Myocardial Injury and Ventricular Dysfunction Related to Training Levels Among Nonelite Participants in the Boston Marathon

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Background—Multiple studies have individually documented cardiac dysfunction and biochemical evidence of cardiac injury after endurance sports; however, convincing associations between the two are lacking. We aimed to determine the associations between the observed transient cardiac dysfunction and biochemical evidence of cardiac injury in amateur participants in endurance sports and to elicit the risk factors for the observed injury and dysfunction.

Methods and Results—We screened 60 nonelite participants, before and after the 2004 and 2005 Boston Marathons, with echocardiography and serum biomarkers. Echocardiography included conventional measures as well as tissue Doppler–derived strain and strain rate imaging. Biomarkers included cardiac troponin T (cTnT) and N-terminal pro-brain natriuretic peptide (NT-proBNP). All subjects completed the race. Echocardiographic abnormalities after the race included altered diastolic filling, increased pulmonary pressures and right ventricular dimensions, and decreased right ventricular systolic function. At baseline, all had unmeasurable troponin. After the race, >60% of participants had increased cTnT >99th percentile of normal (>0.01 ng/mL), whereas 40% had a cTnT level at or above the decision limit for acute myocardial necrosis (≥0.03 ng/mL). After the race, NT-proBNP concentrations increased from 63 (interquartile range [IQR] 21 to 81) pg/mL to 131 (IQR 82 to 193) pg/mL (P<0.001). The increase in biomarkers correlated with post-race diastolic dysfunction, increased pulmonary pressures, and right ventricular dysfunction (right ventricular mid strain, r=−0.70, P<0.001) and inversely with training mileage (r=−0.71, P<0.001). Compared with athletes training >45 miles/wk, athletes who trained ≤35 miles/wk demonstrated increased pulmonary pressures, right ventricular dysfunction (mid strain 16±5% versus 25±4%, P<0.001), myocyte injury (cTnT 0.09 versus <0.01 ng/mL, P<0.001), and stress (NT-proBNP 182 versus 106 pg/mL, P<0.001).

Conclusions—Completion of a marathon is associated with correlative biochemical and echocardiographic evidence of cardiac dysfunction and injury, and this risk is increased in those participants with less training. (Circulation. 2006;114: 2325-2333.)

Key Words: echocardiography ■ exercise ■ natriuretic peptides
the aim of the present study was to determine the associations between the observed transient cardiac dysfunction and injury among amateur participants in endurance sports and to elicit the factors associated with the development of this dysfunction and injury.

Methods

Screening and Approval Process

The protocol was approved by the Partners Healthcare System Human Subjects Review Committee and The Boston Athletic Association. Sixty amateur runners scheduled to participate in the 2004 and 2005 Boston Marathons were recruited by open e-mail invitation sent to local running clubs. We did not approach any individual runner directly; rather, a general e-mail was sent to all local running clubs requesting them to forward it to all their members. We accepted all responders up to 30 subjects per year. The sample size was limited by the combination of the extensive finish line resources required in arranging such a study and the desire to limit any inconvenience and discomfort that a prolonged delay after a marathon may have on subjects. We excluded subjects with a history of cardiovascular disease. Athletes volunteered for the study and provided written consent. No subject refused consent. Comprehensive screening consisted of a general questionnaire to ascertain personal and marathon history, as well as a log of marathon training for the previous 4 months. Assessment included measurement of heart rate, blood pressure, serum biomarkers, and a complete echocardiographic evaluation. Runners were screened <1 week before and immediately (approximately 20 minutes) after completion of the marathon. Liberal oral intake of fluid was encouraged after the marathon to minimize volume depletion.

Echocardiography

Subjects underwent 2-dimensional pulsed-Doppler and color tissue-Doppler (TD) imaging by use of a commercial system (Vivid 7, GE Healthcare, Milwaukee, Wis) and a phased-array transducer. Standard measurements were performed according to American Society of Echocardiography guidelines. Peak pulmonary artery pressure was estimated from the jet of tricuspid regurgitation with the Bernoulli equation, and the mean pulmonary artery pressure (mPAP) was estimated from the pulmonary outflow Doppler acceleration time. Pulsed annular Doppler and TD were used to quantify regional and global systolic and diastolic function. From the pulsed-Doppler mitral annular velocities (peak early [E'] and late [A']), indices of LV diastolic function were recorded.

