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1 **Changes in BNP and cardiac troponin I after high-**
2 **intensity interval and endurance exercise in heart failure**
3 **patients and healthy controls**

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16
17 **Short title:** Exercise-induced biomarker release in HF patients

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30 **To the Editor:**

31 Exercise training represents a cornerstone of contemporary cardiac rehabilitation. Recently, high-
32 intensity interval training (HIT) has been popularized for heart failure (HF) patients (1) and may serve
33 as a superior mode of exercise compared to traditional endurance exercise training. However, there is
34 controversy regarding the safety (2) and the direct effects of HIT on the heart. Previous studies have
35 demonstrated that an acute bout of exercise leads to an increase in cardiac troponin (cTn), a biomarker
36 for cardiac injury, and B-type natriuretic peptide (BNP), a marker for cardiomyocyte stress (3,4).
37 Exercise-induced elevation in these biomarkers is related to exercise intensity and duration (4,5), and
38 may occur to a larger extent in patients with cardiovascular risk factors (6). To date, no previous
39 study: 1. compared changes in cTn and BNP between endurance exercise and HIT, and 2. explored
40 differences in exercise-induced changes in cTn and BNP between HF patients and controls.

41

42 We included 13 pharmacologically and clinically stable HF patients NYHA-class I-III (67 ± 7 yrs;
43 male:female 12:1) with impaired left ventricular ejection fraction ($35\pm 8\%$) and 14 healthy controls
44 (60 ± 6 yrs; male:female 11:3, Table 1). The study procedures conformed to the Declaration of Helsinki
45 and were approved by the local ethics committee. All subjects provided written informed consent. A
46 maximal incremental cycling test was performed on a cycle ergometer (Lode Excalibur
47 v1.52/Ergoline, Ergoselect 200k) to determine peak oxygen uptake (VO_{2peak}). As expected, we found
48 that VO_{2peak} was markedly lower in HF patients than in healthy controls (18.7 ± 4.3 versus 37.2 ± 10.8
49 $mLO_2/kg/min$, $P<0.001$). On visit 2 and 3, subjects performed an isocaloric endurance exercise bout
50 (30-minutes at $65\% VO_{2peak}$) and HIT (10*1-minute at $90\% VO_{2peak}$, alternated by 2.5-minutes at
51 $40\% VO_{2peak}$) in randomized order. Both exercise bouts included comparable warm-up (10-minutes at
52 $40\% VO_{2peak}$) and cool-down (5-minutes at $30\% VO_{2peak}$). Exercise intensity was verified using a heart
53 rate monitor (Polar Electro Oy, RS800, Kempele, Finland). To assess cTnI- and BNP-levels, venous
54 blood samples were obtained at baseline (BASE), post-exercise (POST) and 2-hours post-exercise
55 (2H-POST), and analyzed using high-sensitive cTnI-assays (ADVIA Centaur, Siemens, detection
56 limit: 6 ng/L, upper reference limit: 40 ng/L) and BNP-assays (ADVIA Centaur, Siemens, detection
57 limit: 2 pg/mL, upper reference limit: 100 pg/mL). Changes in cTnI- and BNP-levels after exercise

58 (Δ cTnI, Δ BNP) were analyzed using 3-way Linear Mixed Model analysis, including ‘time’ (Δ BASE-
59 POST, Δ BASE-2H-POST), ‘group’ (HF, controls), and ‘exercise-mode’ (HIT, endurance). cTnI data
60 of the HIT session of one HF patient were classified as statistical outliers (value>2*SD) and hence
61 excluded from analysis.

62

63 We found that baseline cTnI- and BNP-levels were higher in HF patients compared to controls (cTnI:
64 39±133 *versus* 4±10 ng/L, BNP: 80±86 *versus* 8±7 pg/mL, both $P<0.001$), a characteristic observation
65 when examining HF patients and their healthy peers. Interestingly, exercise-induced Δ cTnI was
66 comparable between both exercise bouts, but also did not differ between groups (Figure 1A). Exercise-
67 induced Δ BNP was significantly larger in HF patients compared to controls. Nonetheless, we found no
68 differences in Δ BNP-levels between both exercise-modes (Figure 1B).

69

70 This pilot work indicates that exercise-induced changes in cTnI and BNP were similar between
71 endurance exercise (performed according to current cardiac rehabilitation guidelines (7)) and a single
72 bout of HIT. Although a higher exercise-intensity is associated with a larger cTn-release (4,5), HIT did
73 not induce a larger release in cTnI compared to endurance exercise. We speculate that, despite being
74 performed at high-intensity, the short duration of high-intensity bouts prevents excessive cardiac load
75 (8) and, therefore, does not induce significant biomarker release. Although our observations do not
76 provide information on safety, our data demonstrates that HIT does not cause larger release of
77 biomarkers related to cardiac injury compared to endurance exercise.

78

79 Previous work suggested that cardiovascular risk and/or disease is associated with a larger cTnI-
80 release after exercise (6). In contrast, we found similar changes in cTnI in both groups, whilst HF
81 patients show larger BNP increases than controls. Since BNP is related to cardiomyocyte stress, this
82 finding suggests a higher cardiac load during exercise in HF patients compared to controls. Future
83 studies with hemodynamic monitoring are recommended to confirm these observations. Combined,
84 these data suggest that, despite larger myocardial stress in HF patients, endurance exercise nor HIT
85 lead to excessive release of cardiac biomarkers indicative of acute cardiac damage.

86

87 The authors of this manuscript have certified that they comply with the Principles of Ethical
88 Publishing in the International Journal of Cardiology (9).

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122

123 **Table 1.** Baseline characteristics of HF patients and healthy controls.

Parameter	Heart failure	Controls	P-value
Age (yrs)	67±7	60±6	0.014
Sex (male:female)	12:1	11:3	0.315
BMI (kg/m ²)	28.5±6.5	24.7±4.6	0.088
LVEF	35±8	N.A.	N.A.
Etiology (ischemic:non-ischemic)	7:6	N.A.	N.A.
NYHA class (I:II:III)	1:10:2	N.A.	N.A.
Systolic blood pressure (mmHg)	130±17	130±14	0.988
Diastolic blood pressure (mmHg)	79±9	85±10	0.168
Resting heart rate (/min)	59±8	60±10	0.792
Peak heart rate (/min)	129±16	165±17	<0.001
Peak oxygen uptake (mlO ₂ /kg/min)	18.7±4.3	37.2±10.8	<0.001
cTnI level (ng/L) ¹	39±133	4±10	<0.001
BNP level (pg/mL) ¹	80±86	8±7	<0.001

124 Data is presented as mean ± SD. P-value refers to an unpaired Student's *t*-test for continuous
125 variables and the Chi-Square test for sex. ¹P-value refers to a Mann-Whitney U test. BMI;
126 body mass index. LVEF; left ventricular ejection fraction. N.A.; not available. cTnI; cardiac
127 troponin I. BNP; brain natriuretic peptide.

128

129 **Figure 1**

130 Changes in cTnI (A) and BNP levels (B) immediately after (POST) and two hours after (2H-POST)

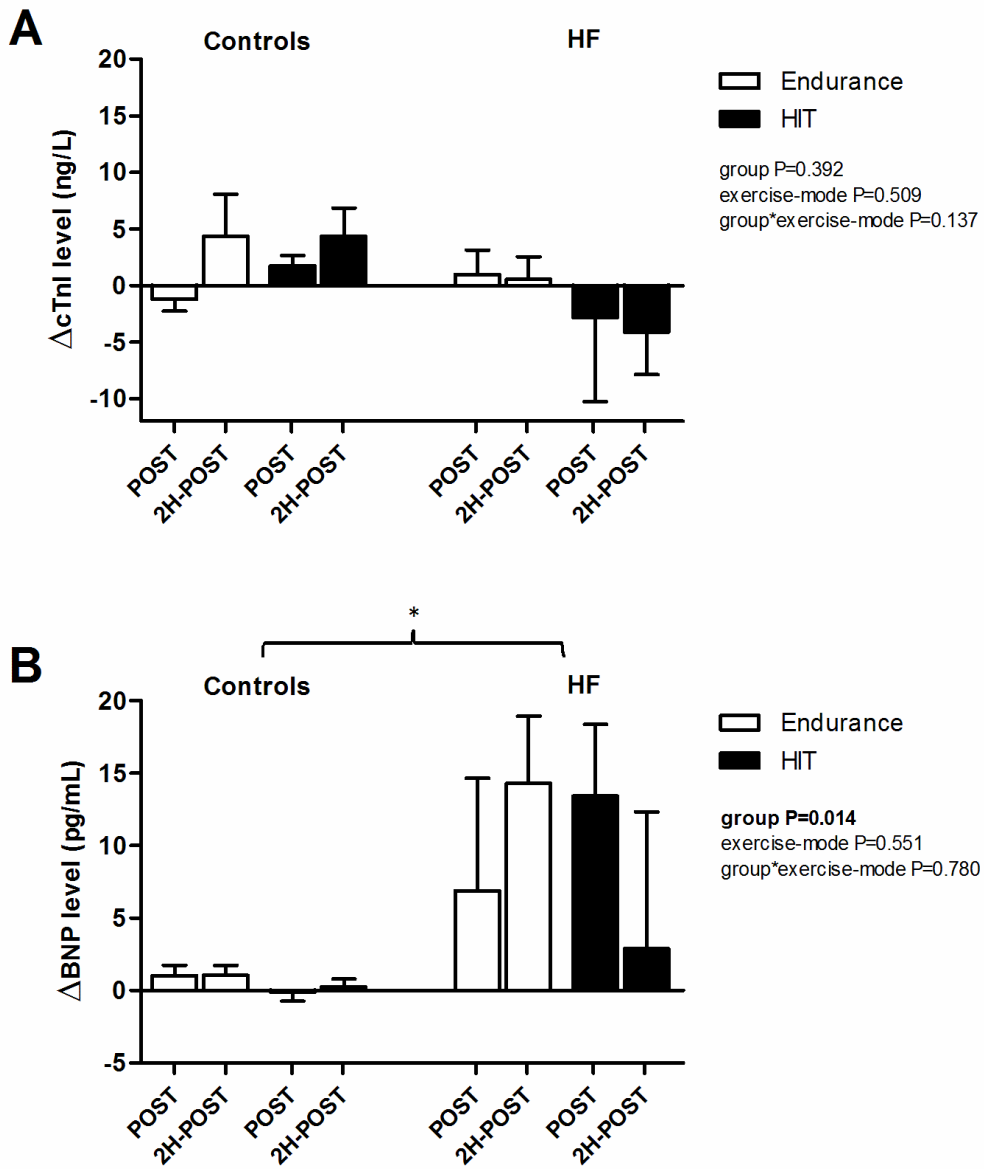
131 exercise compared to baseline. HIT; high-intensity interval training. Error bars represent SE. *group-

132 effect $P < 0.05$.

133

134

135 **Figure 1**



136