



RIGHT VENTRICULAR DYSFUNCTION AND INJURY FOLLOWING MARATHON RUNNING: CORRELATING BIOMARKERS WITH CARDIAC MRI

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ABSTRACT

Background: Although previous studies including endurance athletes following marathon running have demonstrated biochemical evidence of cardiac injury and have correlated these findings with echocardiographic evidence of cardiac dysfunction, in particular the right ventricle, a study of marathon athletes incorporating biomarkers, echocardiography and cardiac MRI (CMR) has not been performed to date.

Objective: To demonstrate the cardiac changes associated with participation in a marathon using serial cardiac biomarkers, echocardiography and CMR.

Results: Fourteen participants (mean age 33 ± 6 years; 8 males) completed the full marathon. Serum myoglobin, creatine kinase and troponin T were elevated in all athletes post-race. There was a strong linear correlation between right ventricular (RV) fractional area change (FAC) as assessed by echocardiography and RV ejection fraction as assessed by CMR ($r=0.96$) post marathon. RV function, using echocardiography, transiently decreased from pre- to post-race (RV FAC $43\pm 5\%$ vs. $34\pm 7\%$, $p<0.05$). There were also post-race changes in LV and RV diastolic filling. While RV systolic changes were transient, both LV and RV diastolic abnormalities persisted up to one week post marathon. We did not find evidence of delayed enhancement of the LV myocardium on CMR suggesting that the increase in cardiac biomarkers post-marathon is not due to myocardial necrosis.

Conclusion: Right ventricular systolic dysfunction transiently occurs post marathon, and has been validated for the first time by CMR. The increase in cardiac troponin following marathon running is due to cytosolic release of the biomarker, and not due to true breakdown of the myocyte as confirmed by delayed enhancement CMR.



INTRODUCTION

Marathon running, involving the participation of both amateur and elite athletes, has increased in popularity over the past decade. Regular and extensive endurance training over the long term, leads to increased left ventricular (LV) chamber size, wall thickness and mass, a condition known as “athlete’s heart”.¹ As opposed to this chronic remodeling process, the acute effects of strenuous exercise on cardiac function, in particular the right ventricle (RV), is a subject of recent interest. Multiple studies have demonstrated echocardiographic evidence of RV systolic and diastolic abnormalities after endurance sports.²⁻⁴ However, quantitative assessment of the RV using echocardiography, due to its complex geometry, is challenging.⁵

Transient changes in cardiac function following marathon running has been correlated with biochemical evidence of cardiac injury, in particular serum biomarkers including myoglobin, creatine kinase (CK) and cardiac troponin T (cTnT).⁶⁻⁸ Previous studies have reported variable rates of elevated cardiac markers, in particular cTnT, in athletes following a number of endurance sports.⁹⁻¹³ Although the mechanism of elevation of cTnT remains unclear, it has been postulated that it may be either due to true myocardial necrosis or increased permeability of cTnT from the cytoplasmic pool.¹⁴⁻¹⁶ The use of cardiac magnetic resonance imaging (CMR), following administration of gadolinium, as a noninvasive method of delineating myocardial necrosis would be able to address this pathophysiologic dilemma.¹⁷⁻¹⁹



Cardiac magnetic resonance imaging, by virtue of its high spatial and temporal resolution, can perform accurate measurements of both LV and RV mass, volume and ejection fraction.²⁰⁻²³ Only a few CMR studies have examined the LV and RV structure and function in endurance athletes,²⁴⁻²⁷ and little is known about its utility following marathon running. No CMR study to date has assessed the response of the RV to endurance exercise in this patient population.

The aim of the current study was two-fold; i) To ascertain the extent and severity of the changes in cardiac function after completion of a full marathon, utilizing serial cardiac biomarkers, echocardiography and CMR; ii) To demonstrate any associations between the degree of elevation in cardiac biomarkers and the amount of delayed enhancement using CMR in this patient population.



METHODS

PATIENT POPULATION

A prospective study was performed on fourteen amateur healthy volunteers participating in the 2008 Manitoba Marathon. Study subjects were recruited and written informed consent was obtained after local institutional board approval from the University of Manitoba. Individuals between the ages of 18 and 40, participating in the marathon (26.2 miles), were included. Patients with preexisting cardiovascular risk factors including diabetes, hypertension, smoking, elevated lipids and a family history of premature coronary artery disease were excluded. Patients with any contraindications to undergo a CMR were also excluded. Height, weight, heart rate and blood pressure measurements were obtained at baseline and immediately following completion of the marathon. Data on training regimens was also collected.

BIOCHEMICAL MARKERS

Serum levels of myoglobin, CK and cTnT were evaluated at four separate time points: i) baseline; ii) immediately following the race; iii) at the time of CMR ; iv) and one week post marathon. Blood was collected into tubes containing EDTA, separated into serum, and immediately placed on ice. The specimens were subsequently frozen at -70°C until analyzed. Myoglobin and CK levels were determined using a Roche™ Elecsys analyzer and a Roche™ 917 analyzer respectively. A four-fold increase in either myoglobin or CK levels, as compared to baseline, was considered to be elevated. Quantitative determinations of cTnT levels were performed using a third generation Roche Elecsys



assay. The 99th percentile for normal subjects for cTnT is 0.01 µg/L, representing the conventional upper limit of normal for this assay.²⁸

CARDIAC IMAGING: ECHOCARDIOGRAPHY AND CMR

All patients underwent a baseline transthoracic echocardiographic (TTE) study one week prior to the marathon, immediately after completion of the race, and one week after the marathon. Parasternal and apical views were obtained using a standard echocardiography machine (GE Vivid 7, Milwaukee, IL, USA) with a multifrequency transducer and tissue Doppler capability. Standard 2-dimensional images, M-mode, spectral and color Doppler, and tissue Doppler imaging (TDI) were performed. A single observer (N.M.), blinded to the clinical data, analyzed the echocardiographic images offline.

