety...
of resistance training in this patient group may result from confusion. The haemodynamic consequences of dynamic resistive exercise training involving small muscle groups at low intensity are very different from the cardiovascular stress elicited by sustained isometric exercise at near maximal intensity. Additionally, improved muscular function allows patients to perform submaximal physical tasks at a lower percentage of maximal voluntary contraction. This will result in a lower cardiovascular load. Despite these theoretical advantages, the lack of randomized studies of sufficient power, in this particular population, is mirrored in the cautious attitude towards resistive exercise in official scientific statements. Nevertheless, there is data to support the benefits of dynamic resistive exercise in CHF, usually as an adjunct to ET, in terms of physical capacity, reversal of endothelial dysfunction, neuro-hormonal modulation, and as an anti-inflammatory approach.

In the present prospective randomized study, we tested the hypothesis that in patients with CHF, combined endurance-resistance training (CT) compared with ET is more effective in improving submaximal exercise capacity, without afflicting gain in peak exercise performance. Changes in prognostic ventilatory parameters and safety issues, including left ventricular remodelling, as well as impact on quality of life are also addressed.

**Methods**

**Subjects**

Consecutive patients (1/1/2000–1/6/2005) referred to the Cardiac Rehabilitation Centre of the University of Antwerp Hospital were enrolled into this prospective randomized trial if the following criteria were met: CHF due to ischaemic or dilated cardiomyopathy, left ventricular ejection fraction (LVEF) ≤ 40%; New York Heart Association (NYHA) functional class II–III; optimal and stable pharmacological treatment (angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers, beta-blockers, spironolactone, and/or diuretics if appropriate). Exclusion criteria were recent acute coronary syndrome or revascularization (< 3 months); actively listed on the transplant list; logistic problems to attend regular exercise training sessions; exercise limited by angina or peripheral arterial occlusive disease; cerebrovascular or musculoskeletal disease preventing exercise testing or training; respiratory limitation (forced expired volume in 1 s and/or vital capacity < 60% of predicted); poorly controlled or exercise-induced cardiac arrhythmias. During the trial, drug therapy remained unchanged. The study was approved by the institution’s research Ethics Committee, and patients gave written informed consent.

**Study design**

The major limitation of CHF patients in daily life activities does not depend on reduced peak aerobic capacity, but rather on limitations in submaximal sustained effort. The premise of the present study was that CT, with a specific focus on improving muscle strength and function, would lead to a larger increase in steady-state workload (SSW), compared with ET.

Secondary endpoints included: VO₂peak, ventilatory prognostic parameters, upper and lower limb strength, and quality of life. In addition, NT-proBNP levels, left ventricular dimensions, LVEF, and safety issues were studied. A patient flow diagram is given in Figure 1.

Since this is an open-label study and patients exercised in small groups of eight patients, it was important to avoid treatment contamination and thus cluster randomization was used. Therefore the first consecutive 30 patients were allocated to the CT arm, the next 30 patients were allocated to the ET arm. This way, patients were unaware of a possibly different training modality and confounding was omitted. In addition, at the time patients participated in their training programme, there was no risk of treatment deviation, since resistance training was not available.

**Cardiopulmonary exercise test**

Symptom-limited cardiopulmonary exercise test (CPET) was performed on a treadmill (Medical Jaeger, Würzburg, Germany) in a non-fasting condition and under medication. Monthly interim CPETs were used to adjust aerobic training intensity. Breath-by-breath gas exchange measurements permitted measurements of ventilation (VE), oxygen uptake (VO₂), and carbon dioxide production (VCO₂) on-line (Cardiovit CS-200 Ergo-Spiro, Schiller AG, Baar, Switzerland). Twelve-lead ECG and heart rate were recorded continuously, whereas automatic cuff blood pressure was measured every 2 min and at peak exercise. A ramp protocol, starting with an equivalent of 20 or 40 W and incremental steps equivalent of 10 or 20 W/min was used. Peak oxygen consumption (VO₂peak) was expressed as the highest attained VO₂ during the final 30 s of exercise. Maximal work-economy was described as maximal workload at VO₂peak (Wattmax/VO₂peak). Submaximal work-economy was defined as oxygen uptake at a standard submaximal workload; for each patient this identical workload was re-assessed at the end of the training. At the end of the test, patients recuperated during 3 min at a level equivalent to 25% of maximal performance. Measurements were stopped at VO₂peak half time (T½VO₂). The First Ventilatory (VT1 or aerobic threshold) and the Second Ventilatory Threshold (VT2 or anaerobic threshold) were defined. Circulatory Power was calculated as VO₂peak × peak systolic blood pressure (mmHg: mLVO₂/kg⁻¹/min⁻²). The slope of the relation between VE and VCO₂ was determined by linear regression, excluding the non-linear part after reaching VT2. Exercise tests were supervised by an expert team consisting of physiotherapists and physicians that were unaware of previous CPET results and of the patients’ participation in the training programme. Online analysis of VE/VO₂ and VE/VCO₂ curves permitted to encourage patients to exercise up to exhaustion.

