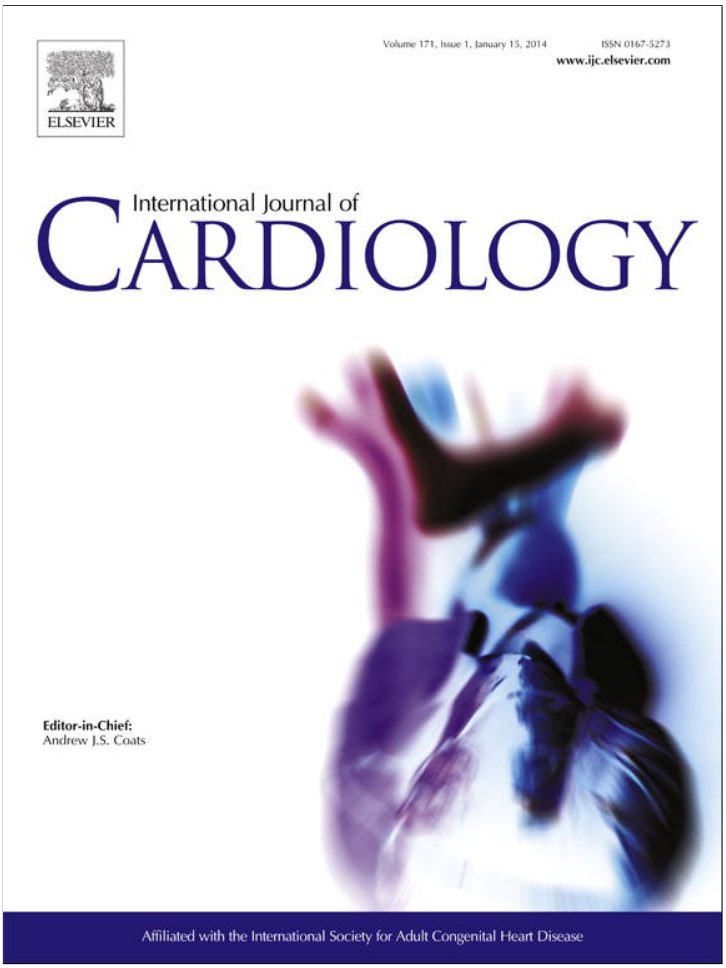

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Letter to the Editor

The impact of exercise intensity on cardiac troponin I release

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The intracellular enzyme cardiac troponin I (cTnI) has been shown to increase after prolonged endurance exercise, while athletes do not demonstrate clinical signs of cardiac damage or an acute myocardial infarction [1]. To obtain information for the clinical interpretation of cTnI tests in athletes, several studies identified predictors of post-exercise cTnI levels. Based on a review of the literature, Shave and colleagues proposed that exercise intensity and exercise duration primarily influence post-exercise cTnI levels [1]. Also, others suggested that a threshold in exercise intensity may be needed for substantial cTnI release [2]. An important limitation of this previous work was the small variation in exercise intensity between subjects due to inclusion of a single exercise modus. Therefore, we compared the exercise-induced cTnI levels between marathon runners and walkers that covered a similar distance. We hypothesized that the magnitude of cTnI responses were importantly related to the level of exercise intensity.

Sample size calculations (SPSS SamplePower v3, IBM, USA) revealed that 23 subjects per group were necessary to detect differences between runners and walkers (power 80%, $\alpha = 0.05$, correction for 5% drop-outs). Twelve men and eleven women participated in the Eindhoven Marathon (42.2 km), while a group of 23 sex-, age- and BMI-matched subjects participated in the Nijmegen Marches (40.6 km). A venous blood sample was taken for cTnI analysis (Centaur TnI-Ultra, Siemens, Breda, the Netherlands) at baseline and within 15 min post-exercise. Assay imprecision was 5.3% at 0.08 μg/L and 3.0% at 27.2 μg/L. A cTnI-value of 0.04 μg/L is the clinical cut-off value for myocardial infarction. Heart rate was measured continuously during exercise using a 2-channel ECG chest band system (Polar, Kempele, Finland). Exercise intensity was calculated by dividing the mean heart rate during exercise by the maximal predicted heart rate according to the formula of Tanaka ($208 - 0.7 * age$) [3]. Before participation oral and written information was given, after which all participants provided written informed consent. The Medical Ethical Committee of the Radboud University Nijmegen Medical Centre approved the study which was conducted in line with the Declaration of Helsinki. All cTnI values were log-transformed for statistical analysis. Changes over time were assessed using repeated measures ANOVA. A chi-square test was used to compare the number of subjects above the clinical threshold between runners and walkers. Data was reported as the relative risk score (RR) with 95% confidence intervals (CI). The relation between cTnI release and exercise intensity was determined using linear regression modeling.