LV interventricular septal thickness (IVS), posterior wall thickness (PWT), mass, cavity dimensions and volumes, and left atrial (LA) size indexed to body surface area were determined from 2-dimensional images in accordance with the American Society of Echocardiography (ASE) guidelines.²⁹ RV cavity dimensions, RV fractional area change (FAC) and tricuspid annular plane systolic excursion (TAPSE) were determined. Continuous-wave Doppler was used to measure the peak velocity across the tricuspid valve in the apical 4-chamber or right ventricular inflow view, and the maximal peak pressure gradient was estimated using the simplified Bernoulli equation to calculate the pulmonary artery systolic pressure (PASP).³⁰ The ratio of the mitral regurgitant jet to the left atrial cavity was measured with 2-dimensional color flow Doppler imaging as a



qualitative index of the severity of mitral regurgitation (mild=1; moderate=2; moderate to severe=3; and severe=4).³¹

LV diastolic function was assessed using both conventional and novel diastolic parameters. Transmitral LV filling velocity at the tips of the mitral valve leaflets was obtained from the apical 4-chamber view using pulsed wave Doppler echocardiography. The transmitral LV filling signal was traced manually to obtain the following variables: peak early (E) and late (A) transmitral velocities, and E/A ratio.³²

Tissue-Doppler derived indices were recorded at the septal and lateral mitral annulus of the LV and the lateral tricuspid annulus of the RV. A sample volume of 6 x 6 mm was positioned along the basal septal and lateral walls of the LV and basal lateral wall of the RV in the apical 4 chamber view. These indices included peak systolic (S'), early (E') and late diastolic (A') velocities. The dimensionless index of lateral and septal E/E' was calculated. For peak RV systolic strain using tissue Doppler, the sample volume was placed along the base of the lateral tricuspid annulus in the apical 4 chamber view. A strain length of 12 mm, defined as the greatest value on the strain curve, was used to calculate strain.^{32,33} Regional analysis of endocardial velocities and strain was performed offline using dedicated computer software (EchoPac, Version 7.01, General Electric).

Cardiac magnetic resonance imaging was performed on all study participants at baseline and within three days after marathon completion using a 1.5 T scanner (Avanto, Siemens, Erlangen, Germany). Transverse images were acquired using an inversion recovery (IR)



prepared dark blood HASTE sequence (TR 600 ms, TE 26 ms, 6 mm slice thickness, 1.8 mm interslice gap, matrix 256 X 104). Cine bright-blood images in the 4 chamber long axis and 2 chamber long axis planes were performed using a breath-hold balanced steady-state free precession (b-SSFP) sequence (TrueFISP, TR 42 ms, TE 1.2 ms, FA 70°, 6 mm slice thickness, matrix 192 × 174). Cine b-SSFP short-axis images then encompassed the entire LV from the base to the apex (stack of 10 sequential short-axis slices; TR 64 ms, TE 1 ms, FA 80°, 8 mm slice thickness, 1.6 mm interslice gap, matrix 192 × 132) to obtain a LV ejection fraction (LVEF). For LV mass calculation, the myocardial volume was multiplied by the myocardial specific gravity of 1.05 g/cm³.³⁴ For RV mass calculation, only the RV free wall was used, excluding the interventricular septum as previously described.³⁵

To evaluate for myocardial edema, dark blood T2-weighted turbo spin echo short axis images were obtained (TR 1800-2100 ms, TE 74 ms, 8 mm slice thickness, 4 mm interslice gap, matrix 256 X 175). Late gadolinium enhancement images were obtained after 10 minutes of 0.2 mmol/kg injection of Gadolinium (Gd-DTPA, Magnevist, Schering, Germany) using a T1-weighted IR-prepared multislice TrueFISP sequence with magnitude and phase sensitive reconstruction. Images were acquired sequentially in the short axis, followed by horizontal and vertical long axis images (TR 700 ms, TE 1.0 ms, FA 40°, 8 mm slice thickness, 1.6 mm interslice gap, matrix 192 × 144). A single observer (D.S.J.), blinded to the clinical data, analyzed the CMR images offline. Quantitative analysis was performed using dedicated computer software (ARGUS, Siemens).



STATISTICAL ANALYSIS

The data are summarized as mean \pm SD, number (percentage), or median and interquartile range (IQR). Paired t-tests was used to compare continuous variables. Chi-square and Fischer exact tests were applied to compare categorical variables. One-way analysis of variance (nonparametric with Dunn testing) was used to compare baseline, immediate, and 1-week post-race cardiac biomarker and echocardiographic values. Linear regression values were calculated using Pearson's correlation coefficient. A p value less than 0.05 was considered statistically significant. The Statistical Analysis System 8.01 (SAS Institute, Cary, NC) was used to perform the analysis.



RESULTS

BASELINE CHARACTERISTICS

A total of 762 participants (545 males, 217 females) completed the 2008 Manitoba Marathon with a mean finishing time of 254 ± 43 minutes. Our study population included 14 patients (mean age 33 ± 6 years), of which 8 were males and 6 were females. The baseline characteristics pre- and post- race are listed in table 1. None of the participants reported any significant medical co-morbidities, and they were all free of cardiovascular risk factors. The majority of patients ($n=10$) were moderately trained, having run less than 40 miles per week (mean 26 ± 8 miles) and the remaining four were highly trained (mean 53 ± 12 miles). The mean time to completion of the full marathon was 245 ± 68 minutes. The subjects' weights, heights and BMI did not change significantly following the marathon as compared to baseline (Table 1). As compared to baseline, the heart rate increased and the systolic and diastolic blood pressures decreased following the marathon. These parameters had recovered to baseline values at one week follow-up.

BIOCHEMICAL MARKERS

Serum myoglobin and CK levels were all within normal range at baseline (Table 2). After marathon completion, myoglobin levels increased significantly from a median of 34 mg/L (IQR 21-97 mg/L) at baseline to 703 mg/L (IQR 446-2038 mg/L) immediately after the race. Similarly, CK levels increased significantly from 160 U/L (IQR 127-209 U/L) at baseline to 518 U/L (IQR 391-1714 U/L) following completion of the race. Both myoglobin and CK levels normalized at one week followup in all patients.



Serum levels of cTnT were $< 0.01 \mu\text{g/L}$ in all participants at baseline (Table 2). Immediately following completion of the full marathon, all patients demonstrated an elevated serum cTnT with a median value of $0.31 \mu\text{g/L}$ (IQR $0.22\text{-}0.68 \mu\text{g/L}$), above the 99% reference limit. At the time of CMR imaging post marathon, all patients demonstrated persistent elevations in serum cTnT levels with a median value of $0.27 \mu\text{g/L}$ (IQR $0.21\text{-}0.58 \mu\text{g/L}$). At one week post marathon, the cTnT levels returned to normal.