**Measurement of peripheral skeletal muscle and respiratory muscle strength**

With the use of a multifunctional fitness-machine (Unica, Technogym, Gambetola, Italy), the 1 Repeated Maximum (1RM, the highest weight...
that can be lifted once with correct form throughout a complete range of motion) of nine different skeletal muscle groups was measured (M. Quadriceps or leg strength, M. Pectoralis major and minor or butterfly, M. Latissimus Dorsi or pull down, M. Serratus Anterior or chest press, M. Biceps Brachii or arm curl, M. Deltoideus or push up forward, M. Triceps Brachii or arm extension, M. Trapezius or pull down backwards, M. Rhomboideus or pull backwards). Maximal strength of the upper limbs was defined as the combination of three movement patterns (pull down forward, chest press, and butterfly). Maximal inspiratory (Pimax and % PImax predicted) and expiratory pressure (Pmax and % Pp predicted) were determined by technicians unaware of the trial participation of the patients. Evaluation was done with patients in an upright position, breathing through a flanged mouthpiece inside the lips (MasterLabPro 4.3, Jaeger, Würzburg, Germany). All measurements were made according to the recommendations of the European Respiratory Society.11,12

Exercise training

Endurance training intensity
For both CT- and ET-trained patients, ET target heart rate (THR) was calculated as 90% of the heart rate achieved at VT2. Heart rate transmitters (Polar T31™, Polar Electro Oy, Kempele, Finland) were used for immediate feedback to adjust the automated and customized training guidance provided by the TechnoGymSystem (TGS™). After each interim CPET, THR was recalculated and reloaded on the personal training-key of the TechnoGymSystem (TGS™). The training key, when introduced in the training device, steers training-parameters (intensity or speed and inclination are adjusted every 15 s according to the individualized THR). Information on SSW achieved at the THR during training sessions is gathered on the training key. At the end of each session, data collection is downloaded on to the mainframe and a new training programme is loaded on the key.

Resistance training intensity
For nine different muscle groups (see Measurement of peripheral skeletal muscle and respiratory muscle strength), initial training intensity was set at 50% of 1RM, with an increase to 60% after 2 months. Repetitions were slowly increased from 1 × 10, 1 × 15, 2 × 10 to 2 × 15. Between each series of repetitions 1 min rest was allowed. Patients were instructed in correct lifting techniques, to avoid Valsalva manoeuvre and hand gripping.

Training protocols
Patients trained in hospital on an ambulatory base, three times a week for 60 min. Every training session started with 5 min of warming-up exercises and ended with a 5 min cool-down and relaxation. Training sessions were supervised by an experienced physiotherapist and nurse. Patients were centrally monitored using ECG telemetry. The training programme consisted of 70 sessions that were to be completed in 6 months. Prior to the start of the programme, patients agreed to that absenteeism for more than 1 week would lead to exclusion. With the exception of two patients that dropped out because of medical reasons (see Results), the adherence and compliance therefore were excellent.

The ET group (Figure 2) trained for 8 min on five different training devices (treadmill, bicycle, stair or step, arm-cycling, half recumbent, or reclined cycling). When changing from one device to another, 2 min of recuperation time was introduced. After 4 months, training time per device was increased to 15 min (three devices).

During the first 2 months, patients assigned to the CT group (Figure 3) trained for almost 40 min on the Fitness equipment (Unica, Technogym, Gambetola, Italy), whereas only 10 min were spent on ET. The next 2 months, resistance training was reduced to 30 min (nine muscle groups, two times 15 repetitions each) and ET was increased to two times 8 min. During the last 2 months, ET was progressively introduced and very soon exercise times of 10, 12, and 15 min were achieved on three devices. The remainder of the exercise session was spent on resistive training using four major muscle groups (M. Quadriceps, Mm. Pectoralis, M. Serratus Anterior, and M. Latissimus Dorsi; two times 15 repetitions).

