Favourable effects of exercise training on NT-pro-BNP plasma levels in elderly patients after acute myocardial infarction

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Abstract

Background: regional or global impairment of left ventricular (LV) systolic or diastolic function leading to increased LV wall stress results in increased circulating levels of N-terminal pro-brain natriuretic peptide (NT-pro-BNP).

Objective: this study aims at evaluating the effect of exercise training (ET) on NT-pro-BNP plasma levels in older patients recovering from acute myocardial infarction (AMI).

Design: prospective randomised study.

Setting: Academic Medical Centre.

Subjects: forty older patients (33 males and 7 females) who experienced AMI.

Methods: patients were randomised into two groups, each composed of 20 patients: Group A were enrolled in a 3-month exercise-based cardiac rehabilitation (CR) programme and Group B were discharged home with generic instructions to continue physical activity. NT-pro-BNP, cardiopulmonary and Doppler-echocardiographic parameters were measured at baseline and at 3-month follow-up.
Keywords: NT-pro-BNP, elderly, cardiac rehabilitation, myocardial infarction, left ventricular remodelling

Introduction

Exercise-based cardiac rehabilitation (CR) in patients recovering from acute myocardial infarction (AMI) has several beneficial effects on cardiovascular functional capacity, quality of life, risk factor modification, psychological profile, morbidity and mortality [1]. However, these results were obtained mainly in middle-age coronary population, because elderly patients are usually not included in CR programs and less represented in clinical trials [2].

Despite these limitations, a number of studies have shown that also in older patients recovering from AMI, exercise-based CR may confer several favourable effects on functional capacity, quality of life, coronary risk and psychological profile [3–5].

Brain natriuretic peptide (BNP), a peptide hormone released from the cardiac ventricles in response to myocyte stretch, is synthesised as an inactive pro-hormone that is split into the active hormone BNP and the inactive N-terminal fragment (NT-pro-BNP). BNP has several systemic effects, including vasodilation, increase in urinary volume and sodium output, and inhibition of sympathetic nervous system and renin–angiotensin system [6]. The predominant pathophysiological process at the base of increased plasma levels of BNP and NT-pro-BNP is regional or global impairment of left ventricular (LV) systolic or diastolic function, leading to increased LV wall stress [7].

BNP is a highly sensitive and accurate method for the detection of LV systolic [8] and diastolic dysfunction [9], and both BNP and NT-pro-BNP are strong predictors of morbidity and mortality in patients with heart failure and coronary heart disease [10, 11]. BNP is also a powerful independent predictor of LV remodelling in patients after AMI [12]. Particularly in elderly population, the changes in BNP after an acute coronary event assume a more important relevance since BNP increases with age [13] and BNP values have been demonstrated to have prognostic significance in elderly subjects [14], in older functionally impaired patients [15] and in elderly patients with coronary heart disease and heart failure [16]. Therefore, changes in NT-pro-BNP after AMI in elderly population with an intervention such as exercise training (ET) may be particularly relevant for the prognosis of these patients. However, the behaviour of BNP after AMI in older patients and its relationship with exercise-induced improvement in cardiovascular capacity in the elderly has not as yet been characterised.

Therefore, the purpose of this study was to investigate the influence of ET on NT-pro-BNP plasma levels and on cardiovascular capacity in older patients recovering from AMI.

Methods

Study population

Forty patients, ≥65 years recovering from AMI, were studied. We excluded patients with post-infarction residual myocardial ischemia, severe ventricular arrhythmias, atrio-ventricular block, chronic heart failure or very severe reduction of left ventricular ejection fraction (LVEF = 30%), hypertrophic cardiomyopathy, valvular disease requiring surgery, pericarditis and severe renal dysfunction (i.e. creatinine > 2.5 mg/dl).

At hospital discharge, patients were randomised into two groups (A and B), each composed of 20 patients, who were similar for age, severity of coronary artery disease, coronary risk factors, type of coronary event or LV ejection fraction (Table 1). Group A patients were enrolled in a formal 3-month ET program, whereas Group B patients were discharged with routine instructions to continue physical activity and maintain a correct lifestyle.

All patients underwent a Doppler echocardiography and a cardiopulmonary exercise test (CPX) before or soon after hospital discharge (mean days from AMI: 11 ± 3) and after 3 months. Owing to its superior stability during laboratory procedures, NT-pro-BNP was determined instead of BNP, before and at 3-month follow-up.