ECHOCARDIOGRAPHY

At baseline, all echocardiographic indices, including LV and RV chamber size, volumes, and systolic function were within normal limits (Table 3). Left ventricular dimensions, volumes and ejection fraction remained unchanged between premarathon and postmarathon time points. As compared to baseline, RV end diastolic diameter, RV end diastolic area, and RV end systolic area increased post marathon and the RV fractional area change (FAC) decreased significantly ($43\pm 5\%$ versus $34\pm 7\%$, $p < 0.05$) (Table 3, Figure 1). The decline in RV FAC improved at one week follow up. A similar trend was observed in TAPSE which decreased significantly ($2.6\pm 0.5 \text{ mm}$ to $1.6\pm 0.4 \text{ mm}$, $p < 0.05$). While there were no significant change in LA size and volume following completion of the marathon, the RA volume increased significantly ($40\pm 14 \text{ ml}$ to $55\pm 13 \text{ ml}$, $p < 0.05$) (Table 3). There was an increase in peak pulmonary artery systolic pressure (PASP) after the race ($16\pm 4 \text{ mm Hg}$ to $37\pm 3 \text{ mm Hg}$, $p < 0.01$) (Table 4). The degree of mitral regurgitation remained unchanged throughout the course of the study (Table 4).



Both conventional and novel diastolic parameters of the LV and RV are listed in Table 4. There was a reduction in early LV transmitral diastolic filling velocities (0.8 ± 0.2 cm/s vs. 0.6 ± 0.2 cm/s, $p < 0.01$) and an increase in late transmitral filling (0.5 ± 0.1 cm/s vs. 0.6 ± 0.2 cm/s, $p < 0.01$) which resulted in a decrease in the E/A ratio (1.6 ± 0.2 vs. 1.0 ± 0.2 $p < 0.01$) following completion of the race.

There were similar changes in diastolic function as assessed by tissue Doppler imaging, which are less load dependent measures of relaxation as compared to conventional measures of transmitral filling (Table 4).³² Early LV mitral annular velocity (E') decreased while late mitral annular velocity (A') increased both at the septal and lateral annuli of the left ventricle following the race. At one week follow-up, the E' and A' were persistently abnormal as compared to baseline. The E/E' ratio of the lateral and septal annuli remained within the normal range throughout the course of the study. The LV lateral and septal mitral annular systolic velocities (S') were not significantly different pre- and post- race (Table 4, Figure 2). Although the conventional LV diastolic parameters including E, A and E/A ratio recovered one week post race in all athletes, the TDI parameters (E' and A') did not completely normalize (Table 4, Figure 2).

The RV diastolic parameters including S', E', and A' decreased immediately following the race and remained abnormal at one week of followup (Table 4, Figure 2). Right ventricular strain at the base was reduced post-race ($16 \pm 3\%$ to $11 \pm 2\%$, $p < 0.01$). These changes in RV diastolic indices using TDI did not completely recover at one week follow up.



CARDIAC MAGNETIC RESONANCE IMAGING

All 14 participants underwent CMR at baseline and within 3 days of completing the marathon, during which time all patients demonstrated elevated serum cTnT levels with a median value of 0.27 $\mu\text{g/L}$ (IQR 0.21-0.58 $\mu\text{g/L}$). Cardiac magnetic resonance imaging obtained after marathon completion revealed normal LV structure and function (Table 5). The LV mass was increased at $111\pm 13 \text{ g/m}^2$ (normal range: $80\pm 13 \text{ g/m}^2$)^{24,35-36}. Consistent with the echocardiographic findings, although the LA volumes were within normal range post-race on CMR, the RA volume was increased at $51\pm 11 \text{ ml}$ (Table 5). RV structure and function were abnormal on CMR following the marathon (Table 5), similar to the echocardiographic findings (Table 3). The RV volumes were increased post marathon and the RVEF was reduced at $43\pm 5\%$ compared to $64\pm 8\%$ at baseline (Table 5, Figure 1). There was a strong linear correlation between RV FAC as assessed by echocardiography immediately following the race and RVEF as assessed by CMR ($r=0.96$, $p<0.01$) post marathon (Figure 4). Although all patients demonstrated elevated serum cTnT levels at the time of the CMR, there was no evidence of myocardial edema on T2 imaging nor findings of delayed enhancement of the LV myocardium.



DISCUSSION

Although previous studies involving endurance athletes following marathon running have demonstrated biochemical evidence of cardiac injury and have correlated these findings with transient echocardiographic evidence of ventricular dysfunction,⁶⁻¹³ a study of marathon athletes incorporating biomarkers, echocardiography and CMR has not been performed to date. In the current study, we confirmed previous studies that there is a significant increase in cardiac biomarkers of injury after prolonged exercise,⁹⁻¹³ with 100% of the participants demonstrating positive troponin levels. There was echocardiographic evidence of both LV and RV diastolic dysfunction following completion of the marathon which did not completely normalize at one week follow-up. The RV systolic dysfunction detected by echocardiography post marathon was validated for the first time by CMR. Finally, the absence of delayed enhancement on CMR in this patient population following the marathon confirms that the increase in cTnT observed is not due to myocardial necrosis.

Cardiac biomarkers including myoglobin, CK and cTnT are elevated after strenuous exercise such as marathon running.⁹⁻¹³ This finding is expected, as endurance sports can lead to skeletal muscle degradation, resulting in elevated serum myoglobin and CK levels. There is a wide variation in the proportion of athletes (3-63%) who demonstrate elevated cardiac biomarkers after marathon running.⁹⁻¹³ Although Neilan et al. suggested that amateur athletes with less training prior to a marathon are more likely to experience elevated cardiac biomarkers as compared to those with an extensive training background,⁸ a recent meta-analysis by Shave et al. did not confirm this data.¹² Despite a



wide range of training regimens before the marathon, all of the athletes participating in our study demonstrated significantly abnormal biochemical profiles following completion of the marathon.