Left ventricular function and dimensions
Echocardiography was performed on a Hewlett Packard Agilent Sonos 5500 phased-array scanner (Andover, MA) by sonographers who were blinded to the study intervention. Measurements of resting M-mode left ventricular end-diastolic (LVEDD) and end-systolic (LVESD) diameters were taken from the parasternal long axis. Planar radionuclide ventriculography was performed with a 45° inclined double headed gamma-camera type DST-XLI from Sophia Medical Vision of General Electric (GE-SMV). The technicians and observers were unaware of the trial-participation of the patients.

Patients were in supine position. After intravenous administration of the tracer (20mCi—740 MBq of 99mTc-DMP-HSA) and after homogeneous mixture in the blood pool (gated equilibrium technique), LVEF was calculated by the Fourier method for Gated Blood Pool Scan through analysis of the ECG-triggered acquisition data.

References
Linear isokinetic measurements

We used a Linear Isokinetic Dynamometer (Aristokin®, Lode BV, Groningen, The Netherlands) to evaluate maximal and mean Power (Watt or W) and force (Newton or N), time to maximal force (s), maximal and mean explosivity as force developed per unit of time (N/s), and power and force at 0.25 s. In our setting, we applied a row-movement to evaluate the patient’s ability to perform complex movements of both arms and legs. Linear isokinetic speed was set at 100 cm/s and minimal force at 5 N. From five repetitions a mean performance was calculated. Learning effects have been reported with differences of 5-21% between the first and second test using such rotatory isokinetic calculated. Learning effects have been reported with differences of minimal force at 5 N. From five repetitions a mean performance was both arms and legs. Linear isokinetic speed was set at 100 cm/s and minimal force at 5 N. From five repetitions a mean performance was calculated. Learning effects have been reported with differences of 5-21% between the first and second test using such rotatory isokinetic machines. Therefore, patients were not allowed to train on the rowing-machine during the training programme. In addition, patients with chronic or acute low back pain were not tested on the linear isokinetic dynamometer.

Blood analyses

Fasting blood samples were collected between 8 and 9 AM into ethylenediaminetetraacetic acid (EDTA) and serum tubes at baseline and after 6 months. Creatinine and total cholesterol levels were immediately determined. EDTA-plasma was separated by centrifugation and stored at -20°C. Total cholesterol was quantified by refloretometry with Vitros 750 assays, using dry slide technology (Ortho Clinical Diagnostics, Beerse, Belgium). NT-proBNP was determined with a sandwich immunoassay on an Elecsys 2010 (Roche diagnostic, GmbH, 68298 Mannheim, Germany). The analytical range extends from 5 to 35 000 pg/mL. The coefficient of variation was 1.3% (n = 10) at a level of 221 pg/mL and 1.2% (n = 10) at a level of 4091 pg/mL.

Quality of life

NYHA functional class was recorded at baseline and after 6 months training. The Health Complaints Scale (HCS) contains a 12-item self-report subscale of somatic symptoms that are frequently reported by cardiac patients, such as cardiopulmonary symptoms, fatigue, and sleep problems. Patients indicate how much they suffer from a particular symptom on a 5-point Likert scale ranging from ‘not at all’ to ‘extremely’. This scale has previously been used to assess health-related quality of life in patients with CHF, and has been shown to be responsive to the effect of intervention. Recently, the HCS was also used to evaluate cardiac resynchronization therapy in patients with CHF and multidisciplinary rehabilitation in cardiac patients. In the latter study, the HCS was found to be more sensitive to the effect of cardiac rehabilitation compared with standard self-report scales. In the present study, 52 patients completed the HCS at baseline; 45 of these patients (87%) also completed the HCS at the end of the intervention. In order to provide interpretable estimates of magnitude of the treatment effect regarding health-related quality of life, we analysed the proportion of patients who benefited from the experimental intervention. An effect size of 0.20 was used to determine the proportion of patients who improved significantly in cardiac symptoms following intervention.

Safety data

In order to examine the safety of the CT-training programme, patients were monitored until the time of study closure or when death occurred. Patients were followed for an average period of 714 days (±81.4). Measures of safety were defined prospectively as all-cause mortality and non-elective cardiac-related hospital admission. Patients were seen on a regular base at the outpatient heart failure clinic.