The study was approved by the local Ethical Committee. All patients gave their written informed consent.

ET protocol

Group A patients attended the ET programme in the hospital on an ambulatory basis three times a week for 3 months. Training sessions, performed under continuous electrocardiogram monitoring, were supervised by a cardiologist and a graduate nurse. Each session, preceded by a 5-min warming-up and followed by a 5-min cooling-down, was performed by pedalling for 30 min on a bicycle ergometer at 60% of the VO2peak achieved at the initial symptom-limited cardiopulmonary exercise test (CPX-1).

Results: in Group A, ET reduced NT-pro-BNP levels (from 1446 ± 475 to 435 ± 251 pg/ml, P < 0.001) and increased maximal exercise parameters; there was also an inverse correlation between changes in NT-pro-BNP levels and in VO2peak (r = –0.67, P < 0.01), E-wave (r = –0.42, P < 0.01) and E/A ratio (r = –0.60, P < 0.01). In Group B, after 3 months, no changes were observed in NT-pro-BNP levels, exercise and echocardiographic parameters. LV volumes and left ventricular ejection fraction (LVEF) were unchanged after 3 months in both groups.

Conclusions: three months ET in older patients after AMI was associated with a reduction in NT-pro-BNP levels and an overall improvement of exercise capacity, without negative LV remodelling and with improvement in early LV filling. Further investigation is required to evaluate whether in these patients the reduction of NT-pro-BNP levels at 3 months could be useful as a surrogate marker of favourable LV remodelling at a later follow-up.
Table 1. Baseline demographic and clinical characteristics of trained patients (Group A) and untrained controls (Group B)

<table>
<thead>
<tr>
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<th>Group A (trained)</th>
<th>Group B (untrained)</th>
<th>P-values</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>68.6 ± 2.3</td>
<td>68.2 ± 2.6</td>
<td>NS</td>
</tr>
<tr>
<td>Male/female</td>
<td>16 (80)/4(20)</td>
<td>17 (85)/3(15)</td>
<td>NS</td>
</tr>
<tr>
<td>Anterosetal AMI</td>
<td>16 (80)</td>
<td>15 (75)</td>
<td>NS</td>
</tr>
<tr>
<td>Trombolysis/PTCA</td>
<td>2 (10)/18(90)</td>
<td>1.5 (19)/95(5)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension</td>
<td>14 (70)</td>
<td>14 (70)</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>9 (45)</td>
<td>9 (45)</td>
<td>NS</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>18 (90)</td>
<td>17 (85)</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking</td>
<td>12 (60)</td>
<td>13 (65)</td>
<td>NS</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>43.6 ± 4.0</td>
<td>43.7 ± 3.2</td>
<td>NS</td>
</tr>
<tr>
<td>Number of diseased arteries</td>
<td>1.7 ± 0.9</td>
<td>1.7 ± 0.8</td>
<td>NS</td>
</tr>
</tbody>
</table>

ACE, angiotensin converting enzyme; AMI, acute myocardial infarction; ATII, angiotensin II receptor; LVEF, left ventricular ejection fraction; NS, not significant; PTCA, percutaneous transluminal coronary angioplasty.

Laboratory measurements

Fasting blood samples were collected between 8 and 9 a.m. into ethylenediaminetetraacetic acid (EDTA) tubes and serum tubes at baseline and after 3 months. Care was taken to avoid blood sampling within 24 h of ET or CPX. EDTA plasma was separated by centrifugation and stored at –20°C. NT-pro-BNP was determined with a sandwich immunoassay on an Elecsys 2010 (Roche diagnostics, Milano, Italy). The analytical range extended from 5 to 35,000 pg/ml.

Doppler echocardiography

All patients underwent a Doppler echocardiographic study (Hewlett Packard Agilent Sonos 5500 phase-array scanner, Andover, MA, USA) at the beginning of the study and after 3 months. Standard views, including the parasternal long-axis, short-axis at the papillary muscle level, and apical 4- and 2-chamber views, were recorded. The cardiac dimensions were measured according to American Society of Echocardiography guidelines. LV end-diastolic volume (LVEDV) was measured by the Simpson’s rule. An increase in LVEDV from baseline to follow-up was used as an index of LV remodelling. Pulsed Doppler analysis of mitral inflow included measurement of the mitral valve early peak filling velocity (E-wave), the late peak filling velocity (A-wave) and the E to A ratio. Sonographers were blinded to the subgroup allocation.