In the cascade of myocardial dysfunction observed following a marathon race, diastolic dysfunction is the earliest abnormality detected by echocardiography. Similar to other studies,^{8,38-39} we confirmed that both LV and RV diastolic parameters using conventional Doppler and TDI parameters were significantly attenuated post marathon. The reduction in diastolic function was similar for different segments of both ventricles indicative of global diastolic dysfunction. The TDI indices for both the LV and RV did not recover fully at one week of followup, confirming previous studies.⁸ Potential mechanisms to explain these diastolic abnormalities post race include an intrinsic impairment in biventricular relaxation due to altered intracellular calcium transients, beta adrenergic receptor desensitization, and/or myocyte injury due to increased reactive oxygen species production following a marathon.⁴⁰⁻⁴² It remains to be determined whether these diastolic abnormalities are part of a normal recovery process following intense exertion or whether there are any long term cardiac sequela.

A transient depression in RV systolic function and RV dilation after endurance sports has previously been reported.^{3,4,43} In these studies, the observed changes in RV systolic parameters occurred following completion of exercise of greater duration and intensity in comparison to our heterogeneous cohort of participants competing in a marathon.⁴⁴ The transient RV systolic dysfunction observed in our study was likely due to exercise



induced pulmonary hypertension. The increase in pulmonary arterial systolic pressure detected post-marathon, reflected an increased RV afterload, RV dilatation and subsequent decrease in RV FAC. These pathophysiologic findings are corroborated by previous studies.^{4,8,44} The reduction in TASPE as a surrogate marker of RV systolic dysfunction in our patient population is unique, and has not been previously described.

Despite the utility of echocardiography in delineating RV systolic dysfunction, as reflected by RVEDD, RV FAC and TAPSE, in athletes post marathon, an accurate RVEF assessment is not possible due to the complex geometry of this cardiac chamber.⁵ The increased spatial and temporal resolution of CMR imaging however allows for an accurate assessment of RV morphology and function.¹⁹⁻²² The current study confirmed, for the first time, a decrease in RVEF using CMR in patients following completion of the full marathon, corroborating the echocardiographic changes in RV systolic function.

Gadolinium-enhanced CMR is of additional diagnostic value in estimating the extent of cardiac injury and edema in cardiovascular diseases including ischemic heart disease and myocarditis.¹⁷⁻¹⁸ With an in-plane spatial resolution of 1-2 mm, delayed enhancement CMR (DE-CMR) can detect regions of myocardial necrosis that involve less than 1 gram of myocardium, correlating to >2 ng/ml troponin I or >0.1 ug/L cTnT release.^{45,46} Our study is the first to use gadolinium-enhanced CMR to examine the effects of marathon running on cardiac function. Despite all athletes demonstrating positive cTnT levels (median value of 0.31 µg/L (IQR 0.22-0.68 ug/L)) at the time of cardiac MRI, there was no evidence of myocardial edema on T2-weighted images nor evidence of delayed



enhancement suggestive of myocardial necrosis. Two postulated mechanisms of elevated troponin values post marathon include either an increase in myocardial injury due to true breakdown of the myocytes or cytosolic release of the biomarker.¹⁴⁻¹⁶ This finding is instrumental in identifying the etiology of abnormal levels of cTnT after extensive physical exertion. Based on the lack of any delayed enhancement on CMR in our study, we can conclusively rule out myocardial necrosis as an explanation for cTnT rise in athletes participating in strenuous exercise such as the marathon.

LIMITATIONS

There are a number of limitations to acknowledge. Our study is limited by a small sample size with a heterogeneous population. The use of 3D echocardiography would provide improved spatial resolution for accurate noninvasive assessment of RV ejection fraction. Serial CMR examinations, performed immediately following race completion and long term follow-up, would be able to address the transient nature of RV systolic dysfunction detected by echocardiography in this patient population. Future studies will entail the use of a larger patient population with baseline and longer term follow-up using CMR for biventricular structural and functional analysis, perfusion, delayed enhancement and potentially diastolic evaluation in the marathon setting.



CONCLUSION

This is the first study to use CMR in validating RV systolic dysfunction following marathon running. Although cardiac biomarkers are frequently elevated following strenuous exertion, in particular cTnT, it is not due to true myocardial necrosis as confirmed by the absence of DE-CMR in our study.



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REFERENCES

- 1) Pluim BM, Zwinderman AH, van der Laarse A and van der Wall EE. The athlete's heart. A meta-analysis of cardiac structure and function. *Circulation* 1999; 100: 336-44.
- 2) Douglas PS, O'Toole ML and Woolard J. Regional wall motion abnormalities after prolonged exercise in the normal left ventricle. *Circulation* 1990; 82: 2108-2114.
- 3) Perrault H, Péronnet F, Lebeau R and Nadeau RA. Echocardiographic assessment of left ventricular performance before and after marathon running. *Am. Heart J.* 1986; 112: 1026-1031
- 4) Neilan TG, Yoerger DM, Douglas PS, Marshall JE, Halpern EF, Lawlor D, Picard MH, Wood MJ. Persistent and reversible cardiac dysfunction among amateur marathon runners. *Eur. Heart J.* 2006; 27(9):1079-84.
- 5) Dávila-Román VG, Guest TM, Tuteur PG, Rowe WJ, Ladenson JH and Jaffe AS. Transient right but not left ventricular dysfunction after strenuous exercise at high altitude. *J. Am. Coll. Cardiol.* 1997; 30:468-73.
- 6) Pellerin D, Sharma R, Elliott P and Veyrat C. Tissue Doppler, strain, and strain rate echocardiography for the assessment of left and right systolic ventricular function. *Heart.* 2008;89 Suppl 3:iii9-17.
- 7) Siegel AJ, Silverman LM and Evans WJ. Elevated skeletal muscle creatine kinase MB isoenzyme levels in marathon runners. *JAMA.* 1983; 250: 2835-2837.