Statistical analysis

All data are expressed as mean value ± SD. Baseline characteristics of the two groups were compared using the χ² test (numerical/binary data) and the unpaired Student’s t-test (continuous variables). Differences between group and changes over time (baseline vs. 6 months) within each group (time effect), as well as any interaction (different trends over time between groups) were assessed by two-way repeated measures ANOVA. ANOVA was used to determine the independent effect of training modality on the increase in SSW, after controlling for beta-blocker use, gender, VO₂peak, LVEF, and NT-proBNP levels. Logistic regression analysis was used to examine differences in the proportion of patients that improved in quality of life as a function of training programme. All tests were two-sided with a P-value < 0.05 considered statistically significant. However, due to multiple comparisons, particular attention should be directed towards lower P-values (i.e. P < 0.01). All statistical analyses were performed using the software package SPSS, version 15.0 (SPSS Inc., Chicago, IL).

Results

Patient characteristics

Sixty patients were recruited (Figure 1), of whom two patients (CT-group) prematurely discontinued their programme because of lymphoma (n = 1) and ischialgia (n = 1). All patients finished their training according to the randomization protocol.

At baseline there were no statistically significant differences between the CT (n = 28) and the ET group (n = 30) with respect to demographic characteristics, functional class, aetiology, duration of the disease, left ventricular systolic function and dimensions, laboratory measurements, and VO₂peak. SSW at baseline was lower in CT-patients, whereas more patients in the ET-group received beta-blockade (Table 1).

Exercise capacity and prognostic markers

SSW achieved during ET at the predefined THR was documented. Only workloads that were maintained for at least 8 min were considered. The observed increase in SSW was significantly larger in the CT-trained patients (from 39.3 ± 14.6 to 64.1 ± 16.8 W) vs. the ET-group (from 51.4 ± 13.4 to 67.0 ± 14.6 W, P = 0.007 for interaction), whereas the ratio of heart rate/SSW (HR/SSW) decreased (P = 0.002 for interaction). Both groups benefited equally from their training regime in terms of maximal exercise capacity (i.e. VO₂peak, maximal workload) and work economy. T1/2VO₂ decreased significantly in the CT-group (P < 0.001) while it remained unaltered in ET-trained patients (P = 0.001 for interaction). When standardized for maximal workload, the difference was still in favour of the CT-group (P = 0.006 for interaction).

Other prognostic markers such as VE/VCO₂ slope and circulatory power evolved similarly. NYHA functional class improved significantly in both training groups (from 2.7 ± 0.5 at baseline to 1.5 ± 0.7 after 6 months for CT; P < 0.001 and from 2.6 ± 0.6 at baseline to 1.4 ± 0.6 after 6 months for ET-group; P < 0.001; P = 0.9 for interaction).

ANOVA identified the independent effect of training modality on the increase in SSW (P = 0.034), after adjustment for beta-blocker use, gender, VO₂peak, LVEF, and NT-proBNP levels (Table 2).
Peripheral skeletal muscle and respiratory muscle strength
Maximal strength in upper limbs increased significantly ($P < 0.001$ for interaction) in favour of the CT-group and there was a strong trend for improved leg strength ($P = 0.06$ for interaction). PImax and %PImax predicted remained essentially unchanged in both groups, but there was a strong trend for PEmax improvement in the CT-trained patients ($P = 0.06$ for interaction). The observed increase in %PEmax was significantly greater for the CT group ($P = 0.03$ for interaction) (Table 3).

Linear isokinetic measurements
Baseline linear isokinetic parameters were comparable in both groups. There was a highly significant increase in functional measurements in both groups, ranging from 49 to 73% in the CT- and from 21 to 36% in the ET-group. The gain in work capacity observed in the CT-group increased (from 303 to 458 J) with a trend for statistical significance ($P = 0.07$ for interaction) compared with the ET-group (from 349 to 424 J) (Table 3).

Left ventricular remodelling
LVEF increased in both groups (25.8 ± 6.9 vs. 28.5 ± 9.7%, $P = 0.04$ for CT, 23.4 ± 9.4 vs. 29.0 ± 13.5%, $P = 0.004$ for ET, $P = 0.2$ for interaction). There was no significant differential effect of training modality on LVEDD and LVESD (data not shown, all $P > 0.05$ for interaction). NT-proBNP levels remained unchanged in both training groups after 6 months training.

Quality of life
Regarding self-reported, health-related quality of life, 42% (19 out of 42) of patients reported a significant decrease in cardiac symptoms. CT had a significantly more pronounced beneficial effect on health-related quality of life; i.e. 60% (12/20) of CT-trained patients reported a marked decrease in cardiac symptoms when compared with only 28% (7/25) of ET-trained patients (OR = 3.86, 95% CI 1.11–12.46, $P = 0.03$).