From the apical 4-chamber view, color TD images were acquired with the sample volume placed at the basal (tricuspid annulus), mid, and apical levels (moderator band) of the right ventricle (RV). From these images, RV myocardial wall velocities (V\_LVOT), strain (ε), and strain rate (SR), indices of RV systolic function, were measured offline (EchoPac, Version 6.3, GE Healthcare).

Biochemical Studies

Blood was collected into tubes containing EDTA and into serum separator tubes and processed immediately. Assays for all cardiac biomarkers were performed before the first freeze-thaw. None of the specimens demonstrated signs of hemolysis. Quantitative determination of cardiac troponin T (cTnT; Stat T, Roche Diagnostics, Indianapolis, Ind) was measured on a Roche Elecsys 1010 platform. The 99th percentile for normal subjects is 0.01 ng/mL, whereas the cutoff point providing 10% coefficient of variation with this assay is 0.03 ng/mL, thus representing the conventional upper limit of normal for this assay.

N-terminal pro-brain natriuretic peptide (NT-proBNP) levels were measured with an electrochemiluminescence sandwich immunoasay (Elecsys ProBNP, Roche Diagnostics) with the Roche 2010 system. For subjects <=75 years of age, the upper limit of normal is considered 125 pg/mL. Ischemia-modified albumin (Inverness Medical Innovations, Waltham, Mass) was measured by the albumin cobalt binding test on a Roche Hitachi 911 platform. We applied >95 U/mL (97.5th percentile of healthy patients) as the upper limit of normal. In addition, serum sodium was also measured.

Statistical Analysis

Data for cTnT and NT-proBNP are presented as medians with interquartile range (IQR). Data for all other variables are presented as mean±SD. A paired Student t test was used to compare changes before and after the marathon. Pearson and Spearman correlation coefficients were calculated as standard. In order to better understand the relationship of post-race NT-proBNP and cTnT concentrations with structural abnormalities on echocardiography, we performed univariable and multivariable logistic regression analyses. For the evaluation of NT-proBNP, a log-transformed NT-proBNP in the highest tertile was used as the dependent variable. Covariates examined for inclusion in the multivariable models of NT-proBNP and structural abnormalities were age, E' lateral, and A' lateral. To examine the relationship between cTnT and RV strain, cTnT was log transformed and used as the dependent variable in a manner similar to NT-proBNP, and the covariates age and strain at the apex and mid-ventricle were examined. Multivariate statistical analyses were performed with the use of SPSS software (SPSS Inc, Chicago, IL). Odds ratios (ORs) with 95% confidence intervals (CIs) were generated. Runners were stratified into 3 groups according to training mileage: group A, ≤35 miles/wk; group B, 36 to 45 miles/wk; and group C, >45 miles/wk. Parameters of interest were compared by using a 1-way analysis of variance (ANOVA). If the ANOVA showed an overall difference, post hoc comparisons were performed with a Student t test. Comparisons between biomarker concentrations before and after the race were performed with nonparametric tests, whereas differences in post-race values across the 3 training groups were compared with the Kruskal-Wallis test. A 2-sided probability value of <0.05 was considered significant.

The authors had full access to and take responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Baseline Parameters

The participants included 41 men and 19 women (Table 1) with an average age of 41 years (range 21 to 65). The mean training mileage was 42±9 miles/wk, and the average finish time was approximately 4 hours (4 hours 5 minutes, range 2 hours 55 minutes to 5 hours 55 minutes). All runners demonstrated weight loss (158±26 versus 155±26 lb, P<0.001). Heart rate increased (61±12 versus 101±15 bpm, P<0.001) and systolic blood pressure decreased (114±12 versus 101±15 mm Hg, P<0.001) after the marathon. No runner required medical attention.