CPX

All patients underwent an incremental CPX on a bicycle ergometer. Before each test, oxygen and carbon dioxide analysers and a flow mass sensor were calibrated by use of available precision gas mixtures and a 3-1 syringe, respectively. To stabilise gas measurements, patients were asked to remain still on the ergometer for at least 3 min before starting the exercise. After a 1-min warm-up period at 0 W workload, a ramp protocol of 15 W/min was started and continued until exhaustion. The pedalling was kept constant at 55–65 revolutions/min. A 12-lead electrocardiogram (ECG) was monitored continuously during the test, and cuff blood pressure was manually recorded every 2 min. Respiratory gas exchange measurements were obtained breath by breath with the use of a computerised metabolic cart (Vmax 29C, Sensormedics, Yorba Linda, CA, USA). $V_{O2peak}$ was recorded as the mean value of $V_{O2}$ during the last 20 s of the test and was expressed in millilitres per kilogram per minute. At the end of CPX test, patients were asked to identify the primary reason for stopping. Predicted $V_{O2peak}$ was determined by use of a sex-, age-, height- and weight-adjusted and protocol-specific formula outlined by Wassermann et al. [17]. The ventilatory anaerobic threshold (VAT) was detected by two experienced reviewers (C.V. and F.G.) by use of the V-slope method [18]. The $V_{E}$ versus $V_{CO2}$ relationship was measured by plotting ventilation ($V_{E}$) against carbon dioxide production ($V_{CO2}$) obtained every 10 s of exercise ($V_{E}/V_{CO2slope}$); both $V_{E}$ and $V_{CO2}$ were measured in litres per minute. The $V_{E}$ slope was calculated as a linear regression function, excluding the non-linear part of the relationship after the onset of acidic drive to ventilation.

Statistics

Descriptive statistics are given in terms of means ± standard deviation. Comparison between groups for continuous variables was made using Student’s t test. Pearson’s correlation co-efficient was used to assess the association between changes in NT-pro-BNP plasma levels and cardiopulmonary and echocardiographic parameters. Statistical significance was set at level <0.05, for two-tailed probability independent samples. All statistical analyses were performed using the software package SPSS, version 11.0 (SPSS Inc., Chicago, IL, USA).

Results

At entry, patients did not differ in terms of age, sex, severity of disease, LVEF and medications (Table 1). Drug treatment remained unchanged during the study period. No statistically significant differences were found at baseline between Groups A and B in NT-pro-BNP plasma levels and in exercise, cardiopulmonary, clinical and Doppler-echocardiographic parameters.

After the 3-month ET, in Group A, NT-pro-BNP plasma levels decreased while exercise and cardiopulmonary parameters significantly improved (Table 2). A significant inverse correlation was found between changes in NT-pro-BNP levels and changes in $V_{O2peak}$ at 3 months ($r = -0.67,$...
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Trained group (Group A) (n = 20)</th>
<th>95% confidence interval of the difference</th>
<th>Untrained group (Group B) (n = 20)</th>
<th>95% confidence interval of the difference</th>
<th>Differences in changes between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>NT-pro-BNP, pg/ml</td>
<td>1446.5 ± 475.2</td>
<td>345 ± 251</td>
<td>&lt;0.001</td>
<td>1506.2 ± 490.4</td>
<td>1490.4 ± 437.1</td>
</tr>
<tr>
<td>VO2peak, ml/Kg/min</td>
<td>16.3 ± 1.4</td>
<td>20.8 ± 2.4</td>
<td>&lt;0.001</td>
<td>15.7 ± 1.5</td>
<td>15.3 ± 1.6</td>
</tr>
<tr>
<td>VO2AT, ml/Kg/min</td>
<td>12.1 ± 1.1</td>
<td>15.7 ± 1.7</td>
<td>&lt;0.001</td>
<td>12.1 ± 0.9</td>
<td>12.2 ± 0.8</td>
</tr>
<tr>
<td>A-wave, cm/s</td>
<td>58.6 ± 4.3</td>
<td>64.3 ± 5.8</td>
<td>&lt;0.001</td>
<td>58.2 ± 4.2</td>
<td>58.5 ± 4.1</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>0.9 ± 0.1</td>
<td>1.2 ± 0.1</td>
<td>&lt;0.001</td>
<td>0.97 ± 0.1</td>
<td>0.99 ± 0.2</td>
</tr>
<tr>
<td>LVEDV, ml/m²</td>
<td>75.7 ± 15.2</td>
<td>75.13 ± 15.7</td>
<td>0.517</td>
<td>75.9 ± 11.7</td>
<td>77.2 ± 11.1</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>44.8 ± 4.0</td>
<td>44.6 ± 1.5</td>
<td>0.894</td>
<td>44.8 ± 2.1</td>
<td>44.5 ± 1.6</td>
</tr>
</tbody>
</table>