Subject characteristics were comparable between runners (47 ± 12 year, 24.0 ± 2.2 kg/m^2) and walkers (50 ± 14 year, 24.3 ± 2.6 kg/m^2). Both, runners (6 ± 2 h/week) and walkers (4 ± 2 h/week) trained prior to the study on a regular basis ($p = 0.039$). Baseline cTnI levels did not differ ($p = 0.46$) in runners (0.017 ± 0.014 μg/L) and walkers (0.015 ± 0.015 μg/L). All runners (245 ± 29 min) and walkers (512 ± 52 min) successfully completed the exercise bout without clinical signs or symptoms of an acute coronary syndrome. Exercise intensity varied between 54 and 99% of the maximum predicted heart rate in the total cohort, but higher values were obtained in runners compared with walkers ($92 \pm 5\%$ *versus* $70 \pm 9\%$, $p < 0.001$). The exercise-induced increase in cTnI was significantly higher in runners compared to walkers (Fig. 1a). Also, runners demonstrated a higher incidence of cTnI levels above the clinical cut-off value compared to walkers (83 *versus* 17%, RR = 4.7, CI = 1.9–11.8). Exercise intensity demonstrated a strong and positive linear relationship with cTnI levels ($R = 0.752$, $p < 0.001$, Fig. 1b), which was unaffected when the variable 'training hours' ($p = 0.203$) was added to the regression model. Also sex did not impact the magnitude of exercise-induced cTnI elevations (2-way RM-ANOVA exercise * sex: $p = 0.37$), while men ($R = 0.77$, $p < 0.001$) and women ($R = 0.75$,

Abbreviations: ANOVA, analysis of variance; BMI, body mass index; CI, confidence interval; cTnI, cardiac troponin I; ECG, electrocardiogram; RR, risk ratio.

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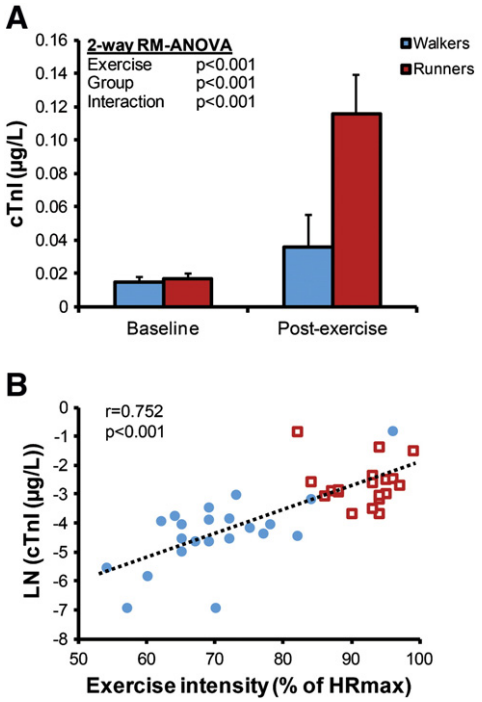

Fig. 1. A) Baseline and post-exercise levels of cardiac troponin I in walkers (blue bars) and runners (red bars). Baseline levels were comparable between groups. Exercise induced a significant increase in cardiac troponin I levels ($p < 0.001$), with larger elevations in runners compared with walkers ($p < 0.001$). Data are presented as mean ± SEM. B) Exercise intensity and post-exercise cardiac troponin I levels were strongly related ($R = 0.752$, $p < 0.001$). Data was LN-transformed to achieve a Gaussian distribution and perform statistics. Walkers are indicated by blue circles and marathon runners by red squares.

$p < 0.001$) demonstrated a comparable correlation between cTnI and exercise intensity.

This study demonstrates a strong relationship between exercise intensity and exercise-induced cTnI release over a large spectrum of observations. Our findings were reinforced by the higher post-exercise cTnI levels ($p < 0.001$) and larger number of subjects that exceeded the clinical cut-off value (83% *versus* 17%) for a myocardial infarction in runners compared to walkers. Also, there is no evidence for a specific exercise intensity threshold that is necessary to elevate post-exercise cTnI levels as runners and walkers both demonstrated a significant increase [2]. Lower exercise intensities simply result in a smaller cTnI-release. In parallel, it was previously shown that there is a modest positive relationship ($r = 0.35$) between running distance and cTnI levels [4]. This implies that a higher cardiac load results in a larger cTnI release, which is predominantly dependent upon exercise intensity.

The underlying mechanism of exercise-induced cardiac troponin release is currently unknown, but several pathways have been proposed [5]. Given the strong relation between exercise intensity and the magnitude of cTnI release, and the fact that cTnI levels also rise at low-to-moderate exercise-intensities, it is unlikely that the elevated cTnI levels reflect irreversible damage, like myocyte necrosis or apoptosis. Instead, the elevated levels of cTnI are more likely to result from 1) increased myocyte turnover, 2) increased cellular release of proteolytic troponin degradation products, 3) increased cellular wall permeability, and/or 4) formation and release of membranous blebs.

Previous studies suggested a potential impact of older age, little running experience, and the presence of cardiovascular disease to relate to higher post-exercise cTnI levels [6–9]. In our study, we found that 56% of the exercise-induced cTnI levels can be explained by exercise intensity. Potential interactions between previously identified factors (like age, fitness level and cardiovascular health) and exercise intensity may have contributed to these findings. Based on the importance of exercise intensity to mediate cTnI-release after exercise, future studies should correct for exercise intensity when examining factors contributing to an increased exercise-induced troponin release.

In conclusion, we have demonstrated that exercise consistently causes an increase in cTnI over a large range of exercise intensities. Moreover, the magnitude of cTnI release is strongly related to exercise intensity, and post-exercise cTnI levels are higher in runners compared to walkers. Accordingly, clinical cut-off levels are more frequently exceeded at high-intensity exercise. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

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