Clinical research

Combined endurance/resistance training reduces NT-proBNP levels in patients with chronic heart failure

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Aims This study was designed to evaluate the effects of combined endurance/resistance training on NT-proBNP levels in patients with chronic heart failure (CHF).

The safety of resistive weight training for patients with CHF is questioned. Possible detrimental effects include an increase in ventricular diastolic pressure and secondary unfavourable remodelling. Circulating levels of the N-terminal fragment of brain natriuretic peptide (NT-proBNP) reflect left ventricular diastolic wall stress and are strongly related to mortality and treatment success in CHF.

Methods and results In this study, 27 consecutive patients with stable CHF and left ventricular ejection fraction (LVEF) <35% were enrolled in a 4 months non-randomized combined endurance/resistance training programme. Blood sampling for measurement of NT-proBNP, functional assessment, cardiopulmonary exercise testing, echocardiography and radionuclide angiography were performed at entry and after 4 months.

After 4 months, exercise training caused a significant reduction in circulating concentrations of NT-proBNP (2124 ± 397 pg/ml before, 1635 ± 304 pg/ml after training, p = 0.046, interaction), whereas no changes were observed in an untrained heart failure control group. NYHA functional class (p = 0.02, interaction), maximal (peak VO2: p = 0.035, interaction; maximal workload: p < 0.00001, interaction) and submaximal (workload at anaerobic threshold: p = 0.001, interaction; rate–pressure product at anaerobic threshold: p = 0.001, interaction) exercise parameters as well as work efficiency (Wattmax/VO2peak: p = 0.0001, interaction) were significantly improved. In addition, a decrease in left ventricular end-systolic diameter was observed in the trained heart failure group (p = 0.016).

KEYWORDS
Exercise training; Resistance exercise; Natriuretic peptides; Chronic heart failure

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Conclusion Four months of combined endurance/resistance training significantly reduced circulating levels of NT-proBNP in patients with CHF, without evidence of adverse remodelling. Exercise training might offer additional non-pharmacological modulation of the activated neurohormonal pathways in the setting of CHF.

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Introduction

Exercise training has become a valid adjunct treatment modality in chronic heart failure (CHF).\(^1\) Most training programs for CHF patients focus on endurance exercise (i.e., aerobic exercise including walking, cycling), which has been shown to benefit exercise capacity\(^2-6\) and to modulate several of the maladaptive processes that characterize the syndrome.\(^7-10\)

Recently published guidelines acknowledge the possible value of resistance training (i.e., isodynamic or non-sustained isometric exercise including lifting, pushing movements) for patients with CHF,\(^11\) but at the same time, the lack of solid proof for its safety is also emphasised. The reluctance to implement resistive weight training is driven by fear of detrimental effects, such as an increase in left ventricular diastolic pressure and wall stress, possibly leading to unfavourable remodelling, myocardial ischemia and malignant arrhythmia.\(^12\)

In patients with symptomatic CHF, muscular atrophy is a major determinant of exercise capacity.\(^13\) Applying prolonged repetitive dynamic aerobic exercises in severely debilitated patients is often poorly tolerated due to local muscular fatigue. Therefore, a combined endurance/resistance training approach, applying both aerobic and rhythmic muscular strength training might be particularly efficient to improve muscle mass building. Moreover, by specifically increasing submaximal exercise capacity, including upper body activities, functional limitations in the performance of daily life tasks (i.e., pulling, lifting) are reduced, resulting in improved quality of life. Small studies have shown the benefits of such an approach in terms of physical reconditioning, restoration of peripheral endothelial dysfunction and reversal of inflammatory processes.\(^14-16\)