Outcome and adverse events
During follow-up, four patients (7%) died; there was no difference in mortality as a function of training programme (two deaths in each group, $P = 0.97$). Regarding cardiac hospitalization during follow-up, there was no significant difference between CT-trained patients (average number of hospitalizations per patient = 1.17 ± 1.3 for CT-trained and average = 1.03 ± 1.8 for ET-trained patients; $P = 0.7$).

No adverse events were reported during the rehabilitation programme. Due to permanent telemetry, controlled by an ECG analysing computer and supervised by a trained nurse, major

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**Table 1** Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Combined training ($n = 28$)</th>
<th>Endurance training ($n = 30$)</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>58 ± 11</td>
<td>59 ± 11</td>
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<tr>
<td>Weight (kg)</td>
<td>75.1 ± 18.2</td>
<td>77.0 ± 14.2</td>
<td>0.674</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.7 ± 5.0</td>
<td>26.2 ± 4.8</td>
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<tr>
<td>Male/Female</td>
<td>18/10</td>
<td>24/6</td>
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<tr>
<td>NYHA II/III</td>
<td>9/19</td>
<td>12/18</td>
<td>0.545</td>
</tr>
<tr>
<td>VO₂peak (mL/kg/min)</td>
<td>18.1 ± 4.5</td>
<td>21.3 ± 6.2</td>
<td>0.060</td>
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<tr>
<td>SSW (W)</td>
<td>39 ± 14.4</td>
<td>51 ± 13.4</td>
<td>0.006</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>26 ± 7</td>
<td>23 ± 9</td>
<td>0.351</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>67 ± 9</td>
<td>59 ± 17</td>
<td>0.084</td>
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<tr>
<td>LVESD (mm)</td>
<td>56 ± 11</td>
<td>48 ± 19</td>
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</tr>
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<td>Ischaemic/Dilated cardiomyopathy</td>
<td>16/12</td>
<td>18/12</td>
<td>0.615</td>
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<tr>
<td>Duration (months)</td>
<td>24</td>
<td>23</td>
<td>0.282</td>
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<td>ACE-inhibitors/AT₁-receptor blocker (%)</td>
<td>96</td>
<td>100</td>
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<tr>
<td>Beta-blockers (%)</td>
<td>57</td>
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<tr>
<td>Diuretics (%)</td>
<td>85</td>
<td>70</td>
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<tr>
<td>Aspirin (%)</td>
<td>25</td>
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<tr>
<td>Statins (%)</td>
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<tr>
<td>Spironolactone (%)</td>
<td>71</td>
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<tr>
<td>Amiodarone (%)</td>
<td>32</td>
<td>37</td>
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<tr>
<td>Digoxin (%)</td>
<td>39</td>
<td>30</td>
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<tr>
<td>Warfarin (%)</td>
<td>50</td>
<td>40</td>
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<tr>
<td>NT-proBNP (pg/mL)</td>
<td>2225 ± 2076</td>
<td>2275 ± 3521</td>
<td>0.161</td>
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<tr>
<td>Creatinine (mg/dL)</td>
<td>1.31 ± 0.43</td>
<td>1.37 ± 0.66</td>
<td>0.642</td>
</tr>
</tbody>
</table>

Data are mean ± SD or numbers of patients or percentages. NYHA, New York Heart Association classification; VO₂peak, peak oxygen consumption; SSW, steady state workload; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; ACE, angiotensin-converting enzyme; NT-proBNP, N-terminal pro-brain natriuretic peptide.
There was no unfavourable effect of the CT programme on ven-
tive and endurance exercise (CT) in CHF patients. Several interest-
ting findings emerged from the present study:

To our knowledge, the present randomized trial is the largest to
arrhythmic disturbances were excluded. No patient was hospital-
during the training programme. Two patients were excluded
because of lymphoma (n = 1) and isialgia (n = 1).

Discussion

To our knowledge, the present randomized trial is the largest to
compare ET with a programme that combines both dynamic resis-
tive exercise (CT) in CHF patients. Several interesting findings emerged from the present study:

1. the observed increase in sub-maximal exercise capacity was
larger in the CT vs. the ET group, which was also reflected in
terms of health-related quality of life; despite the initial focus
on resistive exercise training in the CT-group, the achieved
in peak exercise capacity (i.e. VO2 peak, maximal work-
load) was similar.

2. There was no unfavourable effect of the CT programme on ven-
tilatory prognostic parameters. In fact, T1/2VO2 improved signifi-
cantly in patients assigned to the combined training regimen.

3. The lack of detrimental effects on left ventricular remodelling
and NT-proBNP levels, the mildly improved systolic function and the
comparable outcome in terms of mortality and morbidity
suggest that CT in patients with CHF is a safe training modality.