A-wave, peak mitral flow velocity during atrial systole; E-wave, peak mitral flow velocity during early filling; HRpeak, heart rate at peak exercise; HRrest, heart rate at rest; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVEF, left ventricular end-systolic volume; NT-pro-BNP, N-terminal fragment of brain natriuretic peptide; RER, respiratory exchange ratio; SBPpeak, systolic blood pressure at peak exercise; SBPrest, systolic blood pressure at rest; VO2peak, peak oxygen consumption; VO2AT, oxygen consumption at anaerobic threshold (ml/kg/min); VO2peak, peak oxygen consumption; WattAT, workload at anaerobic threshold; Wattmax, maximal workload.

- **Table 2.** NT-pro-BNP concentration, clinical, exercise and Doppler echocardiographic parameters (mean ± SD) at baseline and at 3-month follow-up
Favourable effects of exercise training on NT-pro-BNP

A previous study from our institution showed the beneficial effects of ET on resting plasma levels of NT-pro-BNP in patients after AMI [19].

In this study, we extended this observation to older patients recovering from AMI. In trained older patients 3 months after AMI, we observed a decrease in NT-pro-BNP plasma levels whereas these remained unchanged in older patients who did not exercise. Both BNP and NT-pro-BNP have been shown to be strong predictors of morbidity and mortality in very elderly subjects [14], in older functionally impaired patients [15] and in patients with heart failure and coronary heart disease [10, 11].

The ET-induced fall in NT-pro-BNP plasma levels in our elderly patients was not accompanied by parallel LV remodelling, thus confirming the absence of negative influence of ET on the evolution of LV function and dimensions after AMI [20–22]. It is likely that the absence of LV remodelling was due to the early follow-up of our patients after AMI (3 months) whereas differences in LV remodelling after AMI between patients undergoing ET and control patients are likely to be observed only after 6 months after AMI [23]. Therefore, it is possible to hypothesise that in older trained patients the reduction of NT-pro-BNP plasma levels 3 months after AMI may translate in the following months into an improvement in LV dimensions.

In fact, other authors evaluated the predictive value of BNP [24] and of NT-pro-BNP [12, 25] on LV remodelling in the first year after AMI in untrained patients and demonstrated that patients in whom LV dilatation developed could be identified by elevated plasma levels of BNP or NT-pro-BNP, both in the early post AMI phase and after 6 months. More recently, Takagi et al. [26] showed that the predictive value of BNP was present also in post AMI patients undergoing exercise-based CR.

We can hypothesise that the reason for the fall in NT-pro-BNP plasma levels in trained older patients was due to a decrease in LV stress. In fact, the significant inverse correlation found between changes in E-wave and NT-pro-BNP plasma levels, a reflection of LV stress [7] (see the Figure Appendix 2 in the supplementary data on the journal website http://www.ageing.oxfordjournals.org), suggests that the increase in E-wave, indicating an improvement in early diastolic filling, might be correlated to a decrease in LV wall stress after 3 months of ET. It is known that changes in LV afterload may translate into changes in Doppler measurements [27]. A reduction of LV systolic stress or afterload leads to a decrease of intraventricular late systolic or early diastolic LV pressure, to an increase in atrio-ventricular pressure gradient in early diastole and thus to an improved early diastolic LV filling [28]. This study extends to older AMI patients, the results of previous studies showing that endurance training is associated with improved diastolic filling in healthy subjects or in younger patients after AMI [19].

In addition, the inverse relationship found between changes in VO2peak and in NT-pro-BNP plasma levels (see Figure Appendix 1) and between changes in VO2peak and in E-wave (see Figure Appendix 3) suggests that the same mechanisms associated with exercise-induced improvement in cardiovascular functional capacity (i.e. improvement in endothelial vascular function and decrease in peripheral vascular resistance) may also lead to a decrease in LV stress reflected by the reduction in NT-pro-BNP plasma levels and the improved LV early diastolic filling.