- 8) Adams JE 3rd, Bodor GS, Dávila-Román VG, Delmez JA, Apple FS, Ladenson JH and Jaffe AS. Cardiac troponin I: a marker with high specificity for cardiac injury. *Circulation*. 1993; 88: 101-106
- 9) Neilan TG, Januzzi JL, Lee-Lewandrowski E, Ton-Nu TT, Yoerger DM, Jassal DS, Lewandrowski KB, Siegel AJ, Marshall JE, Douglas PS, Lawlor D, Picard MH and Wood MJ. Myocardial injury and ventricular dysfunction related to training levels among non-elite participants in the Boston marathon. *Circulation*. 2006; 114(22):2325-33.
- 10) Neumayr G, Pfister R, Mitterbauer G, Eibl G and Hoertnagl H. Effect of competitive marathon cycling on plasma N-terminal pro-brain natriuretic peptide and cardiac troponin T in healthy recreational cyclists. *Am. J. Cardiol*. 2005; 96: 732-735.
- 11) Scharhag J, Herrmann M, Urhausen A, Haschke M, Herrmann W and Kindermann W. Independent elevations of N-terminal pro-brain natriuretic peptide and cardiac troponins in endurance athletes after prolonged strenuous exercise. *Am. Heart J*. 2005; 150: 1128-1134.
- 12) Shave RE, Dawson E, Whyte G, George K, Ball D, Gaze DC and Collinson PO. Evidence of exercise-induced cardiac dysfunction and elevated cTnT in separate cohorts competing in an ultra-endurance mountain marathon race. *Int. J. Sports Med*. 2002; 23: 489-494.
- 13) Shave R, George KP, Atkinson G, Hart E, Middleton N, Whyte G, Gaze D and Collinson PO. Exercise-induced cardiac troponin T release: a meta-analysis. *Med. Sci. Sports. Exerc*. 2007; 39(12): 2099-106.



- 14) Urhausen A, Scharhag J, Herrmann M and Kindermann W. Clinical significance of increased cardiac troponins T and I in participants of ultra-endurance events. *Am. J. Cardiol.* 2004; 94: 696-698.
- 15) Neumayr G, Gaenger H, Pfister R, Sturm W, Schwarzacher SP, Eibl G, Mitterbauer G, and Hoertnagl H. Plasma levels of cardiac troponin I after prolonged strenuous endurance exercise. *Am. J. Cardiol.* 2001; 87: 369-371
- 16) Katus HA, Remppis A, Scheffold T, Diederich KW and Kuebler W. Intracellular compartmentation of cardiac troponin T and its release kinetics in patients with reperfused and nonreperfused myocardial infarction. *Am. J. Cardiol.* 1991; 67: 1360-7.
- 17) Chen Y, Serfass RC, Mackey-Bojack SM, Kelly KL, Titus JL, Apple FS. Cardiac troponin T alterations in myocardium and serum of rats after stressful, prolonged intense exercise. *Jour Appl Phys.* 200; 88(5): 1749-1755.
- 18) Holman ER, van Jonbergen HP, van Dijkman PR, van der Laarse A, de Roos A, van der Wall EE. Comparison of magnetic resonance imaging studies with enzymatic indexes of myocardial necrosis for quantification of myocardial infarct size. *Am J Cardiol.* 1993; 71(12): 1036-40.
- 19) Kim RJ, Wu E, Rafael A, Chen EL, Parker MA, Simonetti O, Klocke FJ, Bonow RO, Judd RM. The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. *N Engl J Med.* 2000; 343(20): 1445-53.



- 20) Sechtem U, Pflugfelder PW, Gould RG, Cassidy MM, Higgins CB. Measurement of right and left ventricular volumes in healthy individuals with cine MR imaging. *Radiology*. 1987; 163(3): 697-702.
- 21) Pattynama PM, Lamb HJ, Van der Velde EA, Van der Geest RJ, Van der Wall EE, De Roos A. Reproducibility of MRI-derived measurements of right ventricular volumes and myocardial mass. *Magn Reson Imaging*. 1995; 13(1): 53-63.
- 22) Cutrone JA, Georgiou D, Khan S, Fischer H, Belardinelli R, Laks MM, Brundage B. Comparison of electron beam computed tomography scanning and magnetic resonance imaging quantification of right ventricular mass: validation with autopsy weights. *Acad Radiol*. 1996;3(5)395-400
- 23) Lorenz CH, Walker ES, Morgan VL, Klein SS, Graham TP Jr. Normal human right and left ventricular mass, systolic function, and gender differences by cine magnetic resonance imaging. *J Cardiovasc Magn Reson*. 1999; 1(1): 7-21.
- 24) Perseghin G, De Cobelli F, Esposito A, Lattuada G, Terruzzi I, La Torre A, Belloni E, Canu T, Scifo P, Del Maschio A, Luzi L, Alberti G. Effect of the sporting discipline on the right and left ventricular morphology and function of elite male track runners: a magnetic resonance imaging and phosphorus 31 spectroscopy study. *Am Heart J*. 2007; 154(5):937-42.
- 25) Scharhag J, Schneider G, Urhausen A, Rochette V, Kramann B, Kindermann W. Athlete's Heart; Right and left ventricular mass and function in male endurance athletes and untrained individuals determined by magnetic resonance imaging. *JACC*. 2002; 40 (10): 1856-63.



- 26) Nassenstein K, Breuckmann F, Lehmann N, Schmermund A, Hunold P, Broecker-Preuss M, Sandner TA, Halle M, Mann K, Jockel K, Heusch G, Budde T, Erbel R, Barhausen J, Mohlenkamp S. Left ventricular volumes and mass in marathon runners and their association with cardiovascular risk factors. *Int J Cardiovasc Imaging*. 2008 Aug 3 (Epub ahead of print).
- 27) Pluim BM, Lamb HJ, Kayser HW, Leujes F, Beyerbacht HP, Zwinderman AH, van der Laarse A, Vliegen HW, de Roos A, van der Wall EE. Functional and metabolic evaluation of the athlete's heart by magnetic resonance imaging and dobutamine stress magnetic resonance spectroscopy. *Circulation*. 1998; 97(7): 666-672.
- 28) Apple FS, Quist HE, Doyle PJ, Otto AP, Murakami MM. Plasma 99th percentile reference limits for cardiac troponin and creatine kinase MB mass for use with European Society of Cardiology/American College of Cardiology consensus recommendations. *Clin Chem*. 2003; 49(8): 1331-1336.
- 29) Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ; Chamber Quantification Writing Group; American Society of Echocardiography's Guidelines and Standards Committee; European Association of Echocardiography. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of