Echocardiography

At baseline, all echocardiographic indices, including chamber and wall dimensions, were within normal limits (Table 1). The time from cessation of running to acquisition of echocardiographic images was similar among all runners (20 minutes) and independent of training status or finish time. There were no significant changes in left atrial dimensions, left atrial area, or right atrial area before versus after the marathon. LV and RV size were normal at baseline (Table 2). Although LV dimensions (not shown), volumes, and ejection fraction remained unchanged, RV dimensions and area increased, and the RV percentage area change decreased (41±7% versus 33±7%, P<0.001). Although heart rates were increased after the marathon, we did not observe fusion of E and A waves either by pulsed-annular Doppler or by...
TABLE 1. Baseline Parameters Among the Amateur Study Participants

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>41±11</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>41 (68)</td>
</tr>
<tr>
<td>Female</td>
<td>19 (32)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>23±3</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>61±12</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>114±12</td>
</tr>
<tr>
<td>Diastolic</td>
<td>69±8</td>
</tr>
<tr>
<td>Average training mileage, miles/wk</td>
<td>42±9</td>
</tr>
<tr>
<td>Left atrial size, mm</td>
<td>34±4</td>
</tr>
<tr>
<td>LV posterior wall thickness, mm</td>
<td>10±1</td>
</tr>
<tr>
<td>LV diastolic dimensions, mm</td>
<td>47±5</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>60±6</td>
</tr>
<tr>
<td>Indexed LV mass, g/m²</td>
<td>104±16</td>
</tr>
<tr>
<td>PASP, mm Hg</td>
<td>20±3</td>
</tr>
<tr>
<td>mPAP, mm Hg</td>
<td>12±3</td>
</tr>
<tr>
<td>RV diastolic dimensions, mm</td>
<td>35±4</td>
</tr>
<tr>
<td>RV fractional area change, %</td>
<td>41±7</td>
</tr>
</tbody>
</table>

There was an increase in both the peak pulmonary artery systolic pressure (PASP) (20±3 versus 41±7 mmHg, P<0.001, n=29/60) and mPAP (12±3 versus 25±6, P<0.001, n=59/60). This increase in mPAP was positively associated with the increase in cTnT (r=0.07, P<0.001) and inversely associated with the average training mileage (r=−0.71, P<0.001). Despite the increase in heart rate, there was a reduction in TD-derived indices of RV systolic function (Table 2). The RV endocardial velocity and e decreased, whereas the SR remained unchanged. The reduction in RV endocardial velocities and strain correlated with the increase in cTnT (RV basal e, r=−0.68; mid e, r=−0.70; and apical e, r=−0.72; P<0.001 for all).

Runners were stratified according to training mileage (Table 3). At baseline, runners who had higher training mileage had increased LV dimensions, reduced ejection fraction, and improved diastolic indices (E’ before the race for those who trained >45 miles/wk 12±2 cm·s⁻¹ versus 10±2 cm·s⁻¹ for those who trained ≤35 miles/wk, P<0.001). Upon completion of the marathon, those participants who averaged ≤35 miles/wk had the greatest increases in PASP, mPAP, RV dimensions, and RV area and the greatest changes in LV diastolic and RV systolic function (Figure 1). Overall, there were no associations between the alterations in PASP, mPAP, RV dimensions, RV area, LV diastolic and RV systolic function, and subject’s age, change in body weight, or gender.

Biochemical Markers

cTnT
Serum cTnT concentrations were <0.01 ng/mL in all participants at baseline. After the race, the median cTnT value was 0.022 ng/mL (IQR 0.03 to 0.06 ng/mL; P<0.001 for difference from before the race), with a post-race range of cTnT values from <0.01 to 0.82 ng/mL. An increase in cTnT >0.01 ng/mL was recorded in 38 subjects (63%), whereas 28 subjects (47%) had cTnT values ≥0.03 ng/mL, and 8 subjects had post-race cTnT values ≥0.10 ng/mL.