Inappropriate activation of the renin–angiotensin–aldosterone (RAA) system and the sympathetic nervous system have profound negative impact on haemodynamic changes and prognosis in CHF. Pharmacologic modulation of these initially compensating neurohormonal pathways has proved particularly rewarding in the management of these patients. The increase in cardiac secretion of natriuretic peptides is considered an important counteractive mechanism which promotes peripheral vasodilation through inhibition of the RAA axis and sympathetic nerve activity, natriuresis and the attenuation of abnormal vascular cell growth.\(^17\) Brain natriuretic peptide (BNP) and the N-terminal fragment NT-proBNP are secreted by ventricular cardiomyocytes and reflect left ventricular diastolic wall stress.\(^18\) Both peptides are useful predictors of mortality and treatment success in CHF.\(^19-20\) Results from a substudy of the Val-Heft trial have recently led to the proposal to use these neurohormonal markers as surrogate endpoints in CHF interventional studies.\(^21\)

The aim of the present study was to investigate the effect of 4 months combined endurance/resistance exercise training on NT-proBNP concentrations in patients with stable CHF and moderate to severe left ventricular systolic dysfunction. In addition, the evolution of functional class, exercise parameters and left ventricular dimensions was assessed.

Methods

Subjects

Twenty-seven consecutive patients with CHF due to ischemic or dilated cardiomyopathy were prospectively enrolled into a single centre, non-randomized 4 months combined endurance/resistance training program at the Cardiac Rehabilitation Centre of the University Hospital of Antwerp. Patients were included if left ventricular ejection fraction (LVEF) was <35% (assessed by radionuclide angiography; DST XLI, GE Medical Systems\(^10\), Buc Cedex, France; tracer: 20mCi/740Mbq 99mTc-Human Serum Albumin) and if they had been stable with regard to symptoms and medical therapy for at least 1 month prior to inclusion. Medication remained unchanged throughout the study period. Consecutive CHF patients (n = 22), who were unable to attend the exercise program because of e.g., logistic problems, were included in the control group. These patients were seen at the outpatient heart failure clinic by the same multi-disciplinary team with at least 4 months intervals and during the same study period. Patients in the control group were included if symptoms and therapy were stable and if medication could be kept unchanged during the 4 months interval. Exclusion criteria were: hypertrophic cardiomyopathy, valvular disease requiring surgery, exercise-induced myocardial ischemia, exercise-induced malignant ventricular arrhythmia, recent myocardial revascularization (<6 weeks), acute myocarditis or pericarditis, severe renal dysfunction (i.e., creatinine >2.5 mg/dl). The study was approved by the Local Ethical Committee. All patients gave their written informed consent.

Training protocol

Patients attended the exercise program in the hospital on an ambulatory base 3 times/week, for 1 h. Training sessions were supervised by a cardiologist, a physiotherapist and a graduate nurse. Each session commenced and concluded with a 5-min warming-up, cooling-down and stretching period. In between these 2 periods, resistance and endurance exercises were performed on an alternate base (Fig. 1). In order to facilitate endurance training, muscle strength and local muscular fatigue were optimized first. Therefore, focus was on resistance training.
(40 min versus 10 min endurance training) during the first 2 months of the program, with a progressive increase in aerobic exercise duration. After 2 months, both training modalities were equivalent in time (each 25 min).

Resistance training (Fig. 1)

Intensity was set at 50% of the pre-training 1-repetitive maximum (1-RM) tests and was increased to 60% after 2 months. Patients were warned against breath-holding during 1-RM testing.

The resistance circuit consisted out of 9 predetermined resistance exercises, involving muscle groups of the lower and the upper limbs and torso (Technogym, type Unica, Technogym SpA, Via Giorgio Pesticaru 20, 47035 Gambettola, Italy: leg extension: Quadriceps; pullover: Latissimus Dorsi; chest press: Pectoralis, Serratus Anterior, Anterior Deltoids and Triceps; pectoral fly: Pectoralis and Anterior Deltoids; arm curl: Biceps; triceps extension: Triceps; shoulder press: Deltoids and Trapezius; rowing: Latissimus Dorsi, Rhomboidei and Posterior Deltoids; lat pulldown: Latissimus dorsi).