- the European Society of Cardiology. *J Am Soc Echocardiogr.* 2005; 18(12): 1440-63.
- 30) Kitabatake A, Inoue M, Asao M, Masuyama T, Tanouchi J, Morita T, Mishima M, Uematsu M, Shimazu T, Hori M, Abe H. Noninvasive evaluation of pulmonary hypertension by a pulsed Doppler technique. *Circulation.* 1983; 68(2): 302-9.
- 31) Zoghbi WA, Enriquez-Sarano M, Foster E, Grayburn PA, Kraft CD, Levine RA, Nihoyannopoulos P, Otto CM, Quinones MA, Rakowski H, Stewart WJ, Waggoner A, Weissman NJ; American Society of Echocardiography. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr.* 2003; 16(7): 777-802.
- 32) 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(2): 474-480.
- 33) Urheim S, Edvardsen T, Torp H, Angelsen B, Smiseth OA. Myocardial strain by Doppler echocardiography. Validation of a new method to quantify regional myocardial function. *Circulation.* 2000; 102(10): 1158-1164.
- 34) Katz J, Milliken MC, Stray-Gundersen J, Buja LM, Parkey RW, Mitchell JH, Peshock RM. Estimation of human myocardial mass with MR imaging. *Radiology.* 1988; 169(2): 495-8.



- 35) Cutrone JA, Georgiou D, Khan S, Fischer H, Belardinelli R, Laks MM, Brundage B. Comparison of electron beam computed tomography scanning and magnetic resonance imaging quantification of right ventricular mass: validation with autopsy weights. *Acad Radiol.* 1996; 3(5): 395-400.
- 36) Milliken MC, Stray-Gundersen J, Peshock RM, Katz J, Mitchell JH. Left ventricular mass as determined by magnetic resonance imaging in male endurance athletes. *Am J Cardiol.* 1988; 62(4): 301-5.
- 37) Semelka RC, Tomei E, Wagner S, Mayo J, Kondo C, Suzuki J, Caputo GR, Higgins CB. Normal left ventricular dimensions and function: interstudy reproducibility of measurements with cine MR imaging. *Radiology.* 1990; 174(3 pt 1): 763-768.
- 38) George K, Oxborough D, Forster J, Whyte G, Shave R, Dawson E, Stephenson C, Dugdill L, Edwards B, Gaze D. Mitral annular myocardial velocity assessment of segmental left ventricular diastolic function after prolonged exercise in humans. *J Physiol.* 2005;569(pt 1); 305-13
- 39) Hart E, Shave R, Middleton N, George K, Whyte G, Oxborough D. Effect of preload augmentation on pulsed wave and tissue Doppler echocardiographic indices of diastolic function after a marathon. *J Am Soc Echocardiogr.* 2007; 20: 1393-1399.
- 40) Dawson E, George K, Shave R, Whyte G, Ball D. Does the human heart fatigue subsequent to prolonged exercise? *Sports Med.* 2003; 33(5): 365-80
- 41) Whyte G, George K, Shave R, Dawson E, Stephenson C, Edwards B, Gaze D, Oxborough D, Forster J, Simpson R. Impact of marathon running on cardiac



- structure and function in recreational runners. *Clinic Scie (Colch)*. 2005; 108(1): 1-8.
- 42) Hart E, Dawson E, Rasmussen P, George K, Secher NH, Whyte G, Shave R. Beta-adrenergic receptor desensitization in man: insight into post-exercise attenuation of cardiac function. *J Physiol*. 2006; 577: 717-25.
- 43) Douglas PS, O'Toole ML, Hiller WD, Hackney K, Reichek N. Cardiac fatigue after prolonged exercise. *Circulation*. 1987; 76(6): 1206-1213.
- 44) Douglas PS, Douglas PS, O'Toole ML, Hiller WD, Reichek N.. Different effects of prolonged exercise on the right and left ventricles. *J Am Coll Cardiol*. 1990; 15(1): 64-69.
- 45) Christiansen JP, Edwards C, Sinclair T, Armstrong G, Scott A, Patel H, Hart H. Detection of myocardial scar by contrast-enhanced cardiac magnetic resonance imaging in patients with troponin-positive chest pain and minimal angiographic coronary artery disease. *Am J Cardiol* 2006; 97: 768-771.
- 46) Selvanayagam JB, Porto I, Channon K, Petersen SE, Francis JM, Neubauer S, Banning AP. Troponin elevation after percutaneous coronary interventions directly represents the extent of irreversible myocardial injury. *Circulation* 2005; 11: 1027-1032.



TABLES

Table 1. Patient clinical characteristics (n=14)

Characteristics	Baseline	Post-race	p value
Age (y)	33±6 (21-42)		
Gender, n (%)			
Male	8 (57)		
Female	6 (43)		
Moderately trained (<40 miles/wk)	10		
Previous marathons	6±3		
Miles/week of training	26±8		
Highly trained (>40 miles/wk)	4		
Previous marathons	5±4		
Miles/week of training	53±12		
Weight (kg)	74±12	73±11	0.87
Height (cm)	175±15	175±15	1.00
BMI (kg/m ²)	24±2	24±2	1.00
Heart rate (bpm)	62±10	86±10	<0.01
SBP (mm Hg)	130±14	109±29	0.02
DBP (mm Hg)	77±9	60±18	<0.01

Values are mean ± SD. y, years; BMI, body mass index; bpm, beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure.