An improvement in arterial endothelial function has been widely shown to occur with ET both in normal subjects and in patients with coronary artery disease, with or without LV dysfunction [29]. This leads to a reduction of systemic vascular resistance and of LV afterload and stress through the increased availability or reduced inactivation of NO, a powerful systemic vasodilator [30]. The NO-induced fall in systemic vascular resistance and increase in peripheral skeletal muscle perfusion may lead to the improvement of cardiovascular functional capacity, as expressed by the increase of VO2peak in our patients after 3 months of ET. Our study confirms previous demonstrations of improved cardiac functional performance and VO2peak with exercise-based CR in elderly patients after AMI [3–5].

We cannot comment on the effect of NT-pro-BNP on LV remodelling after AMI since we restudied our patient 3 months after AMI, and it is well known that the remodelling process is usually observed at least 6 months after the acute event [23]. Prolonged follow-up of these patients may shed more light on the significance of the decrease of NT-pro-BNP in these patients and its correlation with changes in LV volumes.

It is also uncertain whether the conclusions of our study may be applicable to the majority of elderly coronary patients, usually excluded from CR programmes because of the presence of comorbidity or of logistic problems [2]. However, data of literature show that, when elderly patient can be enrolled in an exercise-based CR programme, they can obtain favourable results on functional capacity and on other significant endpoints [3–5] that are superimposable to those observed in younger patient population. Although it is clear that tailored exercise protocols may be necessary.
particular in very elderly patients, our observations may contribute to encourage cardiologists to enrol an increasing number of elderly patients in their CR programmes.

In conclusion, 3-month ET in older AMI patients with moderate LV systolic dysfunction was associated with a significant reduction in NT-pro-BNP plasma levels and an overall improvement of exercise functional capacity, without negative LV remodelling and with improved early LV diastolic filling at Doppler echocardiography. In contrast, no changes in these parameters were found in non-trained older AMI patients.

Whether the reduction of NT-pro-BNP plasma levels could be useful as a surrogate marker of favourable LV remodelling at a later follow-up in older patients after AMI and LV dysfunction remains to be investigated in future research.

Key points
- This study demonstrates that exercise-based CR in older patients after AMI was associated with a decrease of NT-pro-BNP plasma levels and with an improvement of cardiovascular functional capacity while NT-pro-BNP plasma levels and cardiovascular functional capacity remained unchanged in older patients who did not enter the exercise-based CR protocol. The measurement of BNP or NT-pro-BNP, a highly sensitive and accurate method for the detection of LV systolic and diastolic dysfunction in patients after AMI, may predict those patients who will have unfavourable LV remodelling at a later time in the follow-up of elderly patients after AMI.
- NT-pro-BNP plasma levels reduction was correlated to the exercise-induced improvement of cardiovascular functional capacity and of early LV diastolic filling pattern, as expressed by the height of E-wave at Doppler echocardiography, suggesting that ET reduced LV systolic stress and intraventricular pressure in early diastole, likely through peripheral arterial vasodilatation.
- This study confirms, also in elderly post AMI patients, the presence of a favourable effect of ET on the evolution of LV function and volumes 3 months after AMI, a point that had raised much debate in the past.

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Conflicts of interest
None declared.

References
Which model of successful ageing should be used?

Baseline findings from a British longitudinal survey of ageing

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Abstract

Background: there is increasing interest in how to age ‘successfully’ and in reaching consensus over its definition.

Objective: to assess different models of successful ageing, using a British longitudinal survey of ageing in 2000–1.

Setting: community settings in Britain.

Methods: five models of successful ageing were tested on a British cross-sectional population survey of 999 people aged 65+. The models were biomedical, broader biomedical, social, psychological and lay based.

Results: the lay model emerged as the strongest. Respondents who were classified as successfully aged with this model, compared with those not successfully aged, had over five times the odds of rating their quality of life (QoL) as good rather than not good [odds ratio (OR) = 5.493, 95% confidence interval (95% CI) = 2.655–11.364].

Conclusion: the lay-based, more multidimensional, model of successful ageing predicted perceived QoL more powerfully than unidimensional models and should be used to evaluate the outcomes of health promotion in older populations.

Keywords: successful ageing, physical functioning, mental functioning, social functioning, health status, well-being, quality of life, elderly