With cTnT release after completion of the marathon considered as a function of training adequacy, those participants who averaged ≤35 miles/wk in training had the greatest increase in cTnT (P<0.001 across groups; Figure 2) after the race. Among those training ≤35 miles/wk, the median post-race cTnT value was 0.09 ng/mL, whereas all subjects had a post-race cTnT ≥0.03 ng/mL, with a range from 0.03 to 0.82 ng/mL. Also, 50% of subjects in this category had a post-race cTnT >0.10 ng/mL, representing all subjects with cTnT at or above this magnitude in the study. Among those training 36 to 45 miles/wk, there was significantly lower release of cTnT, with a median value of 0.02 ng/mL (P=0.008 versus baseline) and a range of <0.01 to 0.07 ng/mL. Of these subjects, 45% had a post-race cTnT ≥0.03 ng/mL, and none were >0.10 ng/mL. Finally, among those training >45 miles/wk, no appreciable change in median cTnT from baseline was noted (median <0.01; P=0.87 compared with baseline), with only 2 subjects (8.7%) demonstrating post-race cTnT values ≥0.03 ng/mL.

NT-proBNP
At baseline, overall median NT-proBNP concentrations were 106 pg/mL (IQR 65 to 175 pg/mL); after the marathon, NT-proBNP levels were significantly higher (182 pg/mL, IQR 112 to 219 pg/mL, P<0.001 between before and after the race), with a post-race range of NT-proBNP concentrations from 14 to 506 pg/mL. Overall, 54% of participants had levels of NT-proBNP above the upper limit of normal for exclusion of heart failure. Females were more likely than males to show a post-race increase in NT-proBNP concentrations (63% versus 17%, P=0.01), and the increase in NT-proBNP was independently associated with the attenuation in LV early diastolic filling (E’ lateral, OR 8.4, 95% CI 1.3 to 56.0, P=0.026).

In a fashion similar to cTnT, those participants who averaged ≤35 miles/wk had the greatest increase in NT-proBNP (P=0.03 across all 3 training groups) (Figure 3) after the race. Among participants who trained ≤35 miles/wk, the median post-race NT-proBNP value was 182 pg/mL (IQR 112 to 219 pg/mL, P<0.001 compared with before the race), with an overall range of 82 to 506 pg/mL; of this group, 75% had a post-race NT-proBNP >125 pg/mL. Among those...
training 36 to 45 miles/wk, there was lower release of NT-proBNP after the race, with a median value of 94 pg/mL (IQR 56 to 211 pg/mL; P=0.004 versus baseline) and an overall range of 14 to 271 pg/mL after the race. Of these subjects, 45% had a post-race NT-proBNP >125 pg/mL. On multivariate analysis, the increase in cTnT was independently associated with a reduction in RV contractility (RV mid ε, OR 14.0, 95% CI 1.37 to 142.8, P=0.026). Finally, among those training >45 miles/wk, median NT-proBNP concentrations were similarly lower at 106 pg/mL (IQR 64 to 175 pg/mL; P<0.001 versus baseline), with an overall range of 28 to 385 pg/mL and 48% of subjects >125 pg/mL after the race.

Other Biomarkers
Levels of ischemia-modified albumin decreased from baseline (94±6 before the race versus 73±10 U/mL after the race, P<0.001), whereas serum sodium was unchanged (139±2 versus 139±3 mEq/L, P=0.76).

Discussion
Although prior studies involving endurance athletes after exercise have demonstrated biochemical evidence of possible cardiac injury, none have correlated these findings and the risk factors for the development of such abnormalities are unknown. In recreational athletes completing a marathon, we have suggested and correlated echocardiographic and biochemical evidence of cardiac dysfunction and injury. With prolonged exercise, we found increased PAPs, increased RV dimensions, and decreased RV function (which correlated with release of cTnT), as well as alterations in LV diastolic function (which correlated with an increase in NT-proBNP values). Most strikingly, these changes were strongly influenced by the level of preparation undertaken by these amateur athletes, such that the majority of the most marked abnormalities in cardiac structure or function as well as cardiac biomarker changes were seen in those athletes training ≤35 miles/wk before the marathon.