Table 2. Summary of serial cardiac biomarkers for total population (n=14)

Characteristics	Baseline	Post race	1 wk post race	p
Myoglobin (mg/L)	34 (21-97)	703 (446-2038)	80 (53-91)	<0.01
CK (U/l)	160 (127-209)	518 (391-1714)	222 (168-482)	<0.01
cTnT (ug/L)	<0.01	0.31 (0.22-0.68)	<0.01	<0.01

Values are median with interquartile range (95% CI). cTnT, cardiac troponin T; CK, creatinine kinase



Table 3. Two dimensional echo data in patient population

Echo parameters	Baseline	Post-race	Follow-up	p value
<i>LV parameters</i>				
LVEDD (mm)	50±6	50±5	50±4	0.95
LVESD (mm)	33±5	33±4	32±4	0.74
LVEDV (ml)	112±24	110±29	102±32	0.60
LVESV (ml)	40±11	49±25	40±17	0.24
IVS (mm)	8±1	9±1	9±2	0.33
PWT (mm)	8±1	9±1	8±2	0.29
LVEF (%)	65±5	65±5	64±6	0.56
LV mass/BSA (g/m ²)	97±14	104±20	96±23	0.49
<i>LA parameters</i>				
LA diameter (mm)	36±4	36±4	34±4	0.34
LA volume (ml)	45±15	50±22	36±11	0.12
<i>RA and RV parameters</i>				
RA volume (ml)	40±14	55±13*	36±17	<0.05
RVEDD (mm)	30±4	39±3*	31±3	<0.05
RV diastolic area (mm ²)	14±5	18±3*	13±3	<0.05
RV systolic area (mm ²)	8±3	12±3*	7±2	<0.05
RV FAC (%)	43±5	34±7*	43±6	<0.05
TAPSE (mm)	2.6±0.5	1.6±0.4*	2.5±0.4	<0.05

Values are mean ± SD. LVEDD, left ventricular end diastolic diameter; LVESD, left ventricular end systolic diameter; LVEDV, left ventricular end diastolic volume; LVESV, left ventricular end systolic volume; IVS, interventricular septum; PWT, posterior wall thickness; LVEF, left ventricular ejection fraction; BSA, body surface area; LA, left atrium; RA, right atrium; RVEDD, right ventricular end diastolic diameter in parasternal long axis view; FAC, fractional area change; TAPSE, tricuspid annular plane systolic excursion. *Post-race compared to baseline, p<0.05.



Table 4. Conventional and novel diastolic echo parameters in patient population

Echo parameters	Baseline	Post-race	Follow-up	p value
<i>Doppler echocardiography</i>				
MR grade	0.4±0.1	0.6±0.2	0.7±0.2	0.60
Mitral E velocity (cm/s)	0.8±0.2	0.6±0.2 [*]	0.8±0.2	<0.01
Mitral A velocity (cm/s)	0.5±0.1	0.6±0.2 [*]	0.5±0.2	<0.01
Mitral E/A ratio	1.6±0.2	1.0±0.2 [*]	1.6±0.2	<0.01
Mitral E decel time (ms)	210±64	200±69	203±56	0.91
Peak PASP (mm Hg)	16±4	37±3 [*]	12±4	<0.01
<i>Left Ventricle: Tissue Doppler imaging</i>				
Lateral S' (cm/s)	11.1±1.1	9.6±0.3	10.1±1.0	0.44
Lateral E' (cm/s)	12.5±1.2	8.8±1.2 [*]	10.2±1.3 ^{**}	<0.01
Lateral A' (cm/s)	5.0±1.2	8.0±1.1 [*]	6.1±1.1 ^{**}	<0.01
Septal S' (cm/s)	9.9±1.0	8.2±1.0	9.1±1.0	0.36
Septal E' (cm/s)	10.1±1.2	8.0±1.1 [*]	9.2±1.3 ^{**}	<0.01
Septal A' (cm/s)	5.2±1.3	8.3±1.1 [*]	6.2±1.3 ^{**}	<0.01
E/E' lateral	6.4±1.3	6.8±1.0	7.8±1.3	0.39
E/ E' septal	7.4±1.1	7.5±1.0	8.2±1.1	0.79
<i>Right Ventricle: Tissue Doppler imaging</i>				
S' at base (cm/s)	12.2±1.2	8.4±1.1 [*]	11.2±1.1	<0.01
E' at base (cm/s)	11.4±1.1	9.5±1.0 [*]	9.8±1.1 ^{**}	<0.01
A' at base (cm/s)	7.8 ±1.1	10.7±1.0 [*]	9.2±1.1 ^{**}	<0.01
Strain at base (%)	16±3	11±2 [*]	14±1 ^{**}	<0.01

Values are mean ± SD. MR, mitral regurgitation; decel, deceleration; PASP, pulmonary artery systolic pressure. ^{*} Post-race compared to baseline. ^{**} One week followup compared to baseline.



Table 5. Cardiac MRI data in patient population at baseline and post marathon (n=14)

CMR parameters	Baseline	Post marathon
<i>LV parameters</i>		
LVEDD (mm)	51±5	52±6
LVESD (mm)	31±6	30±8
LVEDV (ml)	158±24	162±26
LVESV (ml)	52±21	53±18
LVEDV/BSA (ml/m ²)	83±10	85±12
LVESV/BSA (ml/m ²)	27±11	28±13
IVS (mm)	9±1	9±2
PWT (mm)	9±1	9±1
LVEF (%)	66±6	67±5
LV mass (g)	212±27	210±25
LV mass/ BSA (g/m ²)	114±12	111±13
<i>LA parameters</i>		
LA diameter (mm)	34±6	35±4
LA volume (ml)	50±10	51±12
LA volume/ BSA (ml/m ²)	26±8	27±7
<i>RA and RV parameters</i>		
RA volume (ml)	40±10	51±11*
RVEDD (cm)	30±6	38±6*
RVEDV (ml)	160±22	195±22*
RVESV (ml)	55±20	108±17*
RVEDV/BSA (ml/m ²)	84±12	102±9*
RVESV/BSA (ml/m ²)	29±10	57±8*
RVEF (%)	64±8	43±5*
RV mass (g)	64±6	65±4
RV mass/BSA (g/m ²)	32±4	34±3

Values are mean ± SD. LVEDD, left ventricular end diastolic diameter; LVESD, left ventricular end systolic diameter; LVEDV, left ventricular end diastolic volume; LVESV, left ventricular end systolic volume; BSA, body surface area; IVS, interventricular septum; PWT, posterior wall thickness; LVEF, left ventricular ejection fraction; LA, left atrium; RA, right atrium; RVEDD, right ventricular end diastolic diameter; RVEDV, right ventricular end diastolic volume; RVESV, right ventricular end systolic volume; RVEF, right ventricular ejection fraction; RV, right ventricle. *p<0.05 as compared to baseline.