Per station, 1 set, consisting of 10 repetitions, was performed with a gradual increase (15 repetitions after 1 month, 2 sets of 10 repetitions after 2 months, 2 sets of 15 repetitions after 3 months). As the duration of aerobic training was progressively prolonged, the number of resistance exercises was gradually reduced, resulting in only 4 predetermined exercises at the end of the training program. Patients were instructed in correct lifting techniques, to avoid Valsalva manoeuvre and hand gripping.

Endurance training (cycling and jogging) (Fig. 1)

Intensity was aimed at a target heart rate, defined by cardiopulmonary exercise testing (CPET), as the heart rate achieved at 90% of the ventilatory threshold. Exercise intensity was adjusted on a monthly base (repeated CPET). In addition to individual pulse rate measurements (Polar® Heart Rate Monitor, POLAR Electro Oy, Kempele, Finland), a central monitoring system permitted arrhythmia detection. Patients were unable to alter training intensity as they were individually, permanently controlled by an automated adjusting system (TGS®, TechnoGym System).

Laboratory measurements

Fasting blood samples were collected between 8 and 9 am into EDTA tubes and serum tubes at baseline and after 4 months. Care was taken to avoid blood sampling within 24 h of exercise training or CPET. Creatinine and sodium levels were immediately determined on the serum samples. EDTA-plasma was separated by centrifugation and stored at minus 20 °C. NT-proBNP was determined with a sandwich immunoassay on an Elecsys 2010 (Roche diagnostics, Mannheim, Germany). The analytical range extended from 5 to 35000 pg/ml. The co-efficient 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.

Cardiopulmonary exercise testing and echocardiography

In the trained group, treadmill exercise was performed at baseline, monthly and at the end of the combined endurance/resistance training programme (4 months). In the untrained control heart failure group, 2 CPETs (baseline and after 4 months) were obtained. Depending on age, NYHA class, LVEF and prior exercise testing, 2 protocols were used, aiming at an optimal exercise duration of 8–10 min. After 1 min of walking at 20 or 40 W, incremental load (1 min) was set at 10 or 20 W, respectively.

Exercise tests were assisted by the same expert team and patients were encouraged to exercise until exhaustion. Exhaled air was analysed to determine metabolic gas exchange with a respiratory mass spectrometer (type EOS Sprint, Erich Jaeger GmbH & Co., Hoechberg, Germany). Ventilation (VE), oxygen uptake (VO2) and carbon dioxide production (VCO2) were determined on-line every 15 s. The anaerobic threshold (AT) was defined as the start of a systematic increase in the VE/VO2 relation, without a concomitant increase in VE/VCO2. The ventilatory threshold (VT) was defined as the compensatory increase to lactic acidosis in VE/VCO2. The slope of the relation between VE and VCO2 was calculated by linear regression, excluding the non-linear part after reaching the ventilatory threshold. A 12-lead ECG was continuously monitored, whereas blood pressure was automatically measured every 2 min.
The monthly repeated CPET in the trained heart failure group was used to re-evaluate heart rate achieved at ventilatory threshold. Accordingly, aerobic exercise intensity was adjusted (see Training protocol). Resting M-mode echocardiographic measurement (Hewlett Packard Agilent Sonos 5500 phase-array scanner, Andover, MA, USA) of left ventricular end-diastolic (LVEDD) and end-systolic diameter (LVESD) was performed from the parasternal long axis in the trained heart failure group at baseline and after 4 months training. Pulsed Doppler analysis of mitral inflow included measurement of the mitral valve early peak filling velocity (E), the late peak filling velocity (A) and the E to A ratio. Sonographers were blinded to the study intervention. Radionuclide angiography was obtained at entry and after 4 months.

