Effect of Prolonged Walking on Cardiac Troponin Levels

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Increased cardiac troponin I (cTnI), a marker for cardiac damage, has been reported after strenuous exercise in young subjects. However, little is known about changes in cTnI after moderate-intensity exercise in a heterogenous population or which factors may contribute to this change in cTnI levels. We examined cTnI levels before and immediately after each day of a 4-day long-distance walking event (30 to 50 km/day) in a heterogenous group (67 men, 42 women), across a broad age range (21 to 82 years), with known cardiovascular pathology or risk factors present in many subjects (n = 24). Walking was performed at a self-selected pace. Cardiac TnI was assessed using a standard system (Immulite) with high values (≥0.20 μg/L) cross-checked using a high-sensitive cTnI assay (Centaur). Mean cTnI levels increased significantly from 0.04 to 0.07 μg/L on day 1, with no further increase thereafter ($p < 0.001$, analysis of variance). Backward linear regression found a weak, but significant, association of age ($p < 0.001$), walking speed ($p = 0.02$), and cardiovascular pathology ($p = 0.03$) with postexercise cTnI level (combined $r^2 = 0.11$, $p < 0.001$). In 6 participants (6%), cTnI was increased above the clinical cut-off value for myocardial infarction on ≥1 day. These participants supported the regression analysis, because they were older, walked at higher relative exercise intensity, and reported a high prevalence of cardiovascular pathology. In conclusion, prolonged, moderate-intensity exercise may result in an increase in cTnI levels in a broad spectrum of subjects, especially in older subjects with pre-existing cardiovascular disease or risk factors. **(Am J Cardiol 2010;105:267–272)**

The presence of intracellular cardiac troponin subunits T and I (cTnT and cTnI) in the blood is a sensitive and specific indicator for myocardial injury.[1,2] In recent years, increased circulating cTnT/cTnI concentrations have been reported after prolonged exercise.[2–6] The purpose of our study was to examine baseline and postexercise cTnI levels in a large, heterogenous group of participants undertaking the Nijmegen Marches (The Netherlands), an annual 4-day walking event involving ~40,000 participants. Participants walked 30, 40, or 50 km on 4 consecutive days. Specifically, we examined changes in absolute cTnI levels, identified those with an increase in cTnI above the cut-off value for acute myocardial infarction (AMI), and examined whether postexercise cTnI levels were related to age, gender, body mass index (BMI), relative exercise intensity, core temperature, walking speed, training status, or underlying cardiovascular pathology.

Methods

One hundred nine participants (21 to 82 years of age) were randomly selected 4 weeks before the event (Table 1). All participants completed a minimum distance of 30, 40, or 50 km on 4 consecutive days. The medical ethical committee of the Radboud University Nijmegen Medical Center approved the study and all participants provided written informed consent before participation. This study was conducted in line with the Declaration of Helsinki.

One day or 2 days before the start (day 0), venous blood was drawn and serum was stored for later analysis, and general demographic data were obtained. Before the start of each walking day (which varied from 4 to 7 A.M. depending on the walking distance) and at every 5-km point, heart rate and core body temperature were measured. Immediately after finishing, all measurements from day 0 were repeated.

All measurements were performed in the same laboratory located at the finish area. Measurements were performed from 11 A.M. to 5 P.M. on day 0, and directly after finishing (which varied from 12 to 5 P.M.) for subsequent walking days. The sequence of measurements was similar each day.

On day 0, body weight (Seca 888 Scale, Seca, Hamburg, Germany) and height were measured. In addition, heart rate and blood pressure at rest were measured using an automated sphygmomanometer (M5-1 Intellisense, Omron Health Care, Hoofddorp, The Netherlands) after 5 minutes of seated rest.

Core body temperature was assessed using a portable telemetry system (CorTemp system, HQ Inc., Palmetto, Florida), which has been demonstrated to be safe and reli-

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Table 1
Subject characteristics and details about the presence of (cardiovascular) pathology, presented for the entire group (n = 109) and subdivided for participants who walked 30 km (n = 35), 40 km (n = 45), or 50 km (n = 29) per day

