Changes in vascular and cardiac function after prolonged strenuous exercise in humans

Ellen A. Dawson,1 Greg P. Whyte,1 Mark A. Black,1 Helen Jones,1 Nicola Hopkins,1 David Oxborough,2 David Gaze,3 Rob E. Shave,3 Mat Wilson,4 Keith P. George,1 and Daniel J. Green1,5

1Research Institute for Sport and Exercise Sciences, Liverpool John Moores University, Liverpool; 2School of Healthcare, University of Leeds, Leeds; 3Center for Sports Medicine and Human Performance, Brunel University, Uxbridge, United Kingdom; 4School of Sport, Performing Arts and Leisure, Wolverhampton University, Walsall; and 5School of Sport Science, Exercise and Health, The University of Western Australia, Nedlands, Australia

Submitted 30 June 2008; accepted in final form 20 August 2008

Dawson EA, Whyte GP, Black MA, Jones H, Hopkins N, Oxborough D, Gaze D, Shave RE, Wilson M, George KP, Green DJ. Changes in vascular and cardiac function after prolonged strenuous exercise in humans. J Appl Physiol 105: 1562–1568, 2008. First published August 21, 2008; doi:10.1152/japplphysiol.90837.2008.—Prolonged exercise has been shown to result in an acute depression in cardiac function. However, little is known about the effect of this type of exercise on vascular function. Therefore, the purpose of the present study was to investigate the impact of an acute bout of prolonged strenuous exercise on vascular and cardiac function and the appearance of biomarkers of cardiomyocyte damage in 15 male (32 ± 10 yr) nonelite runners. The subjects were tested on two occasions, the day before and within an hour of finishing the London marathon (229 ± 38 min). Function of the brachial and femoral arteries was determined using flow-mediated dilatation (FMD). Echocardiographic assessment of cardiac strain, strain rate, tissue velocities, and flow velocities during diastole and systole were also obtained. Venous blood samples were taken for later assessment of cardiac troponin I (cTnI), a biomarker of cardiomyocyte damage. Completion of the marathon resulted in a depression in femoral (P = 0.04), but not brachial (P = 0.96), artery FMD. There was no change, pre- vs. postmarathon, in vascular shear, indicating that the impaired femoral artery function was not related to hemodynamic changes. The ratio of peak early to atrial radial strain rate, a measure of left ventricular diastolic function, was reduced postmarathon (P = 0.006). Postrace cTnI was elevated in 12 of 13 runners, with levels above the recognized clinical threshold for damage in 7 of these. In conclusion, when taken together, these data suggest a transient depression in cardiac and leg vascular function following prolonged intensive exercise.

cardiovascular; exercise; marathon; ultrasound; troponins

EPIDEMIOLOGICAL (7, 33) and experimental (18) evidence supports the public health message that exercise training and physical activity have substantial vascular and cardiac health benefits, with an ∼30% reduction in cardiac risk (39). Despite this, it is clear that acute exercise transiently elevates the risk of cardiac events (37), or even sudden cardiac death (SCD) (40), in those at risk. The cardiovascular and physiological responses to prolonged exercise that are implicated in this transient period of increased cardiovascular risk are not well understood.

Previously, we and others have demonstrated that marathon running results in a modest depression in cardiac function, primarily observed in indexes of left ventricular diastolic function (12, 28, 29). This is associated with the sporadic appearance of biomarkers of cardiomyocyte damage (10, 12, 26, 28, 29, 34). However, the changes in cardiac function after prolonged strenuous exercise that occur in different planes of motion (radial, circumferential, and longitudinal) have not previously been studied.

Vascular endothelial function reflects the health of the vessel wall. The dilator response to a 5-min ischemic period, termed flow-mediated dilatation (FMD), reflects the bioactivity of the endothelium derived nitric oxide (NO) (24, 27) and has been widely adopted as a surrogate marker for cardiovascular risk (41). Although exercise training of low to moderate intensity typically enhances FMD and endothelial function in humans (16), intense exercise bouts are associated with inflammation and elevated oxidative stress (5, 13), both of which acutely impair NO-mediated vasodilator function (21). It is also conceivable that prolonged intense bouts of exercise may be associated with NO substrate or cofactor exhaustion. However, the acute impact of prolonged intensive exercise on the vascular endothelium has not been well studied.