Similar effort-related changes have been documented invasively among other groups of athletes performing shorter-term higher-intensity exercise, with the magnitude of the increase being related to the intensity of the exercise. Moderately strenuous cycling for 1 hour among trained competitive athletes was associated with an increase in pulmonary
TABLE 3. Stratification of Baseline and Postmarathon Variables According to Average Training Mileage in the 4 Months Before the Marathon

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A ≤35 miles/wk (n=17)</th>
<th>Group B 36 to 45 miles/wk (n=20)</th>
<th>Group C &gt;45 miles/wk (n=23)</th>
<th>Overall</th>
<th>A vs B</th>
<th>A vs C</th>
<th>B vs C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average training, miles/wk</td>
<td>29±6</td>
<td>43±3</td>
<td>51±2</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Finishing time, min</td>
<td>268±39</td>
<td>245±41</td>
<td>225±29</td>
<td>0.03</td>
<td>0.16</td>
<td>0.19</td>
<td>0.009</td>
</tr>
<tr>
<td>Age, y</td>
<td>40±13</td>
<td>41±11</td>
<td>40±10</td>
<td>0.83</td>
<td>0.55</td>
<td>0.83</td>
<td>0.67</td>
</tr>
<tr>
<td>Male gender, %</td>
<td>59%</td>
<td>70%</td>
<td>74%</td>
<td>0.80</td>
<td>0.29</td>
<td>0.35</td>
<td>0.68</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>101±16</td>
<td>99±20</td>
<td>103±10</td>
<td>0.66</td>
<td>0.53</td>
<td>0.87</td>
<td>0.39</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>115±10</td>
<td>115±12</td>
<td>113±13</td>
<td>0.88</td>
<td>0.94</td>
<td>0.65</td>
<td>0.68</td>
</tr>
<tr>
<td>NT-proBNP, pg/mL, median (IQR)</td>
<td>64 (25–77)</td>
<td>60 (30–81)</td>
<td>63 (19–85)</td>
<td>0.91</td>
<td>0.71</td>
<td>0.95</td>
<td>0.72</td>
</tr>
<tr>
<td>cTnT, ng/mL, median (IQR)</td>
<td>182 (112–219)</td>
<td>94 (56–211)</td>
<td>106 (64–175)</td>
<td>0.03</td>
<td>0.008</td>
<td>0.003</td>
<td>0.84</td>
</tr>
<tr>
<td>RV diastolic dimensions, mm</td>
<td>45±4</td>
<td>46±6</td>
<td>50±4</td>
<td>&lt;0.001</td>
<td>0.31</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>64±6</td>
<td>58±4</td>
<td>55±5</td>
<td>&lt;0.001</td>
<td>0.009</td>
<td>&lt;0.001</td>
<td>0.01</td>
</tr>
<tr>
<td>TD-derived E’ lateral, cm · s⁻¹</td>
<td>10±2</td>
<td>11±2</td>
<td>12±2</td>
<td>0.005</td>
<td>0.08</td>
<td>0.001</td>
<td>0.10</td>
</tr>
<tr>
<td>% Decrease E’</td>
<td>10±2</td>
<td>9±2</td>
<td>10±2</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.05</td>
</tr>
<tr>
<td>TD-derived A’ lateral, cm · s⁻¹</td>
<td>23±10</td>
<td>23±10</td>
<td>19±12</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.26</td>
</tr>
<tr>
<td>RV diastolic dimensions, mm</td>
<td>35±4</td>
<td>35±4</td>
<td>36±3</td>
<td>0.28</td>
<td>0.70</td>
<td>0.29</td>
<td>0.12</td>
</tr>
<tr>
<td>RV area change, %</td>
<td>45±8</td>
<td>41±5</td>
<td>38±4</td>
<td>0.001</td>
<td>0.01</td>
<td>0.001</td>
<td>0.06</td>
</tr>
<tr>
<td>Peak PASP (n=29), mm Hg</td>
<td>20±4</td>
<td>21±3</td>
<td>20±2</td>
<td>0.81</td>
<td>0.53</td>
<td>0.77</td>
<td>0.60</td>
</tr>
<tr>
<td>Mean PASP (n=59), mm Hg</td>
<td>45±5</td>
<td>37±5</td>
<td>32±4</td>
<td>&lt;0.001</td>
<td>0.001</td>
<td>&lt;0.001</td>
<td>0.05</td>
</tr>
<tr>
<td>Mid RV e, %</td>
<td>13±3</td>
<td>12±3</td>
<td>12±3</td>
<td>0.82</td>
<td>0.54</td>
<td>0.70</td>
<td>0.78</td>
</tr>
<tr>
<td>After</td>
<td>35±7</td>
<td>23±5</td>
<td>18±4</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.01</td>
</tr>
<tr>
<td>Mid RV e, %</td>
<td>29±6</td>
<td>26±4</td>
<td>28±7</td>
<td>0.39</td>
<td>0.17</td>
<td>0.45</td>
<td>0.48</td>
</tr>
<tr>
<td>After</td>
<td>16±5</td>
<td>22±4</td>
<td>25±4</td>
<td>&lt;0.001</td>
<td>0.003</td>
<td>&lt;0.001</td>
<td>0.05</td>
</tr>
</tbody>
</table>

