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ORIGINAL PAPER

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N-terminal B-type natriuretic peptide concentrations are similarly increased by 30 minutes of moderate and brisk walking in patients with coronary artery disease

Abstract Elevated concentrations of B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) reflect elevated myocardial wall stress due to volume or pressure overload in cardiac disease. Recently, exercise-induced elevations of (NT-pro)BNP in coronary artery disease (CAD) patients have been reported to result from exercise-induced ischemia associated regional wall abnormalities. Therefore, the study aimed to examine NT-proBNP concentrations in patients with CAD after moderate and brisk walking (MW, BW). We hypothesized that BW induces higher increases than MW. *Methods and results* In randomized order 14 patients with stable CAD (12♂/2♀; 63 ± 9 years; LV ejection fraction: 59 ± 9%) of a out-patient rehabilitation group performed MW with 4.5 ± 0.6 km/h (mean heart rate: 80 ± 11/min) or BW at their allowed upper exercise heart rate of 102 ± 9/min with a speed of 6.2 ± 0.6 km/h for 30 min on a tartan track on two separate days. Blood samples were taken before, immediately, 1 h, 3 h and 1 day after exercise to determine NT-proBNP and cardiac troponin T (cTnT). Echocardiographic LV function was determined before and 1 h after exercise. Median concentrations of NT-proBNP significantly increased from 222 to 295 ng/l (MW) and from 222 to 296 ng/l (BW) without a difference between both modalities. cTnT remained below the detection limit of 0.01 µg/l. LV functions remained unchanged. A cut-off level of 250 ng/l distinguished CAD patients with elevated exercise-induced increases in NT-proBNP and a diminished LV ejection fraction at rest. *Conclusion* BW and MW induce similar increases in NT-proBNP in CAD patients without myocardial damage, which have to be considered when NT-proBNP is determined. Derived from the exercise-induced increase in NT-proBNP, the myocardial strain in BW is not elevated in comparison to MW.

Key words Brain natriuretic peptide – coronary heart disease – exercise – prevention – rehabilitation

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Introduction

Primarily synthesized by cardiomyocytes, elevated concentrations of B-type natriuretic peptide (BNP) and its cleaved inactive fragment N-terminal pro-BNP (NT-proBNP) reflect elevated myocardial wall stress by myocyte stretch due to volume or pressure overload in cardiac dysfunction, congestive heart failure, cardiomyopathy and other cardiac diseases [6, 13, 15, 18]. Today both markers are considered as useful tools in cardiovascular diagnostics, guidance of drug therapy and risk stratification [9, 11, 30]. However, exercise-induced elevations in healthy subjects have been demonstrated previously [10, 19,

20, 22], which seem to be without patological significance [25, 32]. On the other hand, exercise-induced elevations of BNP and NT-proBNP in patients with coronary artery disease (CAD) have recently been reported to result from exercise-induced ischemia associated regional wall abnormalities [5, 34, 35, 37]. Therefore, it was the aim of the present study to examine if rehabilitative exercise in CAD patients induces increases in NT-proBNP and cardiac troponin T (cTnT) as well as affections of left ventricular (LV) function. In addition, the influence of physical activity on NT-proBNP concentrations in CAD patients should be determined to investigate, if prior physical activity can lead to misinterpretations in NT-proBNP values in CAD patients.

We hypothesized that 30 min of brisk walking (BW), but not 30 min of moderate walking (MW), induce an increase in NT-proBNP concentrations in patients with stable CAD. The presence of myocardial damage should be verified by elevated cardiac troponin T (cTnT) concentrations or a decrease in LV function after walking.

Methods

Study population

A total of 14 patients (12 men, 2 women; age: 63 ± 9 years; height: 177 ± 7 cm; weight: 83 ± 14 kg; LV enddiastolic volume: 133 ± 25 ml, range 88–198 ml; LV ejection fraction: 59 ± 9%, range: 45–75%) with stable coronary artery disease took part after informed consent in the study, which was approved by the institutional review board. All participants weekly exercise 90 min at the institutional out-patient cardiovascular rehabilitation kinetotherapy group for at least 6 months (range: 6 months to 18 years). Patients either had no angina pectoris or stable angina pectoris at a CCS I level, and did not suffer from dyspnoe or had congestive heart failure at a NYHA I level. Three patients suffered from one vessel disease, 3 patients from two vessel disease, and 8 from three vessel disease. A history of myocardial infarction was present in 9 patients, 8 patients had received a coronary artery bypass graft and 5 a percutaneous coronary intervention. As cardiovascular medication 14 patients received acetylsalicylic acid, 13 β-blockers, 10 ACE antagonists or AT-1 receptor antagonists and 2 diuretics.