In the present study, we measured changes in endothelium-dependent vasodilatation of the brachial and superficial femoral arteries before and after the London marathon. We also determined circulating concentrations of cardiac troponin I (cTnI) and measured cardiac motion in three planes using state-of-the-art physiological assessment of myocardial stress and strain. We hypothesized that a prolonged intensive bout of exercise would be associated with impaired vascular and cardiac function responses.

METHODS

Participants and Settings

Fifteen male nonelite runners (mean ± SD) age 32 ± 10 yr (range 23–63), body mass 72.7 ± 7.4 kg (range 65.5–86.6), height 1.79 ± 0.05 m (range 1.69–1.8), and participating in the London Marathon 2007 (distance 42.2 km) volunteered and provided written, informed consent. Exclusion criteria included any personal and/or early (<50 yr) family history of cardiopulmonary disease, including diagnosis and treatment for hypertension, angina, myocardial infarction, and peripheral vascular diseases. The study conformed to the standards set by the Declaration of Helsinki, and ethical approval was obtained from Liverpool John Moores University Ethics Committee.

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
Design

Data were collected at an initial assessment ~24 h before the completion of the race and again within 60 min of race completion. On both testing days, measures were collected within a 2-h period to minimize any impact of diurnal variation. Postrace, subjects arrived at the testing venue within 30 min and were then directed immediately to one of the testing stations. The difference between subjects in posttesting of, for example, FMD or echocardiographic measures was therefore in the order of 15–20 min. Race conditions were warm with temperatures reaching 21°C at midday.

Procedures

Vascular ultrasound assessment of FMD. After an initial assessment of body mass, patients rested in the supine position for ~10 min. Heart rate (HR) and mean arterial pressure were determined from an automated sphygmomanometer (GE Pro 300V2, Dinamap, Tampa, FL) on the left arm. A 10-MHz multifrequency linear array probe attached to a high-resolution ultrasound machine (T3000, Terason, Burlington, MA) was used to assess the femoral and brachial artery function.

The brachial artery was assessed with the right arm extended and supported at an angle of ~80° from the torso. A rapid inflation-deflation pneumatic cuff was positioned on the imaged arm, distal to the olecranon process, with the artery imaged in the distal third of the upper arm. The superficial femoral artery was assessed with the lower leg slightly elevated. The rapid inflation-deflation pneumatic cuff was positioned ~15 cm below the inguinal ligament, with the artery imaged in the proximal third of the thigh, at least 5 cm distal from the bifurcation and above the cuff position. We assessed both brachial and femoral FMD to determine whether changes observed were specific to the most active muscle beds or more generalized to the circulation as a whole.

Ultrasound parameters were set to optimize longitudinal, B-mode images of the lumen-arterial wall interface. Continuous Doppler velocity assessment was also obtained and was collected using the lowest possible insonation angle (always <60°), which did not vary during each study. Dynamic range and Doppler gain settings were similar between the machines (31).

Conduit artery endothelium-dependent dilation was assessed via the FMD response. Baseline scans assessing resting vessel diameter and flow were recorded in the final minute of the initial rest period. The occluding cuff was then inflated to >200 mmHg for 5 min. Diameter and flow recordings resumed 30 s before cuff deflation and continued for 3 min thereafter (6). Posttest analysis of conduit artery diameter was performed using custom-designed edge detection and wall-tracking software, which is independent of investigator bias (6, 45). The software automatically detected the peak of the waveform and synchronized it with the artery diameter at 30 Hz. Ultimately, from this synchronized diameter and velocity data, blood flow (the product of cross-sectional area and Doppler velocity) and shear rate ([4 × velocity]/diameter) were calculated at 30 Hz.

Peak diameter following cuff deflation was determined using an automated algorithm (6, 45) and FMD was calculated as the percentage rise from the preceding baseline diameter. The time to peak diameter (in seconds) was calculated from the point of cuff deflation to the time of peak postdeflation diameter. Postdeflation shear rate data, derived from simultaneously acquired velocity and diameter measures at 30 Hz, was exported to a spreadsheet, and the area under the shear rate curve (SR_{AUC}) was calculated for data up to the point of maximal postdeflation diameter (FMD) using the Riemann sum technique for each individual. SR_{AUC} represents the stimulus for FMD (32).

