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RESEARCH LETTER

Cardiac Biomarker Kinetics and Their Association With Magnetic Resonance Measures of Cardiomyocyte Integrity Following a Marathon Run: Implications for Postexercise Biomarker Testing

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Habitual physical activity reduces cardiovascular risk, yet exercise can acutely increase a variety of myocardial injury biomarker concentrations.[1] Their kinetics and release mechanisms remain incompletely understood. We recently demonstrated that marathon running transiently increases contemporary cTnI (cardiac troponin I) concentrations and concomitantly results in compromised myocardial tissue integrity.[2] Specifically, elevated postmarathon cTnI concentrations correlated with increased mean myocardial tissue water diffusivity (MD). An increased myocardial MD may point to increased cell membrane permeability as a mechanism for exercise-induced cardiac biomarker elevations through leakage from the cytosolic pool into the circulation. We assessed the kinetics of exercise-induced changes in novel and conventional cardiac biomarkers following a marathon run and related them to MD as measure of cardiomyocyte integrity.

We recruited 12 men aged ≥45 years competing in the 2017 Amsterdam Marathon. Blood samples were collected at the following 6 time points: 1 week (baseline) and 1 hour premarathon, directly (±1 hour) postmarathon, at the time of magnetic resonance imaging examination postmarathon (4±2 hours postmarathon), 1 to 2 days postmarathon, and 2 weeks postmarathon (recovery). In this post hoc analysis, we measured cTnI by conventional (cTnI; Siemens ADVIA Centaur TnI-Ultra) and single-molecule counting assays (SMC-cTnI; Singulex Clarity cTnI system), hs-cTnT (high-sensitivity troponin T; Roche Cobas), cMyC (cardiac myosin–binding protein C; EMD Merck Millipore), sST2 (soluble suppression of tumorigenicity 2; Critical Diagnostics Presage ST2 Assay), and BNP (B-type natriuretic peptide; Siemens Centaur). Furthermore, magnetic resonance imaging was performed at baseline, 4±2 hours after finishing the marathon (postmarathon), and at recovery.[2] Cardiomyocyte integrity was assessed using diffusion-weighted magnetic resonance imaging to estimate myocardial MD. The Medical Ethical Committee of the Amsterdam University Medical Centers approved the study. Participants provided written informed consent. Data are presented as mean±SD, median [interquartile range] or frequency (%). The data that support the findings of this study are available from the corresponding author upon reasonable request.

A total of 11 men (age 51 [50–56] years; BMI, 23.6±1.1 kg/m^2) finished the marathon in 3:43 (3:28–4:34) hours:minutes at 89±5% of their predicted maximum

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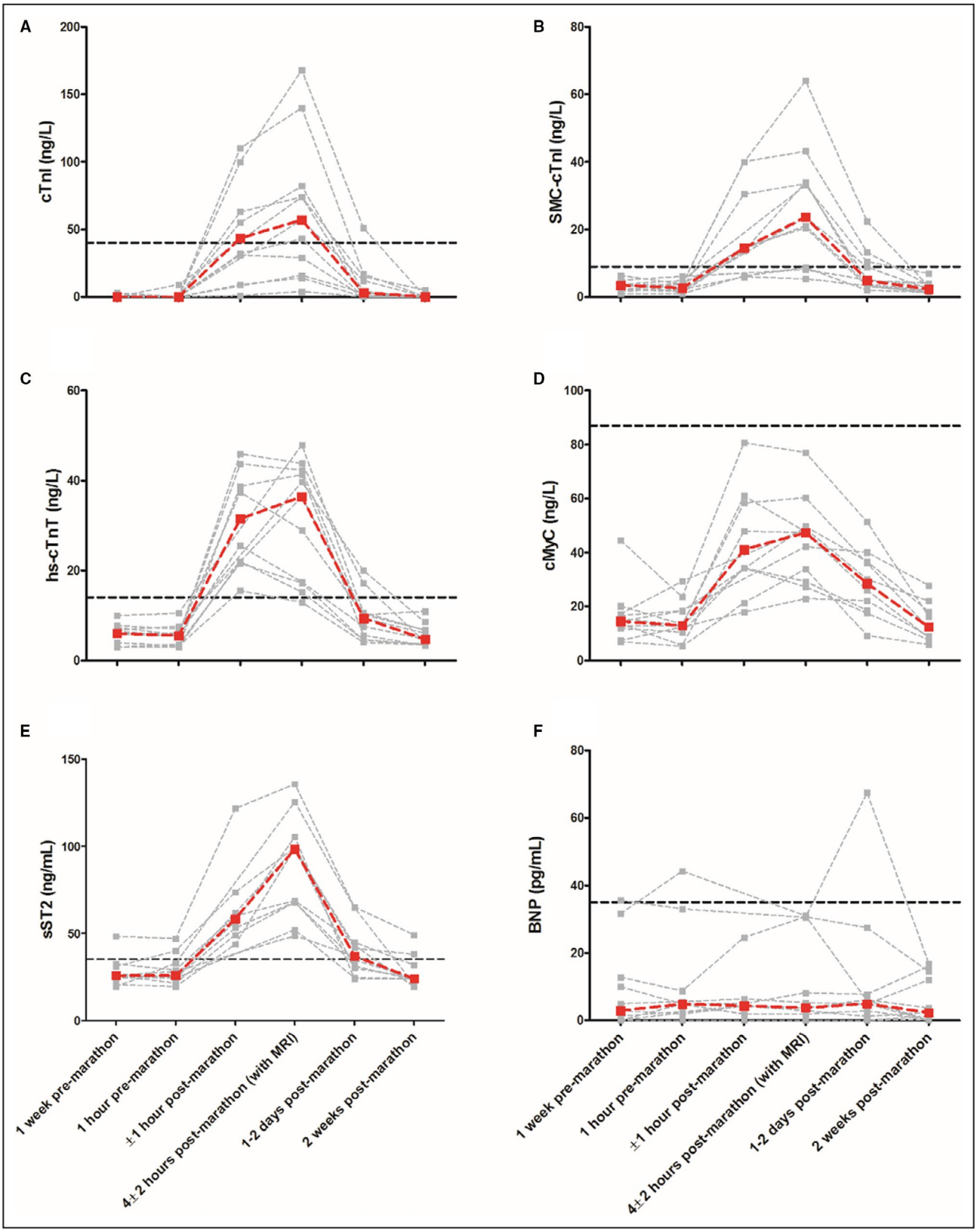

