Clinical Chemistry 61:10
1246–1255 (2015)

Review

Biomarker Changes after Strenuous Exercise Can Mimic Pulmonary Embolism and Cardiac Injury—A Metaanalysis of 45 Studies

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BACKGROUND: Biomarkers are well established for diagnosis of myocardial infarction [cardiac troponins, high-sensitivity cardiac troponins (hs-cTn)], exclusion of acute and chronic heart failure [B-type natriuretic peptide (BNP), N-terminal proBNP (NT-proBNP)] and venous thromboembolism (D-dimers). Several studies have demonstrated acute increases in cardiac biomarkers and altered cardiac function after strenuous sports that can pretend a cardiovascular emergency and interfere with state-of-the-art clinical assessment.

METHODS: We performed a systematic review and metaanalysis of biomarker and cardiovascular imaging changes after endurance exercise. We searched for observational studies published in the English language from 1997 to 2014 that assessed these biomarkers or cardiac function and morphology directly after endurance exercise. Of 1787 identified abstracts, 45 studies were included.

RESULTS: Across all studies cardiac troponin T (cTnT) exceeded the cutoff value (0.01 ng/mL) in 51% (95% CI, 37%–64%) of participants. The measured pooled changes from baseline for high-sensitivity cTnT (hs-cTnT) were +26 ng/L (95% CI, 5.2–46.0), for cTnI +40 ng/L (95% CI, 21.4; 58.0), for BNP +10 ng/L (95% CI, 4.3; 16.6), for NT-proBNP +67 ng/L (95% CI, 49.9; 84.7), and for D-dimer +262 ng/mL (95% CI, 165.9; 358.7). Right ventricular end diastolic diameter increased and right ventricular ejection fraction as well as the ratio of the early to late transmitral flow velocities decreased after exercise, while no significant changes were observed in left ventricular ejection fraction.

CONCLUSIONS: Current cardiovascular biomarkers (cTnT, hs-cTnT, BNP, NT-proBNP, and D-dimer) that are used in clinical diagnosis of pulmonary embolism, acute coronary syndrome, and heart failure are prone to alterations due to strenuous exercise. Hence, it is necessary to take previous physical exercise into account when a cardiac emergency is suspected.

The positive impact of exercise on cardiovascular and all-cause mortality has been well described. However, strenuous exercise has also been shown to cause notable perturbation in blood chemistry *(1)*. It is estimated that 25 out of every 1000 marathon runners seek medical care after competition *(2)*. Exercise-associated collapse (EAC)[5] is, with rates of 59%–85%, the most common cause seen in the medical tent after prolonged endurance exercise *(3)*. Although EAC is usually benign, it can be life threatening in some cases *(4)*. Over the past several years, numerous studies have evaluated the effects of strenuous exercise on blood concentrations of cardiac biomarkers and hemostatic proteins. Additionally, exercise-induced changes in left ventricular (LV) and right ventricular (RV) functions were also noticed in different studies *(5)*. This issue is of clinical importance because increases in biomarkers after strenuous sports may severely confound the interpretation of biomarker results in athletes presenting acutely to an emergency department and also raise the question for the exact pathomechanism of release when structural and functional dysfunction has been excluded. Many but not all studies suggest that strenuous physical exertion may indeed result in myocardial injury *(6)*. The incidence of biomarker altera-

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Received March 13, 2015; accepted June 18, 2015.
Previously published online at DOI: 10.1373/clinchem.2015.240796

[5] Nonstandard abbreviations: EAC, exercise-associated collapse; LV, left ventricular; RV, right ventricular; BNP, B-type natriuretic peptide; NT-proBNP, N-terminal proBNP; PE, pulmonary embolism; HF, heart failure; ACS, acute coronary syndrome; DVT, deep vein thrombosis; hs-cTnT, high-sensitivity cardiac troponin T; cMRI, cardiac MRI; EF, ejection fraction; RVEDD, RV-end diastolic diameter; E/A ratio, ratio of early (E) to late (A) transmitral flow; tPA, tissue plasminogen activator; LGE, late gadolinium enhancement.

tions [cardiac troponin, D-dimer, B-type natriuretic peptide (BNP), and N-terminal proBNP (NT-proBNP)] and changes in cardiac function, however, vary strongly among these studies. In particular, the small sample sizes in many of these studies may cause imprecise estimation of the postexercise change in biomarkers or cardiac function.

Cardiac troponins are the preferred markers for the diagnosis of acute myocardial infarction but may also be measured in patients with pulmonary embolism (PE) and other acute life-threatening complications including heart failure (HF) and arrhythmias *(7)*. The early diagnosis of these conditions is essential, because immediate treatment is associated with improved prognosis *(8)*. Moreover, an increase in cardiac troponin has been frequently reported to be associated with worse prognosis in patients with acute coronary syndrome (ACS) but also in other acute non-ACS conditions affecting the cardiovascular system such as PE, acute HF, and myocarditis, and ACS measurement has been recommended in the clinical routine *(7)*. Plasma D-dimer is used clinically to exclude venous thromboembolism with a high negative predictive value *(9)*. Circulating concentrations of BNP or NT-proBNP are directly related to the severity of ventricular dysfunction, and values below decision cutoffs are used to exclude acute or chronic HF. Furthermore, natriuretic peptides confer prognostic information in patients with PE and HF *(10)*. RV dilation can be observed in about 25% of patients with PE, and the absence of signs of RV overload or dysfunction excludes PE as a cause of hemodynamic instability in patients with shock or hypotension and is one important marker for decision-making regarding systemic lysis therapy *(8)*.