Echocardiography. A comprehensive examination [two-dimensional (2D), M-mode, Doppler, tissue Doppler, and strain-strain rate imaging by myocardial speckle tracking] was performed by an experienced and qualified sonographer using a commercially available ultrasound system (Vivid 7, GE Medical, Horton, Norway) and a 1.5- to 4-MHz phased array transducer. Images were recorded digitally to disc and analyzed offline (2D strain, EchoPac, GE Medical). A minimum of three consecutive cardiac cycles were measured and averaged. All image acquisitions were made with the subject lying in the left lateral decubitus position. HR was recorded at the start of each scan via ECG.

Left ventricular volume in diastole and systole and ejection fraction were calculated via the Simpsons biplane method from 2D sector scans. Global diastolic function was assessed via peak Doppler mitral flow velocities in early (E) and atrial (A) left ventricular filling and the E/A ratio was calculated. Peak longitudinal systolic (S’), early diastolic (E’), and atrial diastolic (A’) myocardial velocities, as well as E’/A’, were obtained from the septal and lateral left ventricular wall at the level of the mitral annulus using tissue-Doppler imaging.

Strain and strain rate indexes were obtained using a myocardial speckle tracking technique. Radial and circumferential strain and strain rate data were derived from the parasternal short axis view, imaged at the basal level with reproducible anatomical landmarks located for repeat scans. The apical window was utilized for longitudinal assessment using a four-chamber orientation. Offline analysis allowed the derivation of peak strain and peak systolic and peak early diastolic strain rates in six wall segments for all planes. Segmental data were averaged for the purpose of this paper. Strain and strain rates were derived from continuous frame-by-frame tracking of the natural acoustic speckle markers (25) using a block-matching algorithm that assessed displacement and rate of displacement of the “kernel” (22). Myocardial segments were excluded when inaccurate tracking was perceived by either the software or the operator.

cTnI was determined using the TnI-Ultra assay for the Advia Centaur XP immunoassay system (Siemens Medical Solutions Diagnostics, Frimley, Surrey). The assay detection limit was 0.006 μg/l with a linear calibration range up to 50 μg/l (4). The total assay imprecision, as quoted by the manufacturer, was 10% at 0.03 μg/l. The clinical cutoff level for AMI is set at 0.05 μg/l.

Data Analysis

Pre- and postrace values for body mass, blood pressures, and HR (n = 13), vascular ultrasound measurements of the brachial (n = 10) and femoral arteries (n = 9), and left ventricular loading and function (n = 13) were assessed by t-tests. Some subject data were excluded because of inadequate image quality or prolonged time taken to present for repeat testing. The appearance of cTnI in the systemic circulation above assay detection levels was analyzed descriptively due to the fact that no cTnI was observed in prerace blood samples. Delta (pre-post race) values for femoral FMD, diastolic function, hemodynamic loading indexes, as well as postrace cTnI levels were correlated via Pearson’s product-moment analysis. The critical alpha level was set at 0.05, and all analyses were carried out on Statistica software (Statsoft, Tulsa, OK). Data are presented as means ± SD.

RESULTS

All 15 runners finished (229 ± 38 min), were ambulatory, and reported no signs or symptoms of (pre)syncope. Body mass decreased by 1.6 ± 1.4 kg (P < 0.01), systolic blood pressure by 8 ± 9 mmHg (P = 0.01), and mean arterial pressure by 4 ± 4 mmHg (P < 0.01). Left ventricular end-diastolic volume was reduced by 13 ± 15 ml (P = 0.01), and HR increased by 18 ± 11 beats/min (P < 0.01).

Vascular Ultrasound

Shear rate (SR_{AUC}), a measure of the stimulus to FMD, was not significantly different pre- vs. postrace in either the brachial or femoral arteries (Table 1). Resting femoral artery
diameters were similar pre- and postrace (Table 1), whereas femoral FMD was significantly (P = 0.04) reduced (Fig. 1). Resting and peak brachial artery diameters were increased postmarathon (Table 1); however, there was no change in brachial artery function, as determined by FMD (Fig. 1).