	Overall	30 km	40 km	50 km
Characteristics				
Men/women	67/42	22/13	28/17	17/12
Smoking	20 (18%)	3 (9%)	9 (20%)	8 (28%)
Age (years)	57 ± 15	69 ± 6	54 ± 16	48 ± 15
Length (cm)	174 ± 10	171 ± 9	175 ± 10	176 ± 10
Weight (kg)	77 ± 15	73 ± 12	78 ± 15	80 ± 17
Body mass index (kg/m^2)	25.2 ± 3.3	24.9 ± 2.6	25.0 ± 3.2	25.7 ± 4.1
Systolic blood pressure (mm Hg)	138 ± 18	144 ± 19	135 ± 16	137 ± 19
Diastolic blood pressure (mm Hg)	84 ± 10	86 ± 11	83 ± 9	84 ± 11
Previous participation	94 (87%)	35 (100%)	35 (78%)	25 (86%)
Distance trained (km)	491 ± 661	541 ± 458	509 ± 866	398 ± 476
Exercise (hours/week)	3.3 ± 4.3	3.9 ± 6.0	3.3 ± 3.3	2.6 ± 3.2
≥5 times/week ≥30 minutes exercise	91 (83%)	29 (83%)	37 (82%)	25 (86%)
Cardiovascular disease	24 (22%)	15 (43%)	8 (18%)	1 (3%)
Hypertension	22 (20%)	13 (37%)	8 (18%)	1 (3%)
Hypercholesterolemia*	19 (17%)	6 (17%)	7 (16%)	6 (21%)
Myocardial infarction/cerebrovascular infarction	4 (4%)	4 (11%)	1 (2%)	0 (0%)
Diabetes mellitus type 2	2 (2%)	2 (6%)	0 (0%)	0 (0%)
Depression/asthma/rheumatoid arthritis	5 (5%)	2 (6%)	1 (2%)	2 (7%)
Medication				
Medication use	35 (32%)	17 (49%)	13 (29%)	5 (17%)
Antihypertensive drugs	20 (18%)	14 (40%)	6 (13%)	0 (0%)
Statins	14 (13%)	6 (17%)	6 (13%)	2 (7%)
Diuretics	8 (7%)	6 (17%)	2 (4%)	0 (0%)
Anti-inflammatory drugs	(9%)	0 (0%)	(15%)	(10%)

Data are presented as mean ± SD.
* Total cholesterol levels >6.5 mmol, as previously diagnosed by a physician.

able.[7,8] Participants ingested an individually calibrated telemetric temperature sensor the evening preceding day 1. Before the start of each walking day (days 1 to 4) the core temperature of each participant was measured using an external recorder. Baseline core body temperature was defined as the average of 3 consecutive measurements. Similarly, core body temperature was measured every 5 km along the route. Participants ingested a new telemetric sensor when the sensor was eliminated from the body or the transmitted signal was too weak to record. Mean core body temperature during each day was calculated as the average of all measurements, excluding the values derived before the start and after the finish. In addition, the highest value of these measurements was presented as the peak core body temperature.

Heart rate was measured with a 2-channel electrocardiographic chest band system (Polar Electro Oy, Kempele, Finland) simultaneously with core body temperature, using the same data recorder. Mean heart rate during each walking day was calculated as the average heart rate, excluding the values derived directly before the start and after the finish. Mean heart rate during exercise was presented in absolute values (beats per minute) and as a percentage of the predicted maximal heart rate (percentage from 208 to 0.7 × age).[9]

Ten milliliters of blood was drawn from an antecubital vein. After exercise on days 1 to 4, this was performed 10 to 20 minutes after the finish. Whole venous blood was collected in serum-gel Vacutainer tubes and allowed to clot for ~45 minutes. After centrifugation, serum was aliquoted, frozen, and stored at −80°C for later analysis.

Cardiac TnI was analyzed using the STAT troponin I assay for the Immulite 2500 system (Siemens Healthcare Diagnostics, Breda, The Netherlands). Total assay imprecisions were 7.8% at 2.3 μg/L and 7.9% at 29.1 μg/L. The detection level of this assay was set at 0.1 μg/L. However, quality control analysis of our data <0.1 μg/L revealed coefficients of variation of 8.1% and 14.7% at 0.08 and 0.02 μg/L, respectively, which then increased to 24.1% at 0.01 μg/L. Analysis was performed on a single day using the same calibration and setup to minimize variation. After identifying participants with a cTnI >0.2 μg/L, which is used as the clinical cut-off value for diagnosis of AMI, values were cross-checked using a highly sensitive cTnI assay (Centaur TnI-Ultra, Siemens Healthcare Diagnostics). Assay imprecisions of the highly sensitive cTnI assay were 5.3% at 0.08 μg/L and 3.0% at 27.2 μg/L, with a detection limit of 0.006 μg/L.