Increased concentrations of biomarkers can also be observed in other conditions outside their intended use. For instance, clinical specificity of cardiac troponins has decreased at the expense of improved sensitivity. Although cardiac tissue is the exclusive source of cardiac troponin in blood, myocardial injury may also occur in the absence of an ACS *(11)*. Therefore, analytically true-positive increases in troponin concentrations in the absence of ACS are frequent and may confound the correct diagnosis. A huge list of reasons has been compiled taking into consideration potential mechanisms of myocardial injury. Likewise, the negative predictive values of natriuretic peptides and D-dimers are hampered by abnormal values owing to confounders *(12)*.

Combining existing studies in a metaanalysis provides a higher sample size and consequently more precise estimates of biomarker and ventricular parameter changes. We first report a case of a healthy woman who was admitted to our emergency room with suspected PE immediately after participating in a marathon. Next, we report the metaanalysis results of a systematic review we performed to explore the changes in cardiac biomarkers (cardiac troponin, BNP, and NT-proBNP), D-dimer, RV, and LV function after strenuous exercise.

CASE

A 35-year-old female amateur marathon runner was admitted to the emergency room of university hospital Heidelberg because of collapse after running about 10 km in the heat of the summer. The athlete was conscious at presentation. She had no family history of cardiovascular diseases, PE, or deep vein thrombosis (DVT) and she was not pregnant. Blood glucose and electrolyte concentrations were within reference intervals. However, laboratory tests showed an increased high-sensitivity cardiac troponin T (hs-cTnT) of 73 ng/L (99th percentile, 14 ng/L; Roche Diagnostics) and a D-dimer concentration of 9920 ng/mL (reference interval, <500 ng/mL). The electrocardiogram showed a sinus tachycardia (107 bpm) with no significant ST-segment abnormalities. The echocardiography showed normal RV and LV function. Three hours later, the hs-cTnT concentration increased to 149 ng/mL. Meanwhile, PE was ruled out using computed tomography angiography. Seven hours later, the hs-cTnT concentration decreased to 97 ng/L. To exclude myocardial injury, a decision was made to perform a noninvasive procedure, cardiac MRI (cMRI). This showed a LV ejection fraction (EF) of 71% with no signs of myocardial scar or ischemia. One day later, the hs-cTnT concentration decreased to 32 ng/L. Exercise stress test, pulmonary function test, carotid ultrasound, and 24-h Holter monitoring showed no pathological findings. After 4 days of uneventful inpatient monitoring, the patient was discharged from our clinic and her collapse and increase in cTnT were interpreted as a consequence of dehydration during the marathon.

Methods

STUDY DESIGN AND SEARCH STRATEGY

We performed a systematic review and metaanalysis of observational studies published in English from 1997 to 2014. The metaanalysis was performed according to PRISMA (the Preferred Reporting of Items for Systematic reviews and MetaAnalysis) *(13)*. We searched for all prospective or case control studies in which cTnT, cTnI, BNP, NT-proBNP, D-dimer, or cardiac imaging data were evaluated before and after strenuous exercises. We searched the PubMed, EMBASE, ScienceDirect, and SportDiscus databases. Reference lists of original publications and review articles were also carefully reviewed. Key words were "Marathon," "Triathlon," "Exercise," "Troponin," "D-dimer," "Brain Natriuretic Peptide,"

"NT-proBNP," "Echocardiography," "cMRI," "Cardiac biomarkers," "Athletes," and "Exercise induced cardiac damage."

SELECTION OF ARTICLES, DATA EXTRACTION, AND QUALITY ASSESSMENT

We assessed the effects of exercise on cTnT, cTnI, BNP, NT-proBNP, D-dimer, RV-end diastolic diameter (RVEDD), RV-EF, LV-EF, and ratio of early (E) to late (A) transmitral flow (E/A ratio) in human adults within 24 h after completion of exercise. We excluded case reports, review articles, and studies without reference interval values for troponin. Positive values for cTnT and hs-cTnT were defined above 0.01 ng/mL or 14 ng/L, respectively.

Of the 1718 identified articles, 1644 were excluded on the basis of review of the title and abstract (see Fig. 1 in the Data Supplement that accompanies the online version of this article at http://www.clinchem.org/content/vol61/issue10). Two reviewers (F. Sedaghat-Hamedani and E. Kayvanpour) independently assessed full texts of 74 remaining manuscripts. Twenty-nine of these were excluded as case reports (3), review articles (5), and metaanalyses (3). Two had different cutoff values for cTnT, 13 included insufficient information, and 2 were repeated studies. We assessed the quality of the eligible studies using the NHLBI (National Heart, Lung and Blood Institute) quality assessment tool for before–after (pre–post) studies with no control group *(14)*. Disagreements between reviewers were resolved by discussion or by consensus including a third author. For 45 final identified studies, data were extracted, including author, year, sample size, age and sex, type of exercise, biomarkers, mean duration of exercise time, exercise distance, detection assay, and mean values measured before and after exercise, as well as imaging data (see online Supplemental Tables 1–8). For each cTnT (with conventional assay and high-sensitivity assay), cTnI, BNP, NT-proBNP, D-dimer, RV diameter, RV-EF, LV-EF, and E/A ratio data were separately extracted and analyzed. For cTnT, 33; for hs-cTnT, 4; for cTnI, 12; for BNP, 7; for NT-proBNP, 17; for D-dimer, 7; for RVEDD, 8; for RV-EF, 7; for LV-EF, 21; and for E/A ratio, 16 studies were included (see online Supplemental Fig. 1). For cTnT we excluded the study of Fortescue et al. with a large number of individuals (483 runners) owing to their pooled evaluation of cTnT and cTnI *(18)*. All studies were analyzed in a single pool with pre- and postexercise design without a control group.