Echocardiography

Parameters of systolic function were not altered by completion of a marathon except for lateral wall tissue velocity postrace, which increased (Table 2). Conversely, depressed diastolic function was consistent across ultrasound modalities. The general pattern observed was a reduction in early diastolic parameters, an increase in late diastolic indexes and consequently a postrace reduction in E/A ratios (Fig. 2). The E/E' ratios were unchanged pre- to postmarathon (6.02 ± 1.54 to 5.95 ± 1.12), and hence diastolic function declined despite filling pressures being maintained.

cTnI

cTnI was below the detection limit of the assay in all runners prerace. Postrace, detectable cTnI was observed in 12 of 13 runners with cTnI above 0.05 μg/l level used to determine acute myocardial infarction in 7 runners.

The postrace reductions in femoral artery FMD (r² = 0.02–0.34) and diastolic function (r² = 0.00–0.26) were not significantly related to exercise-induced alterations in blood pressure, indexes of preload and afterload, or HR. The relationship(s) between pre-post race changes in FMD and diastolic function were variable but statistically significant for FMD and early diastolic (E') septal tissue velocity (r = 0.78, r² = 0.61) as well as peak circumferential early diastolic deformation rate (r = 0.7, r² = 0.49). Postrace cTnI (r² = 0.00–0.26; P > 0.05) was not significantly associated with postrace alterations in FMD or left ventricular diastolic function.

DISCUSSION

A single bout of prolonged intense exercise resulted in concomitant reduction in femoral artery function and left ventricular diastolic function, as well as the appearance of markers of cardiac damage in nearly all runners. This combined response suggests a period of depressed cardiovascular function and, possibly, elevated cardiac risk soon after running a marathon.

Table 2. Indexes of left ventricular systolic function pre- and postrace

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Prerace</th>
<th>Postrace</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Myocardial speckle tracking</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Circumferential</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak strain, %</td>
<td>−19.9±3.3</td>
<td>−19.7±2.3</td>
<td>0.77</td>
</tr>
<tr>
<td>Peak systolic strain rate, s⁻¹</td>
<td>−1.31±0.19</td>
<td>−1.40±0.15</td>
<td>0.17</td>
</tr>
<tr>
<td>Radial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak strain, %</td>
<td>57.0±12.1</td>
<td>48.7±17.0</td>
<td>0.06</td>
</tr>
<tr>
<td>Peak systolic strain rate, s⁻¹</td>
<td>1.64±0.15</td>
<td>1.73±0.29</td>
<td>0.40</td>
</tr>
<tr>
<td>Longitudinal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak strain, %</td>
<td>−18.7±2.2</td>
<td>−18.3±1.9</td>
<td>0.66</td>
</tr>
<tr>
<td>Peak systolic strain rate, s⁻¹</td>
<td>−1.07±0.17</td>
<td>−1.15±0.17</td>
<td>0.28</td>
</tr>
<tr>
<td><strong>Tissue Doppler imaging</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Septal wall</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak systolic tissue velocity, cm/s</td>
<td>7.04±1.03</td>
<td>6.57±2.66</td>
<td>0.73</td>
</tr>
<tr>
<td>Lateral wall</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak systolic tissue velocity, cm/s</td>
<td>9.20±1.87</td>
<td>11.34±2.88</td>
<td>0.01</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>62±7</td>
<td>63±5</td>
<td>0.76</td>
</tr>
</tbody>
</table>

Values are means ± SE. 2D, two dimensional.
Vascular Changes in Response to Prolonged Intensive Exercise

This is the first study to assess vascular function after a prolonged intense bout of exercise. Our data suggest that prolonged intensive exercise can acutely impair endothelial function, which may theoretically lead to a transient increase in the risk of atherothrombotic events or even arterial spasm postexercise (1, 11). It has been suggested that impaired endothelium-dependent vasodilation, including impaired FMD responses, provides a barometer of cardiovascular risk (41).