Another 2 ml of blood was drawn from the antecubital vein for immediate analysis from the collecting syringe for plasma levels of hematocrit (liters per liter) using a Rapidpoint 400 (Siemens Healthcare Diagnostics, Inc., Tarrytown, New York). In addition, hemoglobin (millimoles per liter) was determined using a B-hemoglobin analyzer (Hemocue AB, ängelholm, Sweden). Relative changes in plasma volume (percentage) were calculated from blood hematocrit and hemoglobin concentrations using Dill and Costill's equation.[10]

Table 2
Details about walking (average time and speed), ambient conditions (minimum and maximum temperatures), and changes in physical parameters (absolute and relative mean heart rates, mean and peak core body temperatures) for all participants (n = 109) across the four walking days

Variable	Day			
	1 (n = 106)	2 (n = 103)	3 (n = 103)	4 (n = 103)
Walking				
Time (hours:minutes)	8:37 ± 1:38	8:57 ± 1:33	8:36 ± 1:47	9:08 ± 2:09
Speed (km/hour)	4.6 ± 0.6	4.4 ± 0.6	4.6 ± 0.6	4.4 ± 0.6
Ambient conditions				
Minimum wet bulb globe temperature (°C)	13.2	14.2	12.3	12.5
Maximum wet bulb globe temperature (°C)	20.6	20.4	19.8	19.4
Physical parameters				
Heart rate during exercise (beats/min)	115 ± 18	108 ± 16	105 ± 15	104 ± 14
Heart rate during exercise (percent maximum heart rate)	72 ± 10	68 ± 9	66 ± 10	65 ± 9
Peak core body temperature (°C)	38.2 ± 0.4	38.3 ± 0.5	38.0 ± 0.5	38.1 ± 0.4
Plasma volume change compared with day 0 (%)	0.2 ± 8.7	2.1 ± 8.1	9.2 ± 10.7	10.8 ± 10.8

Data are presented as mean ± SD.

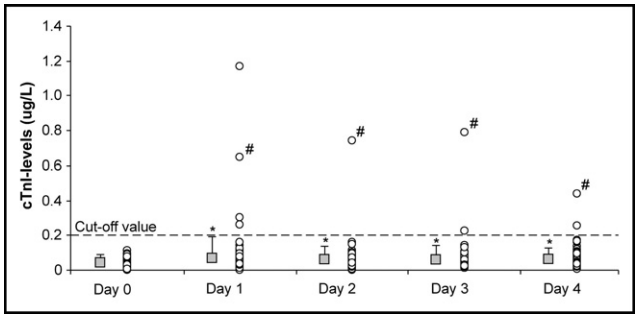

Figure 1. Average *(gray squares)* and individual *(circles)* cTnI data at baseline (day 0) and immediately after the finish on the 4 consecutive walking day (days 1 to 4) in all participants (n = 109). Repeated measures analysis of variance indicated a significant effect of exercise on cTnI levels ($p < 0.001$). *Significant (post hoc) from day 0 at $p \leq 0.05$; #same subject on days 1 to 4. SEs are shown *(error bars)*.

Dry bulb, wet bulb, and globe temperatures were measured every 30 minutes during the 4 days using a portable climate monitoring device (Davis Instruments, Inc., Hayward, California) positioned at the start/finish area. The wet bulb globe temperature index was calculated using the formula: wet bulb globe temperature index = 0.1 ($T_{dry\ bulb}$) + 0.7 ($T_{wet\ bulb}$) + 0.2 (T_{globe}), where T represents temperature.

Statistical analyses were performed using SPSS 16.0 (SPSS, Inc., Chicago, Illinois). All data are reported as mean ± SD unless stated otherwise, and statistical significance was assumed at a p value <0.05. When data demonstrated a non-Gaussian distribution, natural logarithmic transformation was applied. Repeated measures analysis of variance (with day as the independent factor) was used to assess differences across the 5 testing days for cTnI. Post hoc *t* tests with the least square difference correction for multiple comparisons were performed when the analysis of variance reported a significant main or interaction effect. Backward stepwise linear regression analysis was used to identify factors that significantly relate to postexercise cTnI levels. Age, gender, BMI, walking speed, core body temperature, distance trained, and cardiovascular pathology were examined as potential determinants of postexercise cTnI level.

Results

Due to orthopedic problems, 3 participants did not complete day 1, and 2 participants did not finish on day 2. Another participant was excluded from further participation because he exceeded the time limit on day 2. As a result, 103 participants completed the event (94.5%), which was slightly greater than the overall completion rate (89.4%).

Apart from age, baseline characteristics were not significantly different among the 3 groups that walked 30, 40, or 50 km (Table 1). Based on medical history, 22% was diagnosed a priori with cardiovascular disease, with hypertension reported most frequently (Table 1). The 30-km group, including the oldest participants, reported the highest prevalence of cardiovascular disease (Table 1). Participants with prescribed medication predominantly used antihypertensive drugs, statins, and/or diuretics (Table 1).

Exercise was performed under mild ambient conditions, which did not differ across the 4 days (Table 1). Mean walking speed and mean finish time did not differ across days (Table 2). Core body temperature and heart rate increased significantly during exercise (Table 2). When presented as the relative intensity, exercise intensity on the 4 days varied from 72% to 65% of their predicted maximal heart rate. Plasma volume did not change after day 1 or 2, but showed a significant increase on consecutive days ($p < 0.001$, analysis of variance; $p < 0.05$, post hoc analysis; Table 2).

Natural logarithmic transformation was applied to the cTnI dataset for analysis because a non-Gaussian distribution was found. A significant increase in cTnI was found from day 0 to days 1 to 4, with no significant differences across the 4 days of walking (Figure 1). To gain insight into the factors that may contribute to cTnI release, a backward linear regression analysis was performed. Regression analysis identified age (beta = 0.29, $p < 0.001$), cardiovascular pathology (beta = 0.12, $p = 0.031$), and walking speed

Table 3
Details about participants (n = 6) with a positive, clinically relevant, highly sensitive cardiac troponin I test result (99th percentile 0.20 μg/L)

Subject (day)	cTnI (μg/L)	Age (years)/Sex	BMI (kg/m^2)	Distance (km)	Fitness (sport hors/week)	Speed (km/hour)	Exercise (percent HRmax)	CBT (°C)	Pathology
1 (4)	0.25	57/F	25.9	50	5	4.0	63	—	hypertension
2 (1)	0.30	53/F	30.9	50	4	5.4	78	38.6	none
3 (3)	0.20	82/M	24.7	30	0	3.7	56	37.9	none
4 (1)	1.17	79/M	26.2	30	4	3.1	59	37.9	hypertension, COPD
5 (1)	0.26	74/M	21.5	30	1	4.7	64	37.9	atherosclerosis
6 (1)	0.65	75/F	26.9	30	2	4.1	61	38.1	hypertension
6 (2)	0.74					4.1	56	38.2	
6 (3)	0.79					4.6	57	38.2	
6 (4)	0.44					4.6	55	37.9	
Average (n = 6)		70/3 M:3 F	26.0		2.7	4.3	61	38.1	78%
Average (n = 109)		57/67 M:42 F	25.2		3.3	4.5	58	38.2	22%

CBT = core body temperature; COPD = chronic obstructive pulmonary disease; HRmax = maximum heart rate.

(beta = 0.12, p = 0.022) as significant predictors of increased postexercise cTnI levels (all parameters, $r^2 = 0.11$, $p < 0.001$), whereas gender (beta = 0.09, p = 0.073) and distance trained (beta = −0.10, p = 0.052) did not reach significance level.

Five participants showed a "positive" cTnI (above the AMI cutoff) on 1 day (day 1, n = 3; days 3 to 4, n = 1), which was confirmed using a highly sensitive cTnI assay (Table 3). One subject showed a positive cTnI on all 4 walking days (Figure 1). Analysis of these participants revealed that gender distribution, BMI, medication use, core body temperature, and walking speed were comparable to the entire population (Table 3). However, age, relative exercise intensity, and presence of cardiovascular disease of this subgroup was higher than reported for the entire group.

Discussion

Our results indicate that ~9 hours of moderate-intensity walking exercise significantly increases cTnI levels in asymptomatic, nonathletic populations diverse in age and physical activity level, without a cumulative effect over 4 consecutive days. Moreover, when using the cTnI cut-off level for diagnosis of AMI,[1] 6% of our participants reported a positive test on ≥1 day, without reporting clinical symptoms or signs of AMI. Most importantly, we found that advanced age, walking speed, and presence of cardiovascular disease place subjects at greater risk for an increase in cTnI levels after prolonged walking. Nonetheless, only a small portion of the cTnI increase can be explained by these factors.