OUTCOMES

For all extracted biomarkers the mean "change from baseline" for each study was derived as the difference between the mean final and the mean baseline values with their SEs. Medians with ranges or interquartile ranges were converted into means with SDs as described by Hozo et al. *(16)*. The SE of the change from baseline was obtained by the extracted *P* value for the comparison between pre- and postvalues using normal approximation *(17)*. If a *P* value was missing, we imputed the change-from-baseline SE using the baseline and final SDs and an assumed correlation coefficient between pre- and postvalues of 0.3 *(17)*. For the biomarkers cTnT and hs-cTnT the "frequency of increase above the cutoff value" was defined as the proportion of individuals with final concentration exceeding a common cutoff value (for cTnT above 0.01 ng/mL and for hs-cTnT above 14 ng/L).

STATISTICAL ANALYSIS

Using the meta package (version 3.1–2) in R (version 3.0.2, The R Foundation for Statistical Computing, 2013), random effects metaanalyses of the changes from baseline and the frequency of increase above the defined cutoff value were conducted. A positive change from baseline represents a higher final biomarker value in comparison to the baseline value. The higher the "frequency of increase above the cutoff value," the higher the proportion of participants with a biomarker exceeding this cutoff value after endurance exercise. Heterogeneity was quantified by I^2 statistics. In the case of heterogeneity, we also performed sensitivity and subgroup analyses to investigate potential clinical and methodological heterogeneity. The presence of publication bias was addressed, although not explored, by funnel plots and tests of asymmetry because the assumption of an underlying symmetric distribution is not reasonable for the changes from baseline in this clinical setting.

Results

CARDIAC BIOMARKERS CAN INCREASE AFTER STRENUOUS EXERCISE

We analyzed cTnT, hs-cTnT, and cTnI separately. Thirty-three studies, which included a total of 1045 athletes, evaluated changes in cTnT concentration after strenuous exercise. The overall frequency of increase above the cutoff value for cTnT (values above 0.01 ng/mL) after exercise was 51% (95% CI, 37–64) (Fig. 1). However, there was large, statistically significant heterogeneity between studies (I^2, 97.3%; $P < 0.0001$). Four studies evaluated hs-cTnT after physical exertion. In these studies the overall frequency of increase above the cutoff value (values above 14 ng/L) was 83% (95% CI, 70–95) (see online Supplemental Fig. 2). The mean concentration of hs-cTnT before exercise was 4 ng/L (95% CI, 3.0–4.8), which increased to 32 ng/L (95% CI, 13.5–49.6). The change from baseline for hs-cTnT before and after physical exertion was 26 ng/L (95% CI, 5.2–46.0) (Fig. 2). For cTnI, 12 studies, which included

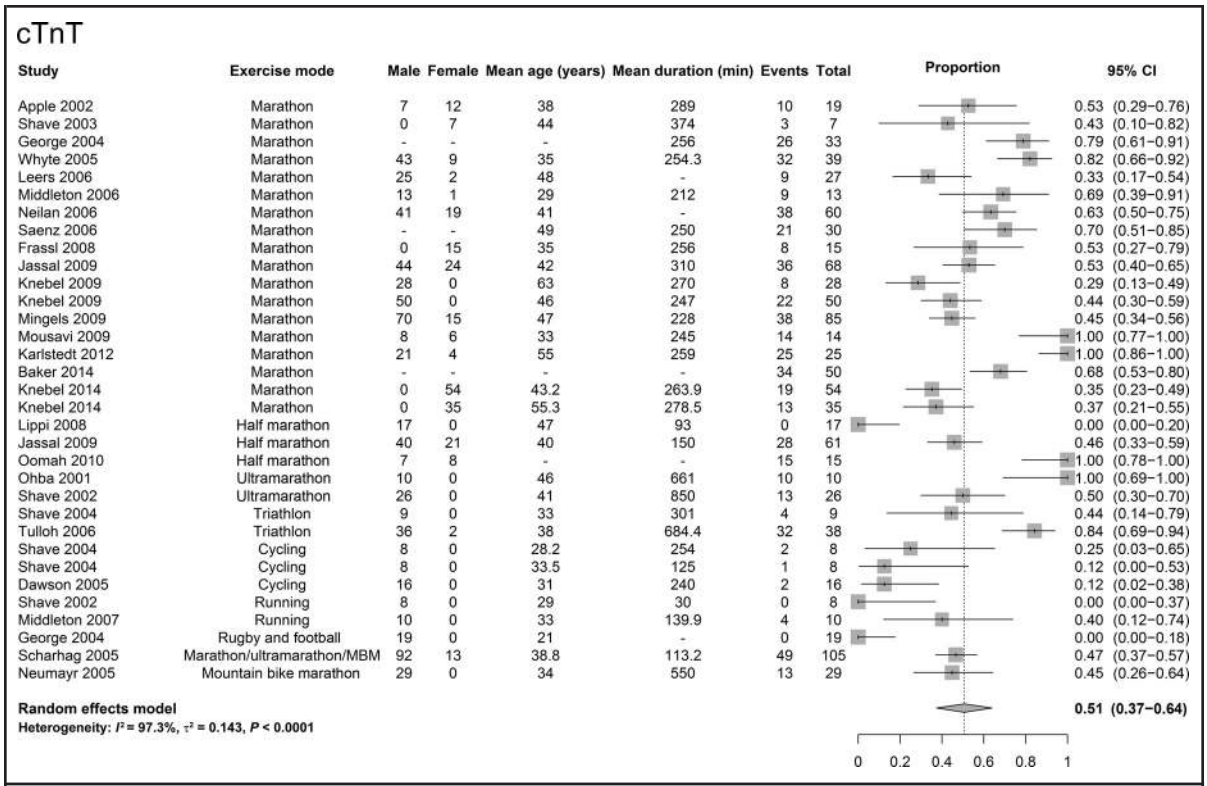

Fig. 1. Forest plot of the frequency of increase above the cutoff value for cTnT (above 0.01 ng/L).