Exercise training is by far the most efficacious way to improve
physical capacity and quality of life in CHF patients. With ET,
relative increases of 10–30% in terms of VO2peak have been
reported, depending on intensity and duration of the programme.
In recent years, the optimal training format for CHF patients has
been the subject of interest. Whereas higher intensity interval
training focuses on peak aerobic capacity,22 training modalities
that also involve dynamic resistive exercise preferentially target
skeletal muscle dysfunction.

Dynamic resistive exercise in chronic heart failure; what is the evidence?

Growing evidence supports the notion that dynamic resistive exer-
cise training, often combined with endurance exercise, is efficient
in patients with CHF.23 In two small separate cross-over studies,
Maiorana and co-workers8,9 demonstrated that CT improved
muscle mitochondrial ATP production rate and higher capillary
permeability. These data were later confirmed in a larger study involving a
total of 39 CHF patients.24 Others have shown increased skeletal
muscle mitochondrial ATP production rate and higher capillary
density,25 neuro-modulation,5 as well as anti-inflammatory effects.4 In an era where evidence based practice is considered
mandatory, there is an implicate need to compare new treatment
strategies, such as CT, with currently accepted therapy. Few inves-
tigators have compared CT head-to-head with ET26,27 in small
studies involving approximately 10 patients in each arm and have
demonstrated significant improvement of skeletal muscle strength.

Table 2 Exercise capacity and prognostic markers

<table>
<thead>
<tr>
<th></th>
<th>Combined training (n = 28)</th>
<th>Endurance training (n = 30)</th>
<th>Differences in changes between groups ANOVA (P-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline 6 months</td>
<td>Baseline 6 months</td>
<td></td>
</tr>
<tr>
<td>Submaximal steady state performance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSW (W)</td>
<td>39.3 ± 14.6</td>
<td>51.4 ± 13.4</td>
<td>67.0 ± 14.6</td>
</tr>
<tr>
<td>Heart rate at SSW (b.p.m.)</td>
<td>102 ± 18</td>
<td>101 ± 20</td>
<td>102 ± 15</td>
</tr>
<tr>
<td>Heart rate/SSW ratio</td>
<td>3.09 ± 1.5</td>
<td>2.02 ± 0.5</td>
<td>1.55 ± 0.3</td>
</tr>
<tr>
<td>Heart rate at rest (b.p.m.)</td>
<td>77 ± 14</td>
<td>76 ± 13</td>
<td>72 ± 12</td>
</tr>
<tr>
<td>Submaximal work economy (W/VO2)</td>
<td>4.3 ± 1.01</td>
<td>4.2 ± 0.9</td>
<td>5.1 ± 1.3</td>
</tr>
<tr>
<td>Maximal exercise capacity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VO2peak (mL/kg/min)</td>
<td>18.1 ± 4.5</td>
<td>21.2 ± 6.2</td>
<td>22.2 ± 6.2</td>
</tr>
<tr>
<td>%VO2 predicted (%)</td>
<td>66.0 ± 13.6</td>
<td>78.5 ± 19.6</td>
<td>83.9 ± 23.5</td>
</tr>
<tr>
<td>Maximal workload (W)</td>
<td>95.4 ± 33.4</td>
<td>106 ± 31.9</td>
<td>141.6 ± 35.3</td>
</tr>
<tr>
<td>%Watt predicted (%)</td>
<td>68.9 ± 19.6</td>
<td>76.1 ± 21.4</td>
<td>105.3 ± 31.9</td>
</tr>
<tr>
<td>Peak heart rate (b.p.m.)</td>
<td>133 ± 25</td>
<td>128 ± 22</td>
<td>135 ± 21</td>
</tr>
<tr>
<td>Work economy (Wattmax/VO2)</td>
<td>5.2 ± 0.8</td>
<td>5.06 ± 0.9</td>
<td>6.5 ± 1.15</td>
</tr>
<tr>
<td>Prognostic markers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VE/VECO2 slope</td>
<td>34.4 ± 7.2</td>
<td>33.2 ± 8.7</td>
<td>31.7 ± 7.4</td>
</tr>
<tr>
<td>T1/2VO2 (s)</td>
<td>304 ± 103</td>
<td>256 ± 67</td>
<td>244 ± 89</td>
</tr>
<tr>
<td>Circulatory power*</td>
<td>2790 ± 1095</td>
<td>3364 ± 1008</td>
<td>3488 ± 1053</td>
</tr>
</tbody>
</table>

Data are mean ± SD.