Statistical analyses

All data are expressed as the mean value ± SEM. The data were tested for normal distribution using the Kolmogorov–Smirnov test, and for homogeneity of variances using Levene’s test. Numerical/binary data were analysed using the χ² test. For continuous variables, inter-, and intragroup comparisons were made using the two-sided unpaired and paired Student’s t-test. Differences between the 2 groups (trained versus control) and changes over time within each group (time effect), as well as any interaction (different trends over time between groups) were assessed by two-way repeated measures ANOVA. Correlations were determined with the Pearson’s or Spearman’s correlation test as appropriate. p-Value <0.05 was considered statistically significant. However, due to multiple comparisons, particular attention should be directed towards lower p-values (i.e., p < 0.01). Sample size or power calculations were not performed prior to the trial design. All statistical analyses were performed using the software package SPSS, version 11.0 (SPSS Inc., Chicago, Illinois, USA).

Results

Patient characteristics

At entry, patients in the trained (n = 27) and the untrained (n = 22) heart failure group did not differ in terms of age, sex, aetiology of disease, LVEF and New York Heart Association (NYHA) functional class (Table 1). As is illustrated in Table 2, both patient groups were on standard medical treatment, without significant difference (p > 0.5). Drug treatment remained unchanged during the study period.

Baseline measurements

Baseline plasma concentrations of NT-proBNP, sodium and creatinine levels are shown in Table 3. No statistically significant differences were measured between the trained and the untrained heart failure group (p > 0.5). Exercise and vital parameters were also comparable between the two groups. NT-proBNP levels correlated significantly with maximal (NT-proBNP versus VO₂peak: r = −0.414, p = 0.003, Fig. 2; NT-proBNP versus Wattmax: r = −0.497, p = 0.0003, Fig. 3) and submaximal exercise parameters (VO₂ at AT: r = −0.297, p = 0.041), as well as with the VE/VCO₂ slope (r = 0.444, p = 0.002).

Four months combined endurance/resistance training reduced NT-proBNP levels (2124 ± 397 pg/ml before, 1635 ± 304 pg/ml after training, p = 0.015; p = 0.046, interaction) (Table 3, Fig. 4A), whereas in the untrained heart failure control group they remained unchanged (p = 0.9, Fig. 4B). In 20 out of the 27 trained patients, NT-proBNP levels were available 4 months after discontinuation of the training programme (Fig. 5: p = 0.015 repeated measures ANOVA). Creatinine and sodium levels did not change in either subgroup. Improved NYHA functional class was observed in the trained group only (from 2.8 ± 0.1 to 2.3 ± 0.1, p = 0.0002; p = 0.02, interaction). There was a significant increase in maximal (VO₂peak: +2.0 ml kg⁻¹ min⁻¹, p = 0.022; p = 0.035, interaction; Wattmax: +34 Watt, p = 0.00001; p = 0.00001, interaction), submaximal (workload at anaerobic threshold: p = 0.0001; p = 0.001, interaction) parameters and work efficiency (Wattmax/VO₂peak: +1.4 Watt ml⁻¹ kg⁻¹ min⁻¹, p = 0.0003; p = 0.0001, interaction) after 4 months training. Baseline NT-proBNP correlated significantly with changes in maximal workload (Fig. 6: r = −0.456, p = 0.017), whereas changes in NT-proBNP were significantly correlated to changes in VE/VCO₂ slope (r = 0.439, p = 0.002). The observed decrease of NT-proBNP from baseline to 4 months was not related to the increase of VO₂peak, nor Wattmax. Resting heart rate