Studies are ranked by publication year and exercise mode [Apple et al. (2002) *(59)*, Baker et al. (2014) *(47)*, Dawson et al. (2005) *(39)*, George et al. (2004) *(37)*, George et al. (2004) *(57)*, Frassl et al. (2008) *(22)*, Jassal et al. (2009) *(53)*, Karlstedt et al. (2012) *(50)*, Knebel et al. (2012) *(48)*, Knebel et al. (2009) *(52)*, Leers et al. (2006) *(55)*, Lippi et al. (2008) *(49)*, Middleton et al. (2006) *(25)*, Middleton et al. (2007) *(60)*, Mingels et al. (2009) *(51)*, Mousavi et al. (2009) *(21)*, Neilan et al. (2006) *(24)*, Neumayr et al. (2005) *(20)*, Ohba et al. (2001) *(45)*, Oomah et al. (2010) *(46)*, Scharhag et al. (2005) *(36)*, Saenz et al. (2006) *(54)*, Shave et al. (2002) *(38)*, Shave et al. (2004) *(40)* Shave et al. (2004) *(41)*, Shave et al. (2004) *(43)*, Shave et al. (2002) *(44)*, Shave et al. (2003) *(58)*, Tulloh et al. (2006) *(42)*, Whyte et al. (2005) *(56)*]. Jassel et al. (2009), Knebel et al. (2009), and Knebel et al. (2012) performed analyses in 2 different patient cohorts and are thus mentioned twice each. MBM, mountain bike marathon. Hyphens indicate data not available.

412 individuals, were evaluated. The mean cTnI concentration before exercise was 18 ng/L (95% CI, 6.4–29.7) vs 67 ng/L (95% CI, 49.0–84.2) after exercise, with a change from baseline of 40 ng/L (95% CI, 21.4–58.0) (Fig. 3). For cTnI, evident heterogeneity between studies was again observed. These heterogeneities could be explained because of differences in training status and performance of participants, different types of exercise with diverse intensity, and different time of blood sample taking after exercise, as well as different cardiac troponin assays used.

In 17 studies, which included 835 individuals, NT-proBNP changes after strenuous exercise were analyzed, with a change from baseline of 67 ng/L (95% CI, 49.9–84.7) (Fig. 4A). For BNP, 7 studies, which included 200 individuals, were evaluated. The BNP increase was less pronounced than for NT-proBNP, with a change from baseline of 10 ng/L (95% CI, 4.3–16.6) (Fig. 4B). The statistical heterogeneities for NT-proBNP and BNP were lower than those in troponin studies with I^2, 66.1% ($P < 0.0001$) and I^2, 76.9% ($P < 0.0002$), respectively. Performing subgroup analyses for exercise type could not reduce heterogeneities in different studies investigating biomarker changes after endurance exercise.

D-DIMER INCREASES SIGNIFICANTLY AFTER ENDURANCE SPORTS

D-Dimer, a product of fibrin degradation with high negative predictive value in ruling out DVT and PE, was evaluated in 7 studies, which included 146 individuals. Six studies in marathon and 1 study in ultramarathon runners analyzed the changes in concentration of D-dimer before and after the race. Altogether,

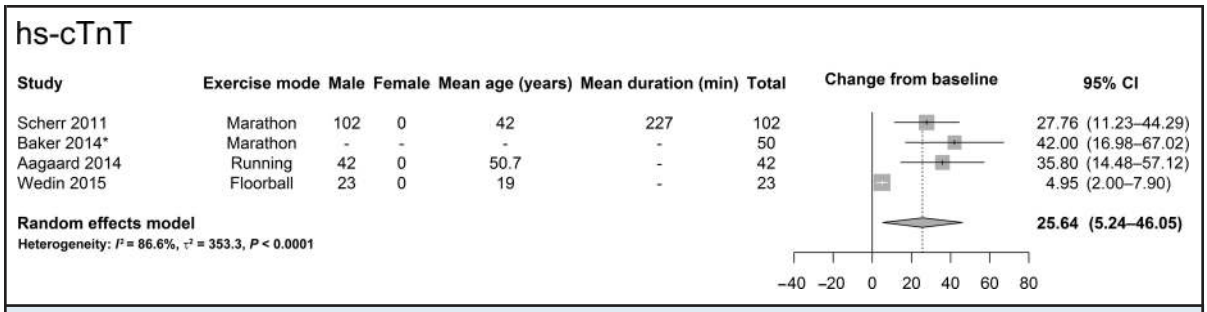

Fig. 2. Change from baseline (in ng/L) for hs-cTnT after endurance exercise is given.

Studies are ranked by publication year and exercise mode [Aagaard et al. (2014) *(62)*, Baker et al. (2014) *(47)*, Scherr et al. (2011) *(63)*, Wedin et al. (2015) *(61)*]. *, In this study hs-cTnT concentration before the race was lower than the detection limit (3 ng/L), because the authors' mean was given as 3 with an SD of 0. Hyphens indicate data not available.