P values for comparisons between groups.
capillary wedge pressure from 8 to 15 mm Hg and mPAP from 14 to 26 mm Hg, whereas, among a group of ultra-
marathon runners performing at high altitude, transiently increased PAP with RV dilatation and RV dysfunction and symptoms were documented without an overall change in a less-sensitive troponin assay. Our data suggest that the increase in pulmonary pressures is likely multifactorial, occurring in association with impaired LV relaxation but also
perhaps reflecting an intrinsic increase in pulmonary vascular resistance.

We excluded subjects with a history of cardiovascular disease. In all participants, baseline echocardiographic indices were normal, making the presence of occult hypertrophic cardiomyopathy, arrhythmogenic right ventricular dysplasia, myocarditis, and aortic stenosis unlikely. Because of the combination of a low cardiac risk group and a lack of evidence of LV wall motion abnormalities suggestive of ischemia in our study and in previous studies, it is unlikely that the cTnT elevation is due to epicardial coronary ischemia. Furthermore, the average finish time for our slowest cohort was 4 hours and 28 minutes, the minimum period required for myofibril degradation and release of this structural protein. The pattern of cTnT release is different than that expected with ischemic injury; therefore, alternative reasons for the elevation in troponin must be considered. In addition to bound troponin, there is also a free cytoplasmic component comprising approximately 8% of cTnT. Release of this cytoplasmic cTnT may explain the early rise of this marker after myocyte damage. Why reversible leakage occurs is unclear, but this leakage may involve oxidative stress, hypoxia, or transient ischemia. In acute pulmonary embolism, similar changes occur with RV dilatation, dysfunction, mild elevations in pulmonary pressure, and increased troponin without obvious ischemia. Importantly, the parallel changes in both echocardiography and the enhanced specificity of the troponin assay employed suggest that the source of cTnT in our subjects is probably of cardiac rather than of skeletal muscle origin.

In addition to changes in cTnT, we noted significant post-race changes in NT-proBNP in our subjects, which we believe reflect changes in diastolic filling after strenuous exercise. Although one suggestion may be that the elevation in natriuretic peptide concentrations in athletes might reflect a physiological response to increased natriuresis, the lack of change in serum sodium in our study subjects makes this unlikely. Notably, post-race values of NT-proBNP were typically higher than those used for the exclusion of heart failure, and like cTnT levels were strongly influenced by prerace preparation. Although elevation of natriuretic peptide concentrations after strenuous exercise was demonstrated previously, to our knowledge this is the first study to correlate changes in NT-proBNP to the development of abnormalities on echocardiography and to demonstrate differences in release magnitude as a function of an athlete’s training.

Our study has several limitations. Although pulsed-Doppler and TD are purported to be less sensitive to alterations in loading conditions and more sensitive to changes in systolic and diastolic ventricular function, they are not load insensitive. A contribution of the increased running time (mean 43 minutes) and more prolonged exercise to the observed increase in biomarkers and echocardiographic abnormalities among the less-prepared cohort cannot be excluded. However, similar to work by others, we found that the association between marathon finish time and the increase in troponin was poor ($r=0.16$). We did not perform follow-up studies to determine the chronology of the changes in cardiac structure and function. However, our group previously reported follow-up data on a similar cohort of subjects participating in the 2003 Boston Marathon. In that smaller study, some similar, albeit smaller and statistically nonsignificant, changes involving the RV and the LV were detected immediately after completion of the marathon. Follow-up echocardiograms in this cohort, obtained within 3 to 4 weeks of completion of the marathon, demonstrated that indices of