SSW, steady state workload; VO2peak, peak oxygen consumption; %VO2 predicted, percentage of predicted peak oxygen consumption; %Watt predicted, percentage of predicted maximal workload; VE/VECO2 slope, slope of expired minute ventilation for carbon dioxide output; T1/2VO2, time to reach half of VO2peak after maximal exercise; Circulatory power, VO2peak × peak systolic blood pressure−1 (mMg · mLVO2/kg·min−1).

*Parameters different at baseline P < 0.05.
The interpretation of reported results of dynamic resistive exercise in CHF is frequently complicated by the lack of sufficient power and the non-randomized trial design. Moreover, the incorporation of home-based activities and the use of unsophisticated tools for resistance training, such as elastic rubber bands, could lead to less strict adherence to prescribed activity. In the present prospective randomized study, both patients assigned to the CT and the ET groups adhered to a strictly tailored exercise programme. Supervised ambulatory training was carried out on dedicated equipment. This set-up allowed close assessment of exercise intensity and work-volume and the early detection of adverse effects. With the use of central ECG monitoring, rhythm disorders could be detected and treated, if necessary, ad hoc. Enrolment of at least 25 patients in both treatment arms permitted a more reliable evaluation of the true effects of CT. The salient findings of this study relate to both efficiency and safety of this specific training modality. Incorporation of strength training in the exercise programme of these CHF patients increased submaximal endurance capacity (SSW) to a significantly larger extent (+63 vs. +31%) than conventional ET, whereas increased peak aerobic capacity was similar. The self-reported reduction in perceived cardiac symptoms in CT-trained patients mirrors these findings. The observed benefits address one of the fundamental restrictions experienced by CHF patients: the disability to engage in submaximal physical activities, not only on a professional and recreational level, but also in sexual contacts. In addition, completion of daily-life tasks in this population may be hindered by upper-body skeletal muscle weakness. In the present study, this problem was adequately tackled in CT-trained patients in whom upper limb strength significantly improved. The more accentuated increase in peak expiratory pressure probably reflects the gain in abdominal muscle force.

Despite the fact that a cautious approach is still advocated in official recommendations on exercise training in CHF patients, scientists correct evaluation of the safety of CT might be able to shift paradigms in the near future. Sustained isotropic weightlifting at high intensity (80 to 90% of 1RM) and its possible detrimental effects are very distinct from dynamic resistive exercise prescription in cardiovascular patients. Several investigators have shown that the acute haemodynamic responses during resistance exercise in CHF patients were similar or lower than for aerobic exercise of comparable intensity. There was no evidence of significant deterioration of left ventricular function during resistance exercises performed at intensities up to 60–70% of 1RM. The fact that in the present study, heart rate at SSW (HR/SSW) decreased significantly after CT training when compared with ET, underscores these findings.

### Table 3: Muscle strength and linear isokinetic measurements

<table>
<thead>
<tr>
<th></th>
<th>Combined training (n = 28)</th>
<th>Endurance training (n = 30)</th>
<th>Differences in changes between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline 6 months (%)</td>
<td>Baseline 6 months (%)</td>
<td>ANOVA (P-value)</td>
</tr>
<tr>
<td>Linear isokinetic measurements</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean power (W)</td>
<td>268 ± 131</td>
<td>401 ± 152 (+49)</td>
<td></td>
</tr>
<tr>
<td>Maximal power (W)</td>
<td>506 ± 233</td>
<td>786 ± 271 (+53)</td>
<td></td>
</tr>
<tr>
<td>Work (J)</td>
<td>303 ± 164</td>
<td>458 ± 203 (+51)</td>
<td></td>
</tr>
<tr>
<td>Maximal force (N)</td>
<td>507 ± 284</td>
<td>786 ± 271 (+55)</td>
<td></td>
</tr>
<tr>
<td>Time to Fmax (s)</td>
<td>0.387 ± 0.13</td>
<td>0.363 ± 0.83 (–6)</td>
<td></td>
</tr>
<tr>
<td>Max. explosive force (N/s)</td>
<td>1483 ± 1274</td>
<td>24 911 ± 19 181 (+68)</td>
<td></td>
</tr>
<tr>
<td>Mean explosive force (N/s)</td>
<td>1781 ± 1134</td>
<td>2679 ± 1149 (+50)</td>
<td></td>
</tr>
<tr>
<td>Force at 0.25 s (N)</td>
<td>390 ± 231</td>
<td>677 ± 264 (+73)</td>
<td></td>
</tr>
<tr>
<td>Power at 0.25 s (W)</td>
<td>65 ± 48</td>
<td>111 ± 55 (+71)</td>
<td></td>
</tr>
<tr>
<td>Skeletal muscles (1RM)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower limbs (kg)*</td>
<td>29.5 ± 15.5</td>
<td>42.3 ± 16.9</td>
<td></td>
</tr>
<tr>
<td>Upper limbs (kg)*</td>
<td>27.3 ± 11.7</td>
<td>40.5 ± 14.5</td>
<td></td>
</tr>
<tr>
<td>Respiratory muscles</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pmax (kPa)</td>
<td>7.2 ± 2.3</td>
<td>7.7 ± 2.5</td>
<td></td>
</tr>
<tr>
<td>%Pmax predicted</td>
<td>92.4 ± 23.5</td>
<td>100.5 ± 22.4</td>
<td></td>
</tr>
<tr>
<td>PEmax (kPa)</td>
<td>11.8 ± 3.6</td>
<td>12.8 ± 3.3</td>
<td></td>
</tr>
<tr>
<td>%PEmax predicted</td>
<td>104.9 ± 22.7</td>
<td>117.4 ± 20.6</td>
<td></td>
</tr>
</tbody>
</table>