D-dimer increased significantly after exercise, with a change from baseline of 262 ng/mL (95% CI, 165.9–358.7). These studies were not significantly heterogeneous (Fig. 5).

STRENUOUS EXERCISE CAN CAUSE ACUTE DYSFUNCTION OF THE RV, BUT NOT THE LV

Finally, the effect of strenuous exercise on RV function was analyzed in 7 studies (232 individuals) with echocardiography and in 5 studies (96 individuals) with cMRI. RV-EF and RVEDD changes in cMRI and echocardiography were measured separately. LV-EF changes were measured in 17 studies (501 individuals) with echocardiography and in 4 studies (82 individuals) with cMRI. RVEDD increased and RV-EF decreased after exercise, whereas no significant changes were observed in LV-EF. The increase of RVEDD measured in cMRI with a change from baseline of 12.1 mm (95% CI, 3.5–20.8) was more evident than in echocardiography, with a change from baseline of 3.7 (95% CI, −0.7 to 8.00) (Fig. 6A). For RVEDD, no heterogeneity was observed in cMRI; however, in echocardiography significant statistical heterogeneity was seen (I^2, 83.1%; $P < 0.0001$). The RV-EF transiently decreased from before to after the endurance sports, with a change from baseline of −7.0% (95% CI, −14.4 to 0.3) in echocardiography and −8.6% (95% CI, −16.4 to −0.7) in cMRI (Fig. 6B). The change from baseline for LV-EF in echocardiography was −2.1% (95% CI, −3.6 to −0.7) compared with 1.9% (95% CI, 0.9–2.9) in cMRI (see online Supplemental Fig. 3). In addition, a decrease of E/A ratio, as an index of LV diastolic filling, was observed immedi-

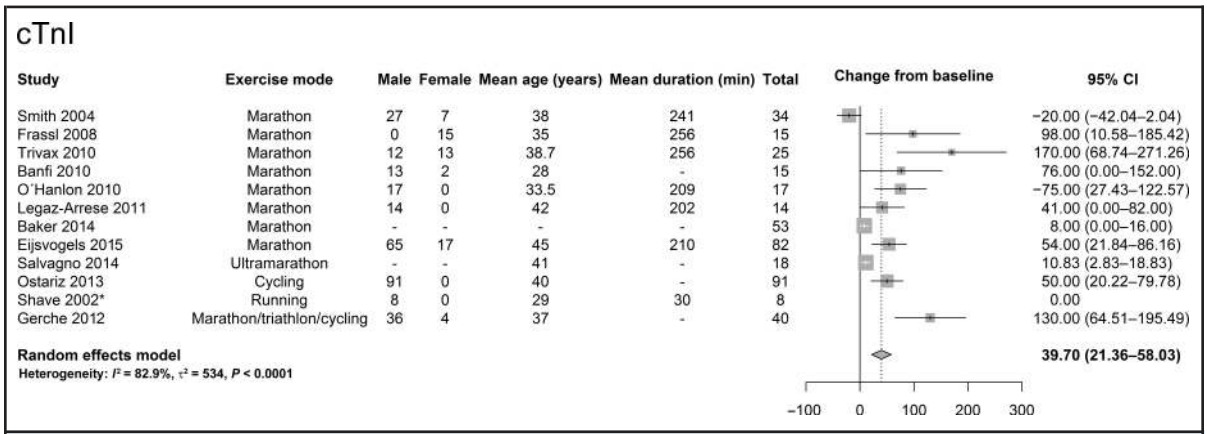

Fig. 3. cTnI change from baseline after endurance exercise (in ng/L).

Studies are ranked by publication year and exercise mode [Baker et al. (2013), Banfi et al. (2010) *(70)*, Eijsvogels et al. (2014) *(23)*, Frassl et al. (2008) *(23)*, La Gerche et al. (2012) *(5)* Legaz-Arrese et al. (2011) *(68)*, O'Hanlon et al. (2010) *(69)*, Salvagno et al. (2014) *(65)*, Serrano Ostariz et al. (2013) *(64)*, Shave et al. *(38)* (2002), Smith et al. (2004) *(71)*, Trivax et al. (2010) *(70)*]. *, In this study cTnI was lower than the detection limit (20 ng/L) at any stage of the study. Hyphens indicate data not available.

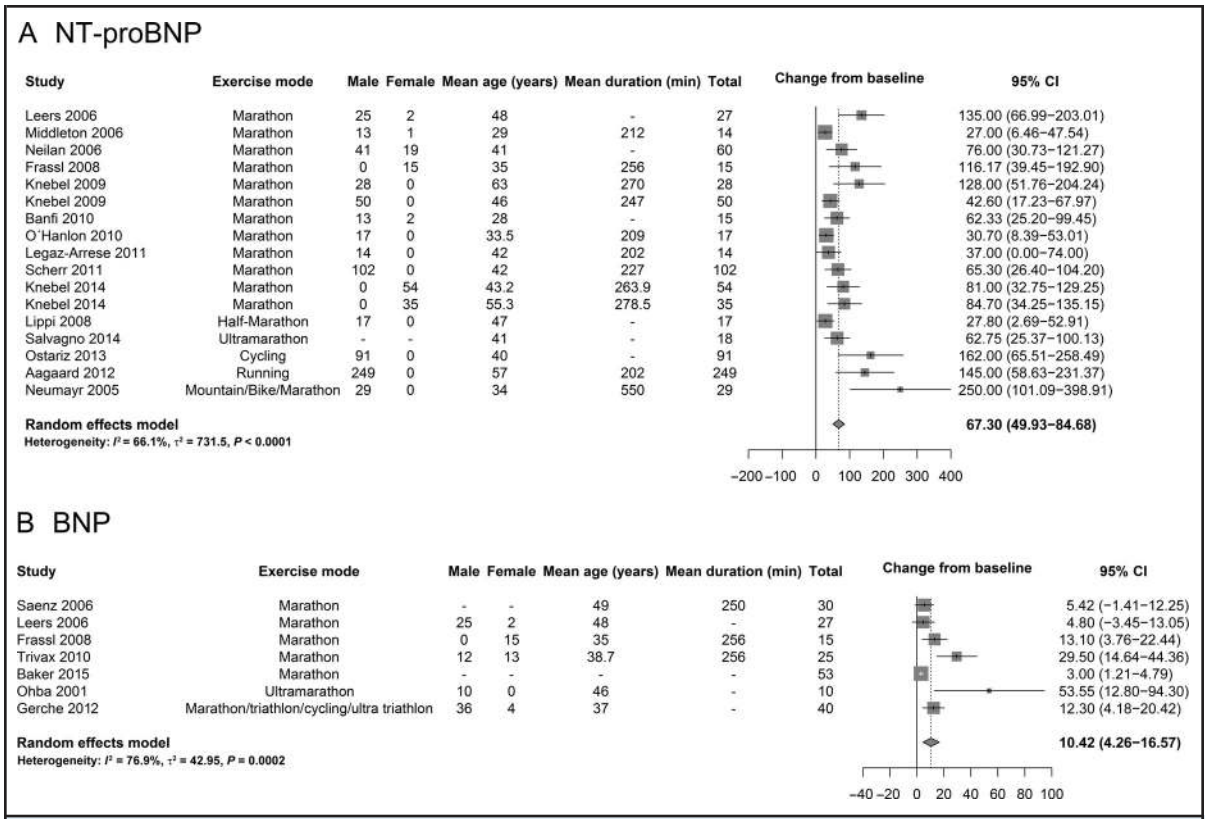

Fig. 4. NT-proBNP (A) and BNP (B) changes from baseline after endurance exercise (in ng/L).

Studies are ranked by publication year and exercise mode. (A), Aagaard et al. (2012) *(72)*, Banfi et al. (2010) *(69)*, Frassl et al. (2008) *(22)*, Knebel et al. (2009) *(52)*, Leers et al. (2006) *(55)*, Legaz-Arrese et al. (2011) *(67)*, Lippi et al. (2008) *(49)*, Middleton et al. (2006) *(25)*, Neilan et al. (2006) *(24)*, Neumayr et al. (2005) *(20)*, O'Hanlon et al. (2010) *(68)*, Salvagno et al. (2014) *(65)*, Serrano Ostariz et al. (2013) *(64)*, *(22)*, Scherr et al. (2011) *(63)*, Serrano Ostariz et al. (2013) *(64)*. (B), Baker et al. (2014) *(47)*, Frassl et al. (2008) *(22)*, La Gerche et al. (2012) *(5)*, Leers et al. (2006) *(55)*, Ohba et al. (2001) *(45)*, Saenz et al. (2006) *(54)*, Trivax et al. (2010) *(70)*. Hyphens indicate data not available.

ately after exercise in 16 included studies. The change from baseline of E/A ratio in echocardiography was −0.4 (95% CI, −0.5 to −0.3) (see online Supplemental Fig. 4).

Discussion

Numerous studies have reported the increase of cardiac biomarkers such as cardiac troponin, BNP, and NT-proBNP after exercise. The presence or increase of such cardiac biomarkers usually reflects myocardial injury and HF in cardiac patients. In this study we performed a systematic review and metaanalysis of studies that evaluated biomarkers and cardiac function before and after strenuous exercise. We demonstrated a statistically significant increase of cardiac troponin, BNP, NT-proBNP, and D-dimer after exercise. As illustrated by the case report in this review, these acute changes in biomarkers and cardiac function after endurance exercise such as marathon and triathlon running can lead to hospital admission and extensive invasive and noninvasive procedures.

Most studies showed significant cardiac troponin increases after exercise. We showed that overall about 51% of individuals had cTnT concentrations that were at least mildly increased above the limit of detection of third-generation cardiac troponin assays (0.01 ng/mL). The metaanalyses of Shave et al. (including 26 studies) and Regwan et al. (including 16 studies) demonstrated results similar to those of our study (including 33 studies), with overall rates of 47% and 51%, respectively *(6, 17)*. The large observational study of Fortescue et al. reported that almost 68% of 482 runners in the Boston Marathon showed cTnT or cTnI increases *(18)*. It should be noted that the previous metaanalysis of Shave et al. included this study in their analysis as an estimation of cTnT increase, which is not totally accurate, as Fortescue et al. did not discriminate between cTnT and cTnI. Altogether, in approximately one-half of participants cTnT concentra-

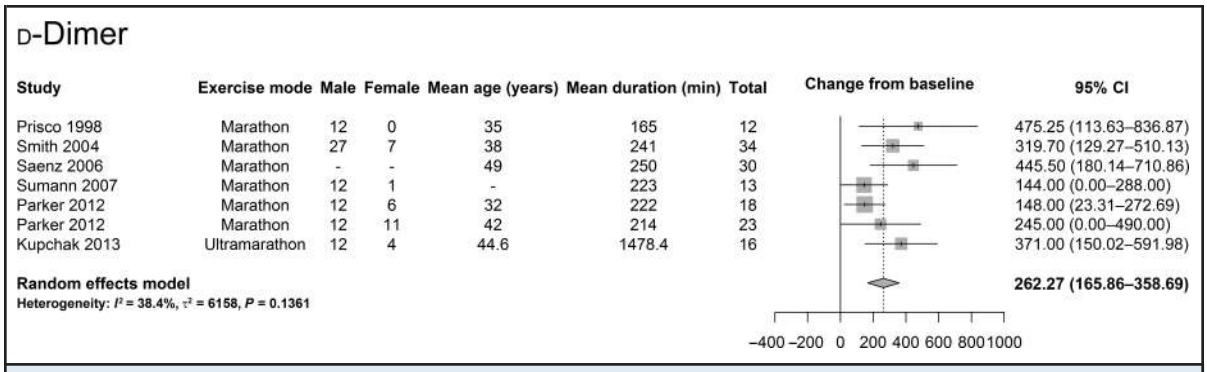

Fig. 5. D-Dimer change from baseline after endurance exercise in ng/mL.

Studies are ranked by publication year and exercise mode [Kupchak et al. (2013) *(28)*, Parker et al. (2012) *(73)*, Prisco et al. (1998) *(27)*, Saenz et al. (2006) *(54)*, Smith et al. (2004) *(71)*, Sumann et al. (2007) *(26)*]. Parker et al. (2012) analyzed 2 different patient cohorts and are thus mentioned twice. Hyphens indicate data not available.

tion postexercise exceeds 0.01 ng/mL and 83% of individuals show an increase in hs-cTnT above the 99th percentile (14 ng/L). The exercise-induced increase in troponin could be due to release of cytoplasmic cTnT and cTnI, because exercise may increase membrane permeability of cardiomyocytes *(19, 20)*. This reversible membrane leakage might be due to increased mechanical stress on the cardiomyocytes, overload with free radicals, increased body temperature, or prolonged acidosis *(19, 21)*.

BNP and NT-proBNP are mostly released from cardiac ventricles in response to volume or pressure overload and myocardial strain *(22)*. These cardiac peptides are powerful biomarkers to identify patients with HF or other causes of wall stress. High concentrations of BNP or NT-proBNP in patients with PE, ACS, and HF are associated with increased mortality *(23)*. The significant increase of BNP and NT-proBNP seems a result of changes in diastolic filling *(24)*. Increase of end-diastolic pressure due to increased cardiac output during prolonged exercise can also release BNP and NT-proBNP *(25)*. In our analysis, the increase of NT-proBNP is more substantial than BNP. This may be due to different elimination patterns of these proteins/peptides. The half-life of BNP is about 20 min, vs 120 min for NT-proBNP, and BNP is mainly eliminated through endopeptidases, whereas the elimination of NT-proBNP is mainly through glomerular filtration *(22)*.

D-Dimer as a primary enzymatic degradation product of fibrin is broadly used as a biomarker with a high negative predictive value in patients with suspected PE, DVT, and acute aortic syndrome *(26–28)*. This meta-analysis demonstrated significant increase of D-dimer after strenuous exercise, which may mimic a thrombotic event in the clinical setting. Physical exertion leads to activation of platelets, coagulation, and fibrinolysis *(29)*. Fibrinolysis may result from release of tissue plasminogen activator (tPA) *(1)*. Catecholamine, vasopressin, or epinephrine release, hypoglycemia, thrombin increase, vascular sheer stress, and muscular injury, which can occur during physical exertion, may release tPA from vascular endothelial cells and lead to increases in D-dimer concentrations *(1, 28)*. It should be mentioned, however, that different assays have been used in different studies for cTnI, BNP, and D-dimer, which makes pooling problematic. None of the included studies provided the percentage of increase above the upper reference interval and the corresponding SE and, therefore, this percentage could not be extracted and pooled in the metaanalysis. As a result of this limitation we pooled the changes from baseline according to each assay used.

It is well known that acute PE can lead to RV dilation and failure, which predicts a worse prognosis *(30, 31)*. In contrast, several studies reported transient depression of RV systolic function and RV dilation after endurance sports without prognostic consequences *(5, 21, 24)*. These transient changes may be due to exercise-induced pulmonary hypertension or volume load *(21)*. The increase of RVEDD was more evident in cMRI measurements (change from baseline, 12.1 mm) in comparison to echocardiography (change from baseline, 3.7 mm). Because cMRI may be more accurate in the estimation of RV volumes and function than cardiac ultrasound, the change from baseline calculated on the basis of cMRI should be more reliable than echocardiography *(32)*. An acute LV dysfunction was not observed, because LV-EF did not significantly change after endurance sport in most studies. Regarding LV-EF, our results were similar to the previous results from Middleton et al., who performed a metaanalysis of LV function in 18 studies reported between 1984 and 2005 *(33)*. They interpreted the −1.9% (95% CI, −1.0 to −2.9) mean change

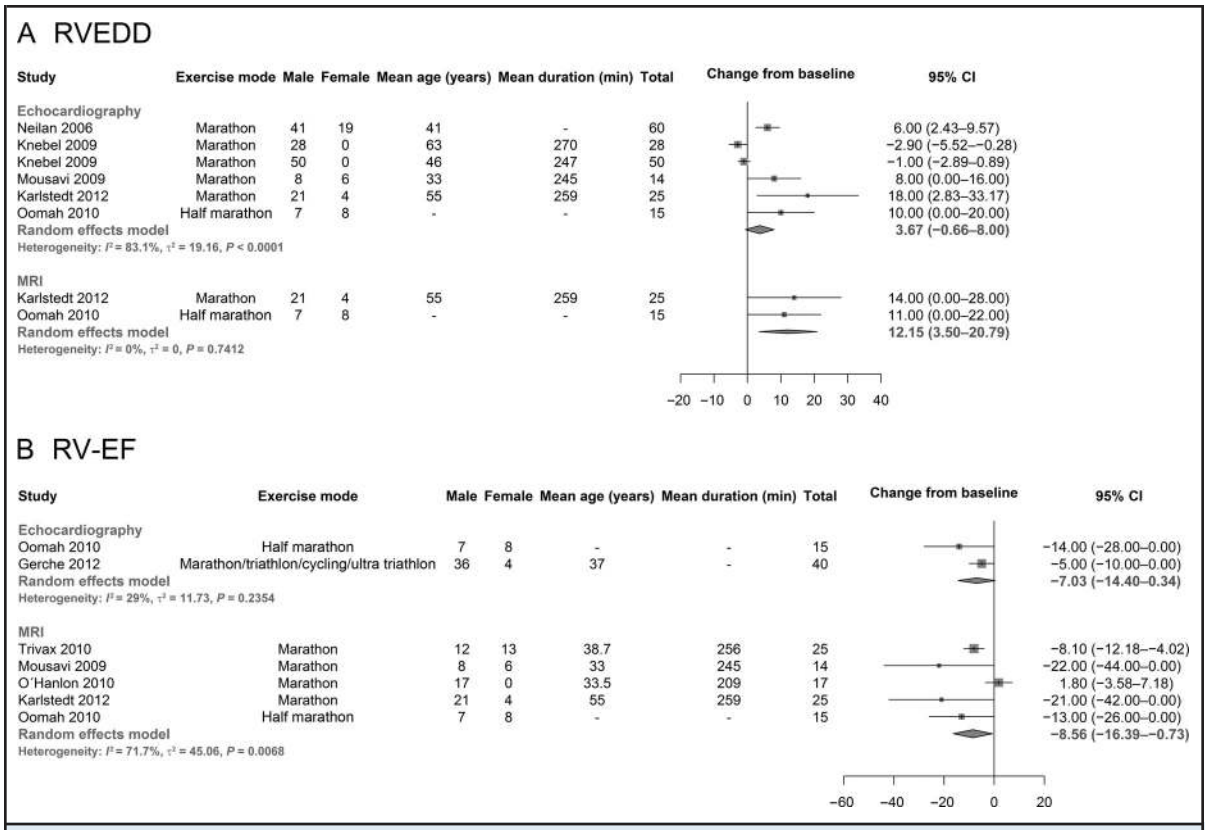

Fig. 6. RV function assessment with echocardiography and MRI.

Data on RV-EF and RVEDD after endurance exercise were evaluated separately. Change from baseline for RVEDD is measured in millimeters (A) and for RV-EF in percentage (B). Studies are ranked by publication year and exercise mode [Karlstedt et al. (2012) *(50)*, Knebel et al. (2009) *(52)*, La Gerche et al. (2012) *(5)*, Mousavi et al. (2009) *(21)*, Neilan et al. (2006) *(24)*, Oomah et al. (2010) *(46)*, O'Hanlon et al. (2010) *(68)*, Trivax et al. (2010) *(70)*]. Hyphens indicate data not available.

of LV-EF from baseline, a change which is physiologically irrelevant, as statistically significant. Regarding diastolic function, a significant reduction in E/A ratio was observed, demonstrating that diastolic filling can be compromised immediately after exercise.

Some studies reported an increase in arrhythmic disorders such as arrhythmogenic RV cardiomyopathy or atrial fibrillation among endurance athletes *(34)*. Recent studies suggest that proarrhythmic substrates may be predominantly expressed in the RV and not in the LV after repetitive sustained exertion *(5)*. In animal models intense exercise causes increased expression of transforming growth factor-β1 in the right and left atria as well as in the RV, which promotes RV-specific fibrosis *(35)*. cMRI could show focal late gadolinium enhancement (LGE), which correlates to fibrotic areas in endurance athletes. In all of the cases, focal LGE was identified in the interventricular septum most often at the insertion site of the RV *(5)*. These fibrotic patches, which could serve as substrates for ventricular tachyarrhythmias and sudden cardiac death, are also found in patients with cardiomyopathies *(35)*.

In conclusion, our analysis highlights evidence that cTnT, hs-cTnT, cTnI, NT-proBNP, BNP, and D-dimer concentrations can significantly increase after endurance exercise. In addition, transient RV dilation and dysfunction can be observed. All these changes can mimic PE, ACS, HF, or cardiac injury. An accurate interpretation of increased cardiac biomarkers after strenuous exercise is thus mandatory. Serial measurements of cardiac troponin may help to differentiate between physiological and pathological changes of cardiac troponin, but, as shown in our case report, the cardiac troponin values well may mimic those for acute disease *(4)*. Diagnosis of PE or myocardial injury after endurance sports should hence be made on the basis of all available clinical information and not on blood test results only *(4, 8)*. Lack of awareness of this phenomenon may trigger invasive procedures and can be unnecessarily expensive and harmful. Furthermore, it

would be interesting to analyze whether new biomarkers such as microRNAs can rule out pathologic myocardial injury in athletes after endurance exercise.

Author Contributions: *All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.*

Authors' Disclosures or Potential Conflicts of Interest: *Upon manuscript submission, all authors completed the author disclosure form. Disclosures and/or potential conflicts of interest:*

Employment or Leadership: None declared.
Consultant or Advisory Role: E. Giannitsis, Roche Diagnostics.
Stock Ownership: None declared.
Honoraria: None declared.
Research Funding: None declared.
Expert Testimony: None declared.
Patents: H.A. Katus, patent number: 6376206.

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