![Figure 2. Baseline and postmarathon cTnT in groups stratified according to training mileage. At baseline, cTnT was undetectable in any of the groups. After completion of a marathon, a graded cTnT release effect was observed as a function of extent of training, with athletes who trained less (≤35 miles/wk before the race) demonstrating significantly greater increases in post-race cTnT, compared with athletes who trained with a higher weekly mileage.](image1)

![Figure 3. Baseline and postmarathon NT-proBNP values in groups stratified according to training mileage. There was no difference among groups with different levels of training at baseline. Levels of NT-proBNP were increased in all subgroups with prolonged exercise; however, these increases were exaggerated in athletes who trained less (<35 miles/wk before the race).](image2)
systolic function had normalized, whereas changes in indices of diastolic function persisted. Early recovery and the transient nature of the echocardiographic changes involving both the RV and LV have also been reported among other cohorts undergoing more strenuous endurance pursuits.17,31 We also did not perform serial measurement of serum biomarkers after the marathon; however, among marathon runners with a similar mean finish time to our cohort, Scharbagh et al measured cTnT and cardiac troponin I before the marathon and at 15 minutes, 3 hours, and 24 hours after participation.21 They found that cTnT, measured using an identical assay to that used in our study, unlike cardiac troponin I, was highest at 15 minutes after completion of a marathon run and declined thereafter to undetectable levels at 24 hours. Indeed, numerous studies, like this one, have previously shown that troponin T concentrations normalize by 24 hours after endurance sports.32–34 We did not individually estimate the RA pressure, but instead we uniformly added 10 mm Hg. Although this may have overestimated the RV systolic pressure in some subjects, an overall increase would still have been observed. Also, the increase in the estimated mPAP lends further support to the RV systolic pressure data.

To our knowledge, our study is the first to successfully correlate participation in endurance sports with biochemical and echocardiographic evidence of cardiac injury and dysfunction and to demonstrate a strong relationship between extent of training and the presence and magnitude of such cardiovascular abnormalities after marathon running. However, there are no data to suggest that there are long-term sequelae to the increase in biomarkers and echocardiographic evidence of injury in this setting. In contrast, many studies suggest that endurance exercise is associated with a reduction in cardiovascular risk and an increased life expectancy.7,8 Our study does suggest that, to protect against elevations in cardiac biomarkers and echocardiographic evidence of cardiac dysfunction associated with endurance exercise, appropriate preparation is important.

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Disclosures

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References

13. Sohn DW, Chai IH, Lee DJ, Kim HC, Kim HS, Oh BH, Lee MM, Park YB, Choi YS, Seo JD, Lee YW. Assessment of mitral annulus velocity by Doppler tissue imaging in the evaluation of left ventricular diastolic function. J Am Coll Cardiol. 1997;30:474–480.


**CLINICAL PERSPECTIVE**

Increased cardiac biomarkers and alterations in cardiac function are well-described sequelae to participation in endurance sports. However, although multiple studies have independently demonstrated these alterations, none have linked these abnormalities. In fact, to date, convincing associations between the two have not been demonstrated, and risk factors for the development of signs of myocardial damage or dysfunction are unknown. Therefore, we designed this study to determine the associations between the observed transient cardiac dysfunction and injury among amateur participants in endurance sports and to elicit the factors associated with the development of this dysfunction and injury. We found that the extent and the degree of the transient cardiac injury and dysfunction were significantly influenced by the degree of preparation and training. Temporary changes indicating heart stress occurred in marathon runners who trained less than 35 miles per week in the months before the event. However, these changes were milder or absent in those who ran more than 45 miles per week. The protection afforded by training was independent of age and gender. Notably, however, no data suggest that there are long-term sequelae to the biomarker and echocardiographic changes in this setting, and indeed, in contrast, many studies suggest that endurance exercise is associated with a reduction in cardiovascular risk and an increased life expectancy. Our study does suggest that, to protect against elevations in cardiac biomarkers and echocardiographic evidence of cardiac dysfunction associated with endurance exercise, appropriate preparation is important.
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