The participants' last cardiological examination including medical history, determination of routine laboratory parameters, ECG at rest and exercise and Doppler-echocardiography at the Institute of Sports and Preventive Medicine (University of Saarland, Saarbrücken, Germany) was within at least one year prior to the study. During this examination, participants' allowed upper exercise heart rate was routinely derived by a 12-lead exercise ECG on a cycle ergometer started at 25–50 W and increased by 25 W every 3 min until symptom limited exhaustion or significant ECG changes. The exercise ECG was combined with the determination of the individual anaerobic threshold (IAT) by the method of Stegmann et al. [29]. The upper exercise heart rate was defined as the heart rate which did not induce angina pectoris or significant ECG changes and should not exceed the IAT. The mean maximal workload during cycle ergometry was 145 ± 34 W and 1.7 ± 0.2 W/kg bodyweight, respectively. The calculated maximal oxygen consumption (VO_2peak) derived by the formula of Swain et al. [31] was 2291 ± 377 l/min and 28 ± 3 ml/min kg, respectively.

Moderate and brisk walking

Participants either had to walk slowly with a constant velocity of about 4 km/h (moderate walking) or brisk at their allowed upper heart rate (brisk walking) for 30 min after manual randomization by flipping a coin. Although the randamization procedure was blinded and, therefore, not stratified for any exercise or clinical parameters, no differences between the groups "moderate walking – brisk walking" and "brisk walking – moderate walking" existed after post hoc analysis. Exercise heart rates were continously recorded by a heart rate monitor (Polar, Finland), and the rating of perceived exertion (RPE) was documented immediately after exercise by ordinally scaled values between 6 and 20 (7: very very easy; 19 very very difficult) [2]. The tests started at 9 a.m. and the interval between the tests was one week. Participants either walked both tests on a 400 m outdoor tartan track (during the period from July to August) or a 200 m indoor tartan track (during the period from September to December). Outdoor temperaturs ranged from 20–26 °C, indoor temperature was 23 °C. Venous blood samples were taken from an antecubital vein in sitting position before, immediately after, 1 h and 3 h after exercise as well as the next morning between 8 and 9 a.m. Samples were centrifuged and aliquoted within 20 min after assessment and stored at –20 °C until automated analysis using the same batches was performed.

NT-proBNP and BNP

Serum NT-proBNP was measured by chemiluminescence on an automated analyzer (Elecsys®proBNP; Elecsys® 2010; Roche Diagnostics, Mannheim, Ger-

many). The analytical sensitivity of the test is 5 ng/l. Intra- and interassay coefficients of variance at 175 ng/l are 2.7 and 3.2%, respectively. In healthy subjects, the upper reference limit (URL) in men and women under 50 years is 84 and 146 ng/l, respectively, and 198 and 222 ng/l in men and women aged 50–65 years [7, 8].

Additional plasma BNP concentrations were measured in 6 subjects before and after moderate and brisk walking, respectively, on an automated analyzer (Biosite Triage BNP; Access Immunoassay System, Beckman Coulter). The recommended URL is 100 ng/l for men and women [15], the 95th percentile in healthy subjects aged 55–64 years is 72 ng/l for males and 81 ng/l for females, and 63 and 95 ng/l for men and women, respectively, aged 65–74 years.

Troponin T

cTnT was measured by a chemiluminescence immunoassay on an automated analyzer (Troponin T Elecsys® 3rd Generation, Elecsys® 2010; Roche Diagnostics, Mannheim, Germany). The cross reactivity with skeletal TnT and human cTnI is 0.001% and 0.002%, respectively (functional sensitivity 0.01 µg/l with 20% total imprecision, intra- and interassay imprecision at 0.48 µg/l 1.2 and 4.9%). The URL defined as the 99th percentile in healthy subjects is < 0.01 µg/l [1].

CK and CK-MB, creatinine

On an automated analyzer (Synchron CX5®, Beckman Coulter), creatine-kinase (CK) and CK-MB activity were measured enzymatically at 37 °C, and creatinine by the method of Jaffé. Upper reference limits for CK are 171 U/l in men and 145 U/l in women, for CK-MB 28 U/l in both sexes and for creatinine 1.20 mg/dl in men and 1.0 mg/dl in women.

Echocardiography

Doppler echocardiography was performed on a GE System FiVe (GE, Vingmed Ultrasound, Norway) with a 2.5 MHz transducer in accordance with the guidelines of the American Society of Echocardiography on the day of the medical examination as well as on both exercise days 1 h before and 1 h after exercise. Standard parameters were determined in the parasternal and the apical view, LV ejection fraction by use of the Simpson rule, and parameters were determined off-line in a blinded fashion.

Statistics

For statistical calculations the software package Statistica 6.1 (StatSoft Inc., Tulsa, USA) was used. Gaussian distribution was tested with the Kolmogorov-Smirnov test. Normally distributed values are expressed as mean ± standard deviation. Changes in dependent variables were tested by the paired student's t-test and for multiple comparisons by analysis of variance and post-hoc by the test of Scheffé. Normally distributed independent variables were tested by the unpaired t-test. For non-gaussian distributed variables, values are given as medians. Medians were compared by the Wilcoxon test for paired samples and the Bonferroni procedure was used for multiple comparisons. The Pearson correlation coefficient was used to test for relationships between normally distributed variables, for nongaussian distributed variables the Spearman coefficient of correlation was used. An α-error < 0.05 was considered as statistically significant.

Results

Exercise variables

Walking velocities were 4.5 ± 0.6 km/h for moderate walking and 6.2 ± 0.6 km/h for brisk walking ($p < 0.001$). Covered distances of moderate and brisk walking, rating of perceived exertion (RPE), resting and mean exercise heart rates as well as lactate concentrations before (Before) and immediately after moderate and brisk walking (End) are demonstrated in Figure 1.

NT-proBNP

Medians of NT-proBNP concentrations and individual courses for moderate and brisk walking are shown in Figure 2. Absolute as well as exercise-induced increases in NT-proBNP concentrations after moderate and brisk walking were significantly related (absolute NT-proBNP concentrations: $r = 0.92$; $p < 0.001$; increases in NT-proBNP concentrations: $r = 0.88$; $p < 0.001$). Subjects with resting NT-proBNP concentrations above 250 ng/l demonstrated significantly higher exercise-induced increases (Fig. 3 A), and presented a significant lower LV ejection fraction at rest than those with resting NT-proBNP concentrations below 250 ng/l (Fig. 3 B). In addition, the resting heart rate was significantly lower in subjects with NT-proBNP concentrations below 250 ng/l (55 ± 6/min vs 67 ± 5/min; $p < 0.01$). The mean and maximum heart

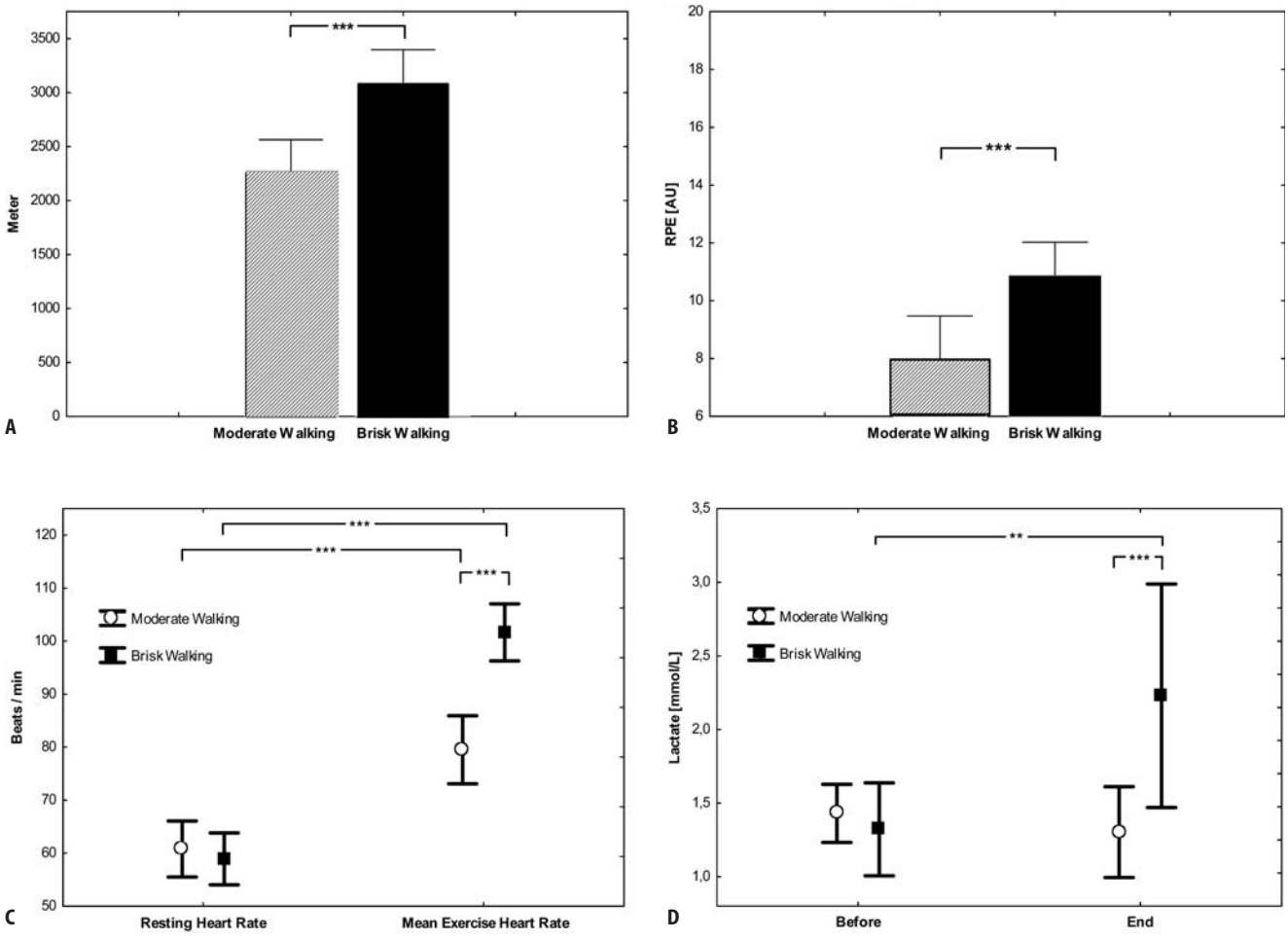

Fig. 1 **A** Covered distances of moderate and brisk walking. **B** Ratings of perceived exertion after moderate and brisk walking. **C** Resting heart rates before and mean exercise heart rates during moderate and brisk walking (interaction: $p < 0.001$). **D** Lactate concentrations before and immediately after moderate and brisk walking (interaction: $p < 0.001$). ***: $p < 0.001$; **: $p < 0.01$

rates during exercise and the ratings of perceived exertion were similar in subjects with resting NT-proBNP concentrations ≤250 ng/l and >250 ng/l. In addition, no difference existed between the groups for cycle ergometric derived maximal power output or calculated VO_2peak (maximal power output and calculated VO_2peak for subjects with NT-proBNP concentrations at rest ≤250 and >250 ng/l: 1.8 ± 0.1 vs 1.6 ± 0.2 W/kg and 28 ± 2 vs 28 ± 4 ml/min/kg, respectively). No correlations were found between the individual VO_2peak levels and resting NT-proBNP levels or exercise-induced increases in NT-proBNP (ranges of p-values: 0.13–0.76). Furthermore, the number of diseased vessels did not differ beween the groups (diseased vessels in subjects with NT-proBNP concentrations at rest ≤250 and >250 ng/l: 2.4 ± 0.9 vs 2.3 ± 0.8) and was not related to the exercise-induced increase in NT-proBNP. Similar results were documented after correction for plasma volume changes by the formula of Dill and Costil [4].

BNP

Plasma BNP concentrations were determined in 6 subjects, demonstrating similar increases after moderate (MW) and brisk walking (BW) from 80 (31–188 ng/l) to 110 ng/l (37–215) for MW ($p = 0.027$) and from 83 (33–159) to 118 ng/l (54–276) for BW ($p = 0.027$). One hour after exercise, concentrations were 93 ng/l (30–215 ng/l) for MW ($p = 0.067$) and 80 ng/l (31–175 ng/l) for BW; 3 h after exercise, concentrations were 116 [36–250] for MW and 94 ng/l [38–226 ng/l] for BW. On the following day, values did not differ significantly from pre-exercise values (MW: 93 [30–184]; BW: 101 ng/l [21–153 ng/l]). NT-

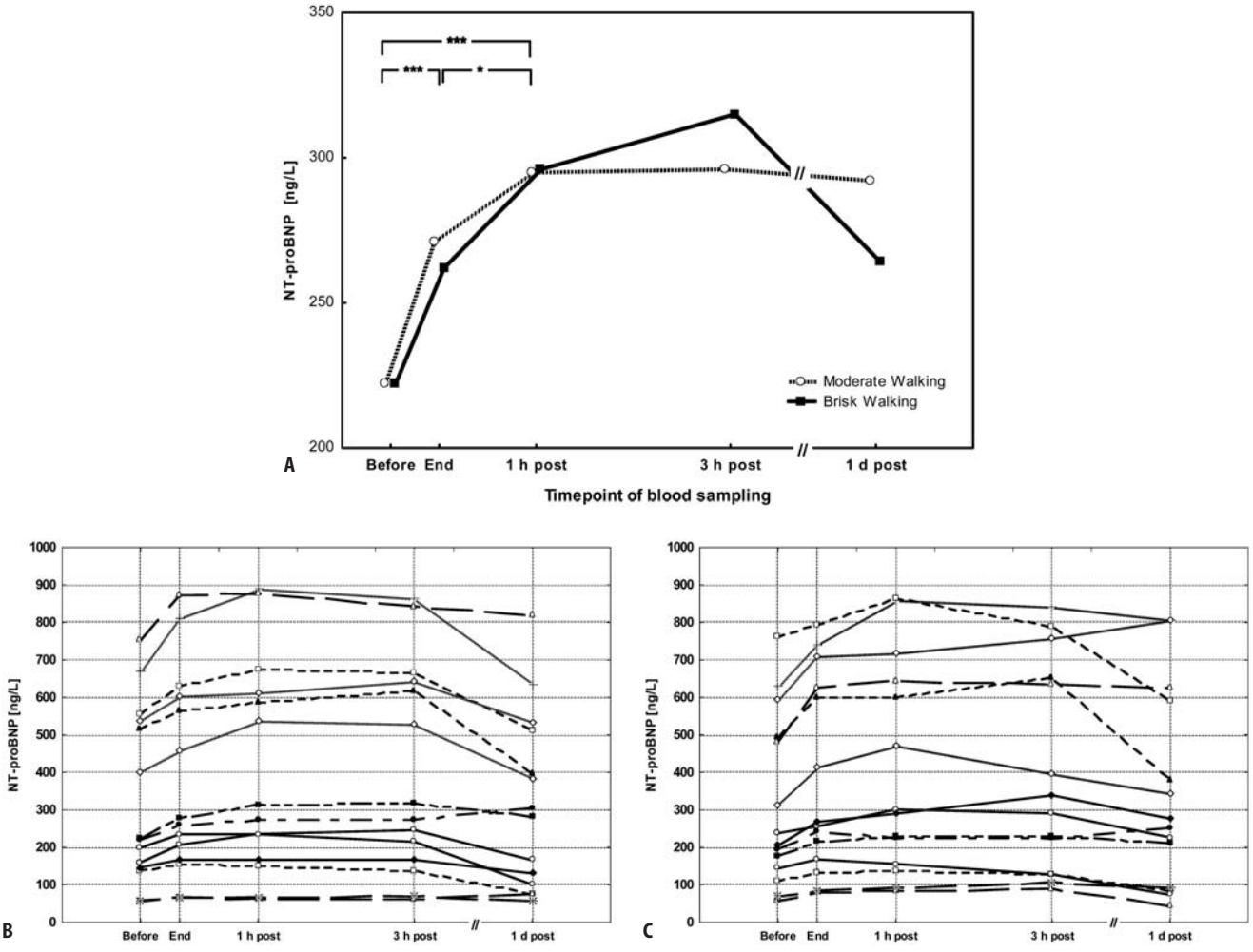

Fig. 2 Medians of NT-proBNP concentrations (**A**) and individual courses of NT-proBNP concentrations for moderate (**B**) and brisk walking (**C**) before (Before), immediately (End), 1 h and 3 h after walking (1 h post and 3 h post) and on the next morning (1 d post). ***: $p < 0.00025$; *: $p < 0.0125$

proBNP concentrations of these 6 subjects also increased immediately after exercise and remained above resting values until 3 h after exercise (before MW: 338 [56–752]; before BW: 360 ng/l [57–629 ng/l]; immediately after MW: 385 ng/l [68–872 ng/l], $p = 0.027$; immediately after BW: 428 ng/l [80–739 ng/l], $p = 0.027$; 1 h after MW: 411 ng/l [64–888 ng/l]; 1 h after BW: 450 ng/l [84–859 ng/l]; 3 h after MW: 431 ng/l [62–862 ng/l]; 3 h after BW: 463 ng/l [90–841 ng/l]). One day after exercise, NT-proBNP concentrations did not differ significantly from pre-exercise values (MW: 281 ng/l [74–818 ng/l]; BW: 304 ng/l [44–806 ng/l]). The coefficient of correlation between the exercise-induced increases in NT-proBNP and BNP immediately after exercise was $r = 0.62$ ($p < 0.03$).

cTnT, CK, CK-MB

Before and at all time points after exercise, cTnT was below the detection limit of 0.01 µg/l in all patients. Concentrations of CK and CK-MB only demonstrated a significant effect over time ($p < 0.001$) without significant differences between moderate walking and brisk walking. CK concentrations for moderate and brisk walking were: Before 103 ± 28 (MW) and 110 ± 46 U/l (BW); End: 118 ± 36 (MW) and 133 ± 57 U/l (BW); 1 h post: 122 ± 38 (MW) and 137 ± 58 U/l (BW); 3 h post: 124 ± 40 (MW) and 149 ± 65 U/l (BW); 1 day post: 146 ± 83 (MW) and 165 ± 68 U/l (BW). CK-MB concentrations for moderate and brisk walking were: Before 9.8 ± 2.8 (MW) and 9.8 ± 2.5 U/l (BW); End: 10.1 ± 2.3 (MW) and 10.2 ± 3.4 U/l (BW); 1 h post: 10.2 ± 2.5 (MW) and 10.3 ± 2.9 U/l (BW); 3 h post: 10.0 ± 2.7 (MW) and 10.7 ± 3.7 U/l (BW); 1 day post: 10.2 ± 2.5 (MW) and 11.4 ± 3.3 U/l (BW).

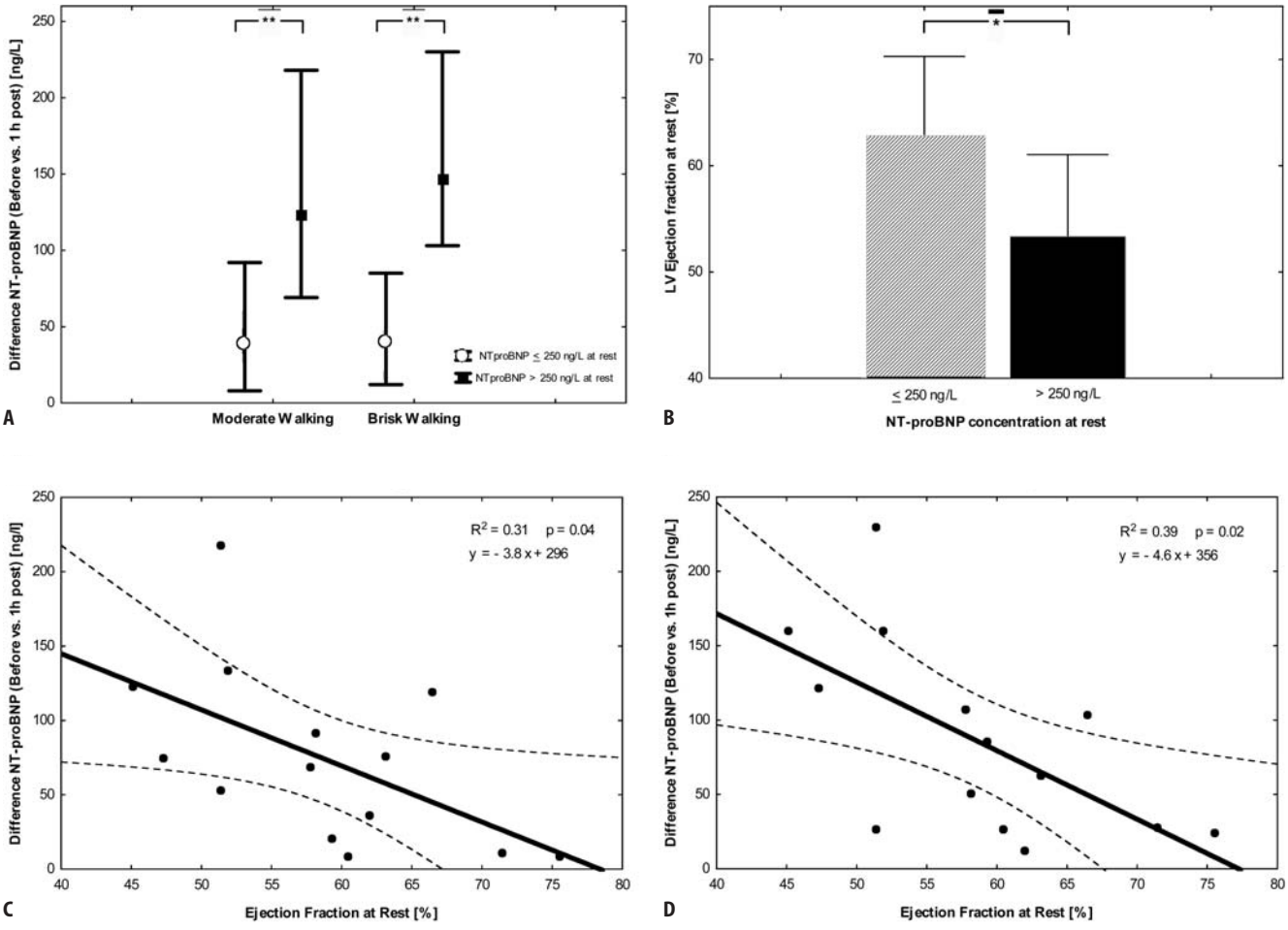

Fig. 3 **A** Increases in NT-proBNP in patients with resting NT-proBNP concentrations below and above 250 ng/l. **B** Echocardiographic LV ejection fraction at rest in patients with resting NTproBNP concentrations below and above 250 ng/l. **C** Correlation between the echocardiographic LV ejection fraction at rest and the increase in NT-proBNP after moderate walking. **D** Correlation between the echocardiographic LV ejection fraction at rest and the increase in NT-proBNP after brisk walking. **: $p < 0.01$; *: $p < 0.05$

Echocardiography

Echocardiographic LV systolic function before and 1 h after exercise remained without significant differences. LV ejection fractions were 60 ± 10% before and 55 ± 11% 1 h after moderate walking, and 58 ± 11% before and 62 ± 11% 1 h after brisk walking. LV diastolic function derived by transmitral flow velocities did not differ either: *E* peak flow velocities were 58 ± 13 cm/s before and 56 ± 10 cm/s 1 h after moderate walking, and 61 ± 15 cm/s before and 55 ± 15 cm/s 1 h after brisk walking. *A* peak flow velocities before and 1 h after exercise were 65 ± 18 cm/s and 68 ± 12 cm/s, respectively, for moderate walking, and 66 ± 12 and 64 ± 12 cm/s, respectively, for brisk walking. The E/A ratios before and 1 h after exercise were 0.95 ± 0.33 before and 0.86 ± 0.28 1 h after moderate walking, and 0.95 ± 0.29 before and 0.88 ± 0.31 1 h after brisk walking. During echocardiography, heart rates were 62 ± 10/min before and 60 ± 10/min 1 h after moderate walking, and 61 ± 15/min before and 61 ± 12/min 1 h after brisk walking.

Both after moderate and after brisk walking, a significant correlation was found between the exercise-induced increase in NT-proBNP and LV ejection fraction at rest (Figs. 3C and 3D), and regression lines did not differ between moderate and brisk walking ($t = 0.09$).

Creatinine

The mean creatinine concentration of the studied subjects was 1.10 ± 0.12 mg/dl and ranged from 0.89 to 1.26 mg/dl. Only two subjects had concentrations above the URL (1.21 and 1.26 mg/dl). No relationship between exercise induced increases in NT-proBNP and creatinine concentrations was found.

Discussion

In contrast to our hypothesis, not only brisk walking but also moderate walking induced increases in NT-proBNP. Furthermore, the increases were similar and did not reflect exercise-induced myocardial damage nor sustained exercise-induced cardiac dysfunction. Nevertheless, left ventricular systolic function at rest was related to the exercise-induced increase in NT-proBNP.

First of all, by the present results exercise-induced increases in NT-proBNP even after moderate daily activities have to be considered, when NT-proBNP is determined in cardiac patients. Therefore, NT-proBNP should be quantified under standardized conditions, excluding that patients have performed relevant physical or sportive activities before blood sampling (e.g. walking, shopping, stair climbing). Otherwise differences in NT-proBNP concentrations might be misinterpreted. This may even be more pronounced in patients with more severe coronary artery disease or congestive heart failure, in whom usual daily activities at home may also result in minor increases in NT-proBNP and BNP [3]. Although the half-life of BNP is shorter than the half-life of NT-proBNP (~20 min vs 60–120 min) [6, 14], elevated BNP concentrations can also be present immediately after moderate or brisk walking, and thus, also lead to misinterpretations – even if pre-exercise concentrations may be reached earlier than in NT-proBNP. If therefore NT-proBNP may have an advantage in the detection of patients with mild or asymptomatic heart disease after exercise as assumed previously by Yeo and colleagues for resting conditions [36] has to be studied in the future.

In the present study, the individual NT-proBNP concentrations did not correlate with maximal power output or VO_2max which is in contrast to a cross sectional study [12], but in accordance with a longitudinal training study with heart failure patients [16]. As most of the patients received β-blockers and ACE antagonists, it can be speculated that the missing difference in the exercise-induced increase in NT-proBNP between brisk and moderate walking may be a result of the β-blockade or ACE inhibition. Until now, the clinical importance of exercise-induced increases in NT-proBNP or BNP, which also have been reported in healthy recreational and professional athletes [10, 19, 20, 22, 33], is still unclear. In healthy endurance athletes, we previously postulated that BNP acts as a cytoprotective and growth regulating hormone in myocardial adaptation on exercise [22, 24], and its exercise-induced increase is without pathological significance [22, 25, 32]. On the other hand, in cardiac patients it has recently been shown that the diagnostic sensitivity for coronary heart disease can be increased by the determination of BNP or NT-proBNP after exercise ergometry [5, 34, 35, 37]. Therefore, different underlying reasons for the release of NT-proBNP or BNP have to be assumed in healthy athletes and CAD patients, but further studies are needed to examine this assumption.

In this study, the exercise-induced increase in NT-proBNP was negatively related to systolic cardiac function. The more the left ventricular systolic function at rest was reduced, the more pronounced was the exercise-induced increase in NT-proBNP. Furthermore, it was possible to distinguish CAD patients with minor from those with major exercise-induced increases in NT-proBNP and reduced LV systolic function by a resting NT-proBNP cut off level of 250 ng/l. This cut off level is close to the optimized cut off level of 214 ng/l suggested by Weber et al. [34] to predict exercise inducible ischemia and the extent of coronary artery disease. Because no relation between the number of diseased vessels and the exercise-induced increase in NT-proBNP could be demonstrated in the present study, the increase may more reflect a subclinical exercise-inducible ischemia in our group of patients. Therefore, in our patients with a pronounced exercise-induced increase in NT-proBNP, a higher myocardial stress may have been present due to elevated ischemia associated wall motion abnormalities during exercise [5]. If patients with a more depressed ejection fraction, diabetics with heart failure and sever endothelial dysfunction [17] or younger athletes, who are excluded from competitive sports due to cardiovascular diseases [23] would have presented a difference in the exercise-induced increases in NT-proBNP between moderate and brisk walking remains speculative, but may be studied in the future.

Neither moderate nor brisk walking induced myocardial damage as shown by the negative troponin T results or a sustained depression in cardiac systolic or diastolic function. Furthermore, no symptoms of ischemia were reported and the rates of perceived exertion did not differ between patients with minor and major exercise-induced increases in NT-proBNP. In consequence, moderate and brisk walking can be regarded as safe when the allowed upper exercise heart rate is not exceeded, which can be determined from the exercise ECG and the individual anaerobic threshold either by cycle or treadmill ergometry [26, 29]. Thus moderate *and* brisk walking prescribed on an individual basis (which could become possible for many patients by an integrated health care system [27]) can be recommended to patients with coronary artery disease for rehabilitative cardiocirculatory training further on. However, because cardiocirculatory training effects have been shown to be superior

for higher walking intensities in CAD patients [21], brisk walking prescribed on an individual basis should be preferred in rehabilitative cardiocirculatory training.

Limitations

Because we did not determine NT-proBNP (and BNP) concentrations on a control-day without exercise, minor individual variations of NT-proBNP (and BNP) over the day can not be excluded, although NT-proBNP and BNP do not underlie a circadian rhythm of release [28]. Furthermore, the surprising result of the similar increase in NTproBNP after brisk and moderate walking can not be explained by the present data, as we did not measure LV pressures during walking. Although it has to be assumed by the present results of NTproBNP levels that LV pressures during brisk and moderate walking are similar or at least without relevant differences, invasive measurements of LV pressures during walking would be needed to prove this assumption.

Conclusion

In conclusion, moderate and brisk walking induce similar increases in NT-proBNP (and BNP) in CAD patients, which have to be considered when NT-proBNP (or BNP) is measured in cardiac patients. Furthermore, it has to be considered that the increases induced by walking are not caused from myocardial damage. Therefore, moderate *and* brisk walking can be regarded as adequate rehabilitative measures in CAD patients with low cardiovascular risks. But if possible, brisk walking prescribed on an individual basis should be preferred, as the myocardial strain derived by the exercise-induced increase in NT-proBNP was not higher than in moderate walking in the present study, but results in higher cardiocirculatory and metabolic responses.

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