Data are mean ± SD.  
Fmax, maximal force; 1RM, one repeated maximum; Pmax, maximal inspiratory pressure performed for at least 1 s; %Pmax, percentage of predicted maximal inspiratory pressure; PEmax, maximal expiratory pressure performed for at least 1 s; %PEmax, percentage of predicted maximal expiratory pressure.  
*Parameters different at baseline P ≤ 0.05.
From a recent meta-analysis, it was concluded that aerobic training in CHF reversed left ventricular remodelling, whereas CT had no effect. However, CT trials incorporated in this analysis were conducted within the past 5 years, whereas the first randomized ET studies originate from the early 1990s. More recently introduced and optimized medical and device therapy might have obscured additional anti-remodelling effects of combined exercise training. In addition, the number of CT-trained patients studied was significantly lower than those enrolled in ET studies. In the present trial, LVEF showed small but comparable changes in both training groups, whereas dimensions remained unchanged. These data at least suggest that dynamic resistive exercise in our patients had no detrimental effect on left ventricular remodelling, whereas systolic function improved. Wisloff et al. recently demonstrated a large beneficial effect on LVEF in patients with post-infarction heart failure using high-intensity interval training. In the present study, disease aetiology could not be identified as a significant determinant of the response to different training modalities (data not shown).

With regard to long-term prognosis, three recently introduced ventilatory parameters were assessed. While changes in the VE/VCO₂ slope and circulatory power were comparable in both trained patients groups, T₁/₂VO₂ was significantly shortened in the CT group but not in ET-trained patients. Faster replenishment of muscle high-energy phosphate stores elicited by resistance training might offer a plausible explanation for this effect.

Despite the fact that the present trial was not powered to study hard endpoints, data on hospital admissions and mortality were collected. Importantly, after a mean follow-up time of 714 days, no statistically significant differences were observed.

Limitations

The objective evaluation of skeletal muscle mass would have aided in providing insights into the beneficial effects of CT. However, with an intensity level of 50–60% of 1RM, it was foreseen that strength and endurance, rather than mass, would be influenced by the prescribed training regimen.

Despite a significant difference in beta-blocker therapy, both ET and CT groups had similar resting and peak heart rate, both at baseline and after 6 months training. It is therefore unlikely that chronotropic incompetence will have influenced exercise capacity differently in both groups. In addition, THR determination through heart rate depending formula, such as the well-known Karvonen formula, was avoided. In fact, individual THR was derived from anaerobic threshold identification via gasanalysis during exercise testing.

In this pilot trial, in which head-to-head comparison of CT and ET in patients with CHF is studied for the first time, the load implemented during resistive exercise training was relatively low. The favourable effects of the CT regimen and the lack of detrimental effects will hopefully provide a strong impetus for future trials using higher loads.

Despite the overall low LVEF, the relatively high VO₂peak of the present patient population might raise some concern on the severity of the underlying disease. In this regard, it should be stressed that CPET was performed on a treadmill, which systematically leads to a 10–15% higher absolute VO₂peak value when compared with bicycle exercise testing.

Conclusions

The present study demonstrates that, compared with ET only, CT in CHF patients is feasible, safe, and more effective in terms of submaximal exercise capacity and health-related quality of life. These findings, together with the fact that the gain in peak aerobic capacity was similar, should provide a strong impetus for larger randomized trials and clinical application of this specific training regimen in this patient population.

Conflict of interest: none declared.

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