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<th>Table 1 Baseline demographic and clinical characteristics of trained patients and untrained controls</th>
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<td>Age (y)</td>
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<td>Male/female</td>
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<td>CAD/IDCM</td>
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<td>LVEF (%)</td>
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<td>NYHA II/III</td>
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<td>CAD = coronary artery disease, IDCM = idiopathic dilated cardiomyopathy, LVEF = left ventricular ejection fraction.</td>
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<th>Table 2 Medical therapy of trained patients and untrained controls</th>
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<td>ACE-inhibitor</td>
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<td>Beta-blockers</td>
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<td>Spironolactone</td>
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<td>ACE-inhibitor = angiotensin converting enzyme inhibitor.</td>
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(p = 0.03) decreased, while peak heart rate was significantly increased (p = 0.03). Submaximal rate–pressure product (rate–pressure product at AT during initial exercise test and measured at a comparable workload after 4 months) significantly decreased in the trained patients (p = 0.023; p = 0.001, interaction), whereas in the control group a significant increase was observed (p = 0.015). Repeated echocardiographic measurements showed a tendency for LVEDD to decrease (69 ± 2 mm before versus 65 ± 3 mm after training, p = 0.069). LVESD was significantly reduced after the training period (58 ± 2 mm before versus 53 ± 2 mm after training, p = 0.016).
These changes were not related to changes in NT-proBNP. LVEF, as assessed by radionuclide angiography, was stable (26 ± 1.3% before versus 28 ± 1.8% after training, \( p = 0.11 \)). Mitral inflow measurements were concordant with NT-proBNP data showing a significant negative relation with the A-wave (reflecting left ventricular end-diastolic pressure) \( (r = -0.470, p = 0.018) \) and a positive relation with the E/A ratio (reflecting filling pressures) \( (r = 0.486, p = 0.014) \).

With the exception of a significant decrease in maximal workrate \( (p = 0.009) \), no changes were noted in the untrained heart failure control group after an interval of 4 months.

### Discussion

The present study indicates that a 4-month combined endurance/resistance training program induced a significant reduction in circulating concentrations of NT-proBNP. Besides an improvement in NYHA functional class in these patients, both maximal (peak VO\(_2\), maximal work rate) and submaximal (workload and rate—pressure product at anaerobic threshold) exercise parameters, as well as work efficiency were significantly improved. These changes occurred without evidence of negative left ventricular remodelling.

Several reports have highlighted the feasibility and safety of endurance training programs, even early after...
myocardial infarction with poor residual left ventricular function. The peripheral effects of comprehensive training protocols are diverse and comprise the enhancement of exercise tolerance, haemodynamics, ventilatory efficiency and autonomic function, the reversal of skeletal muscle atrophy, muscle bioenergetics and histological abnormalities and the attenuation of endothelial dysfunction. Although training effects appear mainly peripheral, central changes, such as improved collateral myocardial circulation and diastolic filling and an anti-remodelling effect are both reassuring and clinically relevant. Interestingly, Braith et al. showed that 16 weeks of endurance training modified resting neuroendocrine hyperactivity in CHF patients. In addition, Adamopoulos and his group provided evidence for an anti-inflammatory response following endurance training. Interplay between neurohumoral changes and the peripheral features mentioned earlier is likely to be important.

Combined endurance/resistance training in CHF: Is it safe?