heart rate. Kinetics of exercise-induced biomarker elevations differed across biomarkers (Figure). Contemporary cTnI increased postmarathon and exceeded the upper reference limit (URL) in 7 participants (64%) and returned to baseline values at recovery (Figure). SMC-cTnI and hs-cTnT had similar kinetics with 8 (73%) and 11 (100%) participants exceeding the URL, respectively. Despite similar release kinetics, postmarathon values of cTnI did

Figure. Cardiac biomarker kinetics following a marathon run.
cTnI measured using a conventional assay (upper reference limit [URL], 40 ng/L; limit of detection [LOD], 6 ng/L; **A**), SMC-cTnI (URL, 8.97 ng/L; LOD, 0.12 ng/L; **B**), hs-cTnT (URL, 14 ng/L; LOD, 3 ng/L; **C**), cMyC (URL, 87 ng/L; LOD, 0.4 ng/L; **D**), sST2 (standard analysis cut point, 35 µg/L; LOD, 1.8 µg/L; **E**), and BNP (clinical cut point, 35 pg/mL; LOD, 2 pg/mL; **F**) measured at 6 time points surrounding a marathon run. Data for each individual participant are shown in gray, with group median values (n = 11) indicated by the red lines. Horizontal dashed lines indicate the URLs and/or clinical cut points. BNP indicates B-type natriuretic peptide; cMyC, cardiac myosin–binding protein C; cTnI, cardiac troponin I; hs-cTnT, high-sensitivity troponin T; MRI, magnetic resonance imaging; SMC, single-molecule counting assay; and sST2, soluble suppression of tumorigenicity 2.

not significantly correlate with cTnT (cTnI r=0.50, P=0.12; SMC-cTnI r=0.42, P=0.20). cMyC increased postmarathon in all participants without exceeding the URL at any time point. One marathon runner (9%) had an elevated sST2 concentration at baseline, whereas all runners had concentrations above the cut point postmarathon. sST2 did not correlate with any of the other cardiac biomarkers (P≥0.10). BNP concentrations showed no effect of exercise (P=0.27).

MD increased postmarathon (1.54±0.08 to 1.67±0.18 mm^2/s; P=0.04) and returned to baseline values within 2 weeks (1.56±0.09 mm^2/s).[2] Postmarathon values of MD correlated with cTnI (r=0.66, P=0.03) and SMC-cTnI (r=0.71, P=0.02), whereas associations with hs-cTnT (r=0.55, P=0.08) and cMyC (r=0.56, P=0.07) did not reach statistical significance. No association of MD with sST2 or with BNP was found.

We only evaluated male runners to preclude any sex-specific variability of cardiac effects within our cohort. Because of logistical constraints of performing elaborate cardiac magnetic resonance imaging exams (duration of ±1 hour) directly (<6 hours) postmarathon, we could not include more than 12 individuals using 2 identical magnetic resonance systems simultaneously. As such, the statistical power of this study was limited.

In this field study, marked transient elevations in novel and conventional cardiac biomarkers were observed following a marathon run, with the highest concentrations at 4±2 hours postrace in all biomarkers except BNP, which unexpectedly did not increase. The magnitude and statistical significance of the association between MD and biomarkers was variable, but largely uniform for myocardial injury markers such as cTnI, SMC-cTnI, hs-cTnT, and cMyC. The lack of association between sST2 and MD or other biomarkers postmarathon suggests a different exercise-induced mechanism of release, which could be explained by leakage from the cell (ie, cTn [cardiac troponin]/cMyC) versus upregulated production (sST2). Although our observations favor a physiological rather than pathological response, the magnitude of cardiac biomarker elevations may still be a surrogate for cardiac vulnerability given their predictive capacity for adverse outcomes.[3]

Notably, although cMyC yields high diagnostic accuracy for acute myocardial infarction,[4] cMyC concentrations postmarathon did not exceed the URL at any time point. This difference between cTn and cMyC concentrations following exercise may relate to the higher molecular mass of cMyC complexes (≈140 kDa) and fragments (≈40 kDa) compared with cTn complexes (cTnI ≈29 kDa, cTnT ≈37 kDa) and fragments (10–30 kDa), suggesting that cMyC may be less likely to leak from the cell into the circulation. Because postexercise cTn elevations can be challenging to interpret in the clinical setting because of concentrations exceeding the URL in the absence of signs of myocardial ischemia, a parallel assessment of cMyC might aid in discerning whether cTn elevations are physiological or pathological in endurance athletes.

ARTICLE INFORMATION

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Disclosures

EMD Merck Millipore (Hayward, CA) was contracted to undertake the analyses of cardiac myosin–binding protein C on a fee-for-service basis and holds no commercial interest. Dr Marber is named as an inventor on a patent held by King's College London for the detection of cardiac myosin–binding protein C as a biomarker of myocardial injury. The remaining authors have no disclosures to report.

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