An interesting observation relating to FMD responses was the lack of effect of the Marathon on arterial function in the brachial artery. It is likely that the brachial and femoral arteries are exposed to different flow and shear rate patterns during bouts of lower limb exercise (16), and some previous findings suggest differential impacts on NO-mediated vasodilation in active and inactive muscle beds (14, 15). Previous experimental evidence also suggests that intensive exercise may impair endothelial function as a consequence of elevated oxidative stress (13, 20) or inflammation (3). Our findings of impaired femoral, but not brachial, endothelial function following a marathon suggest that if elevated oxidative stress or inflammation are responsible for reduced NO bioactivity, then this is a phenomenon isolated to the active muscle bed. It is also possible that NO synthase substrate or cofactor exhaustion may contribute to impaired vasodilator function in the vasculature of the active limb, which is exposed to profound changes in blood flow and shear rate. Finally, some evidence suggests interaction between the sympathetic nervous system and endothelial function (23). However, enhanced sympatholysis in the active muscle would be expected to increase FMD, and sympathetic nervous system outflow is unlikely to be different between the upper and lower limbs of these healthy subjects postexercise. A final issue relates to the increase in baseline diameter observed in the brachial artery after the race, an effect that was not evident in the lower limb. The reason for this is not entirely clear but may relate to different patterns of shear...
stress experienced in the respective vessel beds, in combination with the more direct effect of oxidative stress in the more active limbs.

Cardiac Changes in Response to Prolonged Intensive Exercise

Depressed left ventricular diastolic function has been reported previously after the London (12) and Boston (28, 29) Marathons. The addition of circumferential, radial, and longitudinal strain rate data in the present study clearly demonstrates that the depression in diastolic function postrace is global in nature since all planes of cardiac motion were affected. A role for cardiac damage has been suggested by some (29) but dismissed by others (12). In the current cohort, there was no correlation between the concentrations of cTnI present postexercise with the pre-post race changes in diastolic function, suggesting these phenomena may be independent. An alternate explanation could relate to hemodynamic changes pre- and postrace. Both HR and preload were moderately reduced and could alter diastolic function. However, the lack of correlation between changes in diastolic function with changes in HR and hemodynamic loading provides some evidence that there are alterations in intrinsic relaxation properties of the left ventricle. Evidence of some association between changes in FMD and indexes of diastolic function hint at a role for a shared mechanism, which could relate to oxidative stress (8, 19, 42), but this requires further investigation.

The high prevalence of cTnI in the current cohort (92% above detection levels and 69% above clinical criteria) supports previous Marathon studies (12, 26, 28, 29, 42) that have reported sporadic cardiac troponin release with intense and prolonged exercise. Interestingly, the present troponin data represent the highest incidence of troponin release observed following prolonged exercise (92 vs. 78%; Ref. 35). This may reflect the increased sensitivity of the assay employed. It is possible that cardiac troponin release may arise from the unbound pool found in the cardiomyocyte cytoplasm, and this may therefore reflect a physiological, as opposed to pathological, mechanism (26). In the absence of other signs and symptoms, cTnI elevated above AMI cutoff criteria should not necessarily be taken as evidence of a cardiac event (43).

Limitations

The sample size in the present study is relatively small; however, we believe that the changes that we observed were robust. The findings relating to vascular impairment in the femoral artery were consistent between subjects, and the fact that brachial and femoral changes occurred independently strengthens the likelihood that the changes did not occur by chance alone. The cardiac findings are consistent with previous studies from different laboratories that have assessed aspects of diastolic function and troponins (12, 28, 29). Nonetheless, in studies of small sample size, lack of correlations among parameters should be interpreted with caution.

Another limitation of cardiovascular studies of prolonged exercise is the restriction of assessments to pre- and postrace periods. Clearly, we can detail changes in cardiovascular function in recovery, but we cannot extrapolate directly to physiological changes occurring during exercise. Although we did everything we could under the circumstances to study subjects as soon as the race was completed, differences in posttest timing of measurements cannot be excluded as a confounder. A further limitation of field studies such as this one is that runners were not fasted before the race, and we did not specifically dictate prerace diet. However, studies of the impact of diet on FMD have typically associated impairment with the ingestion of high-fat meals, and it is highly unlikely that any subject would have indulged in such a meal before a marathon. We have also previously shown that fluctuations in blood glucose within the normal range in healthy subjects, as would have been the case in the current experiment, do not alter FMD responses (36). We also collected self-reported data on fluid and food consumption, and no subject reported ingesting a high-fat meal prerace (or indeed any high concentration carbohydