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

NATHALIE M.M. BENDA MD MSc[1]

THIJS M.H. EIJSVOGELS PhD[1,4]

ARIE P.J. VAN DIJK MD PhD[2]

MARIA T.E. HOPMAN MD PhD[1]

DICK H.J. THIJSSEN PhD[1,3]

Departments of [1]Physiology and [2]Cardiology Radboud university medical center, Radboud Institute for Health Sciences, Nijmegen, the Netherlands

[3]*Research Institute for Sport and Exercise Sciences,* Liverpool John Moores University, Liverpool, United Kingdom

[4]*Division of Cardiology,* Hartford Hospital, Hartford, CT, USA

Short title: Exercise-induced biomarker release in HF patients

WORD COUNT: 716

FIGURES: 1

TABLES: 1

Author for correspondence: Dr. Dick HJ Thijssen, Department of Physiology, Radboud university medical center, Radboud Institute for Health Sciences, Philips van Leydenlaan 15,

24   6525 EX, Nijmegen, the Netherlands. Email: dick.thijssen@radboudumc.nl, Tel:

25   +31243614222

26

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 extend 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 ($35\pm8\%$) 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   (ΔcTnI, ΔBNP) were analyzed using 3-way Linear Mixed Model analysis, including 'time' (ΔBASE-

59   POST, ΔBASE-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 ΔcTnI was

66   comparable between both exercise bouts, but also did not differ between groups (Figure 1A). Exercise-

67   induced ΔBNP was significantly larger in HF patients compared to controls. Nonetheless, we found no

68   differences in ΔBNP-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).

89

90

91 **References**

92 1. Ismail H, McFarlane JR, Nojoumian AH, Dieberg G, Smart NA. Clinical outcomes and

93   cardiovascular responses to different exercise training intensities in patients with heart failure:

94   a systematic review and meta-analysis. JACC Heart failure 2013;1:514-22.

95 2. Keteyian SJ. Swing and a miss or inside-the-park home run: which fate awaits high-intensity

96   exercise training? Circulation 2012;126:1431-3.

97 3. Shave R, Baggish A, George K et al. Exercise-induced cardiac troponin elevation: evidence,

98   mechanisms, and implications. Journal of the American College of Cardiology 2010;56:169-

99   76.

100 4. Serrano-Ostariz E, Terreros-Blanco JL, Legaz-Arrese A et al. The impact of exercise duration

101   and intensity on the release of cardiac biomarkers. Scandinavian journal of medicine &

102   science in sports 2011;21:244-9.

103 5. Eijsvogels TM, Hoogerwerf MD, Oudegeest-Sander MH, Hopman MT, Thijssen DH. The

104   impact of exercise intensity on cardiac troponin I release. International journal of cardiology

105   2014;171:e3-4.

106 6. Eijsvogels T, George K, Shave R et al. Effect of prolonged walking on cardiac troponin levels.

107   The American journal of cardiology 2010;105:267-72.

108 7. Piepoli MF, Corra U, Benzer W et al. Secondary prevention through cardiac rehabilitation:

109   from knowledge to implementation. A position paper from the Cardiac Rehabilitation Section

110   of the European Association of Cardiovascular Prevention and Rehabilitation. European

111   journal of cardiovascular prevention and rehabilitation : official journal of the European

112   Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac

113   Rehabilitation and Exercise Physiology 2010;17:1-17.

114   8.   Meyer K, Samek L, Schwaibold M et al. Physical responses to different modes of interval

115   exercise in patients with chronic heart failure--application to exercise training. European heart

116   journal 1996;17:1040-7.

117   9.   Shewan LG, Coats AJ. Adherence to ethical standards in publishing scientific articles: a

118   statement from the International Journal of Cardiology. International journal of cardiology

119   2012;161:124-5.

120

121

122

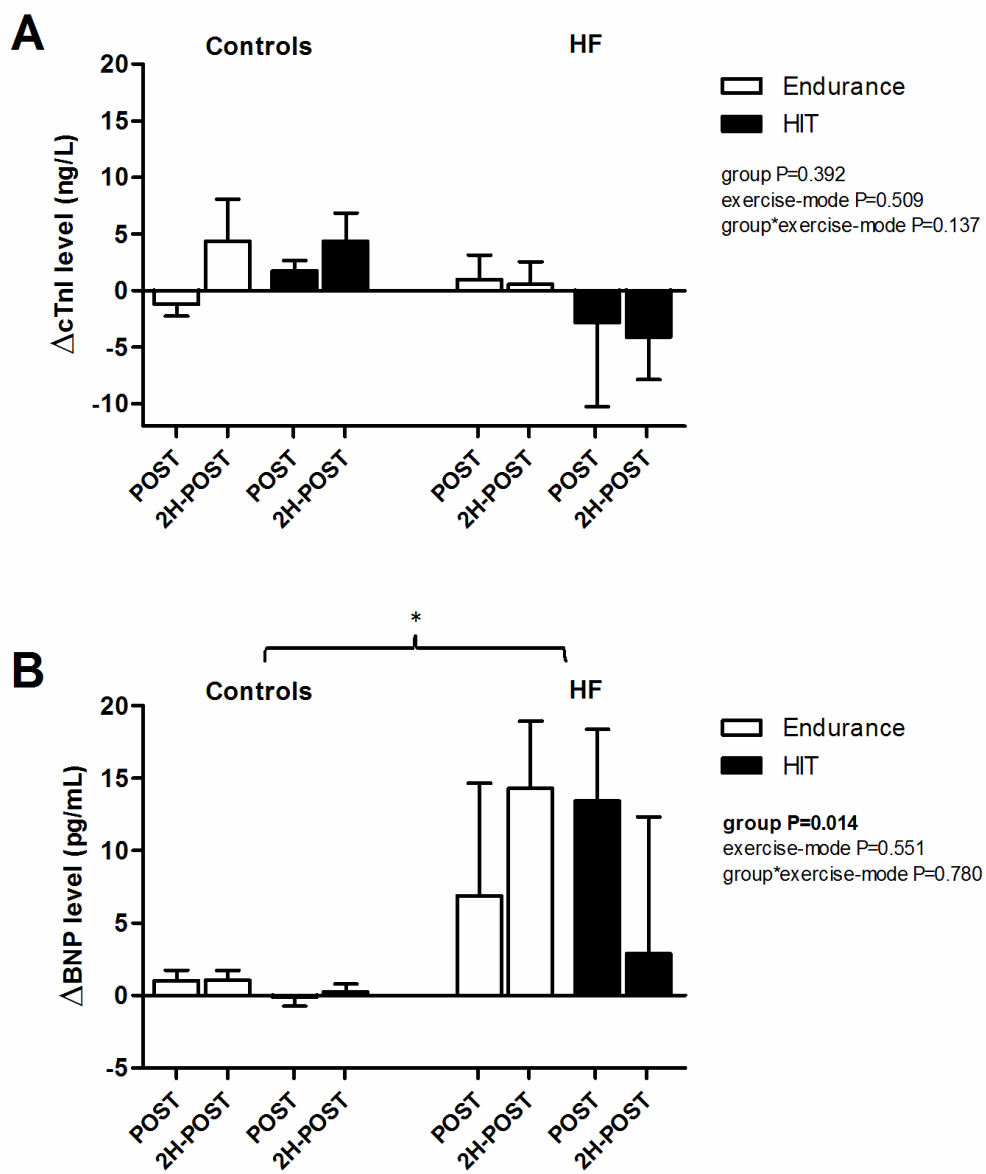123   **Table 1.** Baseline characteristics of HF patients and healthy controls.

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. [1]P-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**