FIGURE LEGENDS

Figure 1. Baseline and post-marathon transthoracic echocardiographic image in the apical 4 chamber view in a participant with a cTnT that increased from <0.01 to 0.54 ug/L. A. Baseline transthoracic echo image demonstrating normal RV structure and function. B. Post marathon evidence of mild RV dilatation (RVEDD 38 mm) and decrease in RV FAC of 35%. C. Post marathon cine-CMR in the horizontal long axis view, confirms the decrease in RVEF of 44%. cTnT; cardiac troponin T; RV, right ventricle; RVEDD, right ventricular end diastolic diameter; FAC, fractional area change; CMR, cardiac MRI; RVEF, right ventricular ejection fraction; LV, left ventricle; LA, left atrium; RA, right atrium.

Figure 2. Tissue Doppler imaging diastolic parameters of the LV and RV respectively, at baseline, post marathon and 1 week followup. **Panel A:** Although the lateral S' of the LV did not change throughout the course of the study, S' of the RV transiently decreased following the marathon and returned to normal. **Panels B-C:** The E' decreased and A' increased post marathon in both the LV and RV, and did not completely normalize at 1 week followup. * $p<0.05$ as compared to baseline; ** $p<0.05$ as compared to baseline.

Figure 3: A strong linear correlation between RV FAC as assessed by echocardiography immediately following the race and RVEF as assessed by CMR post marathon ($r=0.96$, $p<0.01$).

FIGURES

Figure 1.

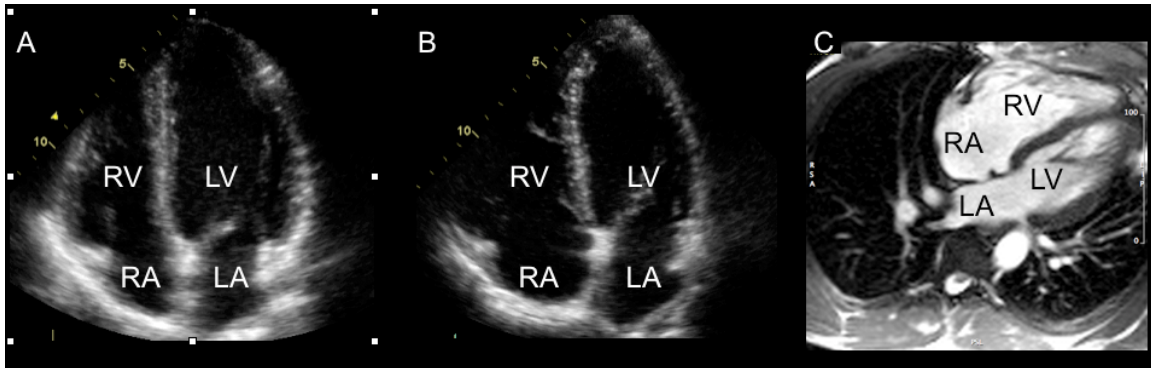
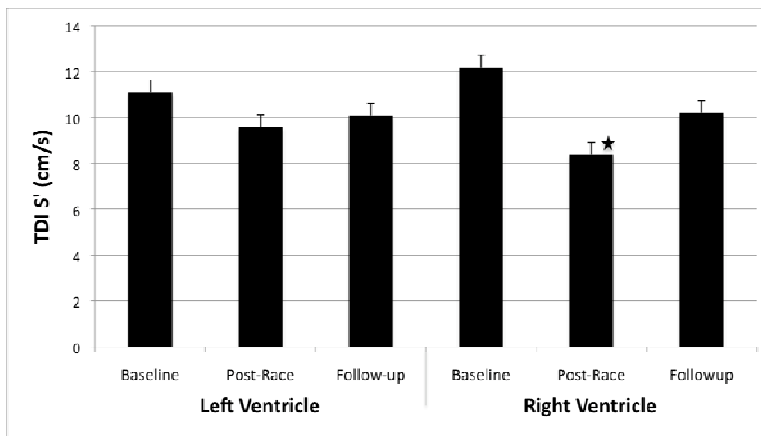
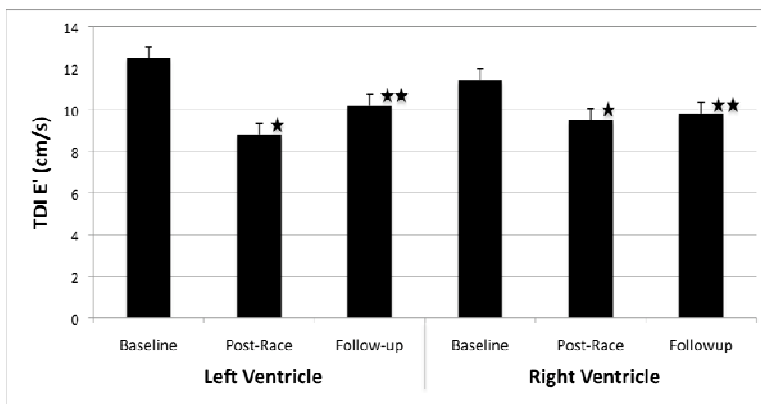


Figure 2.

A.



B.





C.

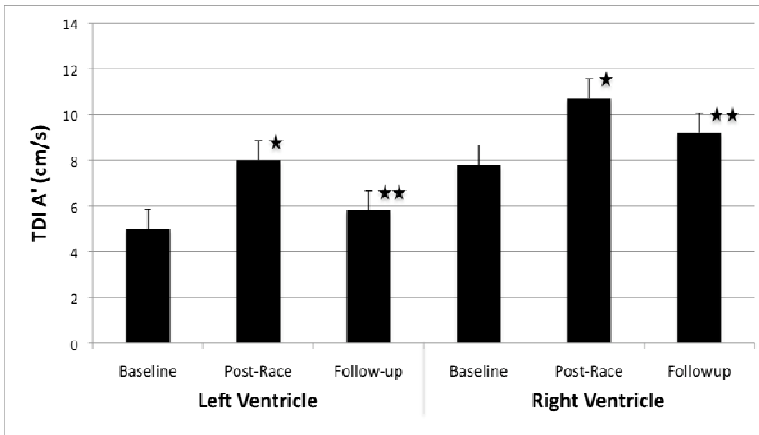


Figure 3.