The increase in cTnI after each day of exercise is consistent with recent reports that exercise can increase cTnI in asymptomatic humans.[11–14] However, our findings are novel in several ways. First, our participants performed moderate-intensity walking exercise in a temperate climate, whereas previous studies typically examined subjects after strenuous, high-intensity exercise such as marathon running or triathlon,[11–14] often performed under challenging conditions.[15,16] Despite these differences, our cTnI increase was comparable to a large cohort of runners (n = 482) at the 2002 Boston Marathon.[17] Second, the exercise-induced increase in cTnI levels was comparable across the 4 subsequent walking days, without a time-dependent change in the number of positive test results. These findings indicate no cumulative effect in cTnI release, or short-term adaptations in cTnI release, when exposed to the same exercise volume on 4 consecutive days. A recent study also reported no consistent change in cTnI levels on 22 days of repetitive cycling exercise in 10 healthy men.[18] The moderate magnitude and short-term duration of postexercise cTnI increase,[19] but also rapid release and clearance, may contribute to this finding.

We also examined factors that might have contributed to cTnI release and found walking speed to relate to postexercise cTnI levels, which reinforces recent observations after short-[20] or long-duration exercise.[21] In addition, we identified, for the first time, that advanced age and cardiovascular pathology relate, at least partly, to higher postexercise cTnI levels. Even after excluding the 6 subjects with a positive AMI cTnI test result in the analysis, similar results were observed. Although advanced age, walking speed, and presence of cardiovascular pathology were related to postexercise cTnI levels, only 11% of the increase in cTnI can be explained. This indicates that exercise-induced cTnI release is likely dependent on various, potentially interacting factors and as such is extremely difficult to predict.

Analysis of cTnI is recommended as a sensitive and specific marker for cardiac damage in the diagnosis of AMI.[1,2,22] Although cTnI levels were higher after exercise, the average increase was modest (~0.03 μg/L) and did not exceed the cut-off value for AMI in most subjects. Changes in cTnI may be related to exercise-induced decreases in plasma volume. However, no change in plasma volume was found on days 1 to 2, and an approximate 10% increase in plasma volume was present on days 3 to 4, making this possibility unlikely. A remarkable finding in our study is that 6% of our participants demonstrated a cTnI increase above the AMI cut-off value on ≥1 day. Although clinically these cTnI values may initially be of concern, subjects reported no clinical signs of (acute) cardiac damage.

Post hoc analysis of the cTnI-positive group (n = 6) revealed that presence of cardiovascular pathology and age

were higher compared to the entire group (n = 109, Table 3). This reinforces our previous findings from the multivariate analysis. Nonetheless, exercise-induced increase in cTnI cannot be explained exclusively by these factors. Note that 5 subjects showed a positive cTnI test result on a single day, whereas exercise and personal factors were not different from the other 3 days of the event. This emphasizes that prolonged exercise may result in a circulating cTnI value above the current clinical cut-off for AMI, which is modestly related to, but not fully dependent on, a number of the factors that we examined.

Our findings raise an important question regarding the underlying mechanism for cTnI release. Possibly, cTnI release is related to the increase in myocardial work (and thus myocardial oxygen uptake) that is influenced by the exercise-related increase in heart rate. Another potential mechanism relates to oxidative stress, because a recent study demonstrated that oxidative stress is strongly associated with an increase in cTnI.[23] Because aging[24] and cardiovascular pathology[25] are related to increased oxidative stress, one may hypothesize that oxidative stress contributed to the increase in cTnI. Unfortunately, this remains unanswered in our study. Myocardial damage could be triggered by various factors, including wall stress, coronary artery spasms, increased stress on atherosclerotic plaques, and ischemia.[26] Nonetheless, the cTnI increase was small and not associated with symptoms of cardiac injury. Indeed, it may well be possible that the increase in cTnI did not reflect myocardial "damage", but rather an increase in membrane permeability during prolonged increases in heart rate that, when accompanied by decreased renal blood flow during exercise, leads to a small increase in cTnI release and a decreased clearance. Our study cannot distinguish among these possibilities. Ultimately, it should be emphasized that exercise has important cardioprotective effects and this study should not be taken as evidence against the cardiovascular health benefits of (low-intensity) physical activity.

A recent study has reported a biphasic cTnT release during and after completion of a marathon in young men.[12] Because little is known about the time course of postexercise cTnI release, it is possible that we measured cTnI during the nadir in some subjects. Moreover, various groups may differ in their exercise-induced cTnI release kinetics or clearance. Accordingly, we may have underestimated the true prevalence of postexercise increases in cTnI above the clinical cut-off value.

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