There is growing consensus that exercise training provides important symptomatic relief in patients with CHF. However, several technical issues, such as optimal training intensity and duration, and the value of resistance exercise remain unresolved. The haemodynamic burden of weight lifting has also largely prevented the integration of non-sustained isometric exercise in conventional training protocols. However, the advantages of the introduction of isodynamic exercises of selected muscle groups at moderate intensity could be highly relevant in patients with poor physical condition due to CHF. First, optimization of muscle strength and local muscular fatigue is often a prerequisite to enable severely debilitated patients to perform endurance exercise. Several investigators have indeed stressed the relation between exercise capacity and muscle mass. Second, resistance training concentrates on daily encountered activities, by means of improving submaximal endurance and enhancement of muscle mass and strength, thus providing more self-support and quality of life. Besides lower body exercises (Quadriceps muscles), focus is on upper body activities (Latissimus dorsi, Triceps, Biceps, Deltoids, Pectoral, Trapezius, Serratus Anterior muscles), which are traditionally not incorporated in endurance training programs. An important benefit of upper-body resistive training is that it more closely meets the patient’s vocational and avocational goals. Finally, studies that specifically addressed the haemodynamic impact and the issue of myocardial ischemia induced by resistance versus aerobic training in patients with coronary artery disease, showed responses that were in favour of the former training modality. Indeed, lower heart rate and higher diastolic blood pressure could result in improved coronary artery filling. Moreover, the pressor response to resistance exercise is determined by the percent of maximal voluntary contraction, as well as the muscle mass involved. Thus, increased muscle strength as a result of training, leads to a relatively lower rate–pressure at any given load, because the load now represents a lower percentage of the maximal voluntary contraction. This phenomenon could also be observed in the present study, where exercised patients showed a significantly lower rate–pressure product at a comparable submaximal workload (i.e., workload at anaerobic threshold) after 4 months training. Together with the increase in subendocardial perfusion (secondary to higher diastolic blood pressure), the decrease in venous return, left ventricular diastolic volume and wall stress, may explain the lower incidence of ischemia during this type of exercise. Exercising isolated muscle groups, without imposing the cardiovascular burden of whole body exercise, could therefore be of particular interest in patients with CHF. Maiorana and colleagues have shown that circuit weight training (cycle ergometry, treadmill walking and resistance weight training) induced a significant increase in peak oxygen consumption, exercise duration, muscular strength and improvement of peripheral vascular function, without any short-term adverse events. A recently conducted study in a patient group with CHF showed that a combined endurance/resistance training protocol elicited an anti-inflammatory effect. In a smaller study comparing endurance versus combined endurance/resistance training, Delagardelle et al. showed improved exercise capacity, strength parameters and left ventricular function with the latter training modality.

The results of the present study add to the evidence that a combined training protocol offers both a safe and effective approach in patients with moderate to severe left ventricular dysfunction. Although long-term follow-up data are not yet available, we observed no adverse events (i.e., hospitalization, myocardial ischaemia or revascularization, severe arrhythmia, heart transplantation) during the study period. The fact that, in the present study, end-systolic left ventricular diameter decreased after the training period, advocates against the anticipated harmful haemodynamic effect of resistive weight training in CHF patients. The lack of relationship between changes in NT-proBNP levels and left ventricular dimensions is more difficult to explain. However, contrary to natriuretic peptide levels, which more quickly respond to different loading conditions of the ventricles, left ventricular re-modelling probably needs more time. In both studies by Giannuzzi et al. and Hambrecht and co-workers, in which improved left ventricular function and remodelling were observed, the training intervention lasted for 6 months. Caution is necessary when relying on the reproducibility of natriuretic peptide measurements in patients with stable CHF. However, it is reassuring that after 4 months NT-proBNP levels did not significantly change in the untrained heart failure group. This was also the case for the repeated measurements in the trained group, 4 months after discontinuation of the training programme. In addition, the significant relationship between NT-proBNP and the important prognosticator VE/VCO₂ slope in the present study, supports the validity of the studied natriuretic peptide.
In terms of efficacy, a 4-month combined endurance/resistance training improved NYHA functional class and exercise parameters to an extent comparable to most endurance programs. The most relevant change seen from the exercise physiology standpoint in this study is the impressive improvement in maximal workload. The inverse relation between baseline NT-proBNP and changes in $\text{Watt}_{\text{max}}$ suggests that benefits for patients with high diastolic wall stress at entry might be less important. This hypothesis deserves to be studied in a larger patient group. It also raises the question whether a cut-off NT-proBNP level could be identified above which a combined endurance/resistance training program should not be advocated and whether optimization of wall stress (i.e., increasing diuretic dosage or decreasing afterload) could reverse this phenomenon. There appears to be no causal relation between the changes in NT-proBNP and the improvement of both maximal oxygen consumption and workload. This probably illustrates that the observed increase in exercise capacity is the result of peripheral adaptations, while the decrease in NT-proBNP at least suggests that these results are obtained without negatively impacting on diastolic wall stress and left ventricular remodelling.

**Exercise training and neurohormonal activation**

During the past two decades, research in the field of CHF has unravelled a network of neurohormonal pathways, whose inappropriate activation seems to play a critical role in the progression of the disease. As a consequence, pharmaceutical interventions aimed at interrupting the RAA axis and the adrenergic nervous system have been successful in reducing both morbidity and mortality in these patients. However, attempts to obtain more profound antagonism with sympatholytic drugs on top of standard therapy (i.e., ACE-inhibitors, beta-blockers) are disappointing. Although theoretically attractive, trials with endothelin receptor blockers have not resulted in clinical benefit. These sobering results have led to the contention that a ceiling effect could have been reached and that non-neurohormonal therapeutic targets should be pursued. To our knowledge, the present study is the first to examine the effect of combined endurance/resistance exercise training on resting plasma levels of NT-proBNP in patients with CHF. The exact mechanism leading to the observed decrease in NT-proBNP concentration remains to be resolved. Although some authors have provided evidence for changes in left ventricular performance and central haemodynamics after endurance training, the assertion that exercise training in CHF patients derives its beneficial effects through peripheral adaptations, such as a decrease in left ventricular afterload, is conceivable. Moreover, Belardinelli et al., have shown that a 2-month endurance training program improved left ventricular diastolic filling in patients with dilated cardiomyopathy. The fact that end-systolic diameter of the left ventricle was significantly decreased, together with the tendency for left ventricular end-diastolic dimensions to be reduced, suggests that lower diastolic wall stress in the present study could have caused a decrease in NT-proBNP secretion. Contrary to previously published studies, a high proportion of patients enrolled in the present study (59%) were on beta-blocker therapy. Therefore, the present data provide evidence that exercise capacity in CHF patients receiving optimized neurohormonal antagonists can be enhanced through combined/endurance training. In addition, the idea that training could offer an alternative way to further modulate these activated systems is tempting. Whereas some studies have suggested an improvement in morbidity and mortality with endurance training, a large multi-centre study will be required to definitively solve this matter.

**Limitations**

The major limitations of this study were the small number of patients and the lack of a randomized design. Although the control group was matched for relevant demographic characteristics, exercise parameters and NT-proBNP levels, we cannot rule out selection bias. Despite the lack of long-term follow-up at present, however, we believe the significant reduction in circulating levels of NT-proBNP provides further impetus to pursue the implementation of combined endurance/resistance exercise programs in larger patient groups and to compare its effects with purely aerobic exercise training. No additional information is provided on the influence of the implemented training protocol on other relevant neurohormones, such as angiotensin II, aldosterone and noradrenaline. When designing the protocol, we decided to investigate the evolution of a neurohormonal marker combining both prognostic accuracy and technical advantages, such as limited fluctuations due to posture, the absence of a diurnal pattern or interference due to delay in handling of blood samples. Latini et al., recently underscored the robustness of natriuretic peptides as solid prognostic markers in CHF. From the 5 neurohormones (BNP, renin, endothelin, noradrenaline, aldosterone) assessed in a group of 4300 patients with moderate to severe heart failure, BNP was the most powerful indicator for poor outcome. The predominance of patients with ischaemic heart disease resulted in an imbalance of males and females included in the present study; whether the results of this investigation is therefore applicable to both sexes should be further studied. On the basis of the large numbers of multiple comparisons, it can not be excluded that some of the correlations are significant by chance alone.

**Conclusions**

Combined endurance/resistance training induced a significant reduction in circulating concentrations of NT-proBNP, and an overall improvement of exercise capacity, without negative left ventricular remodelling. Whether the reduction of circulating levels of NT-proBNP...
could serve as a surrogate marker of improved prognosis remains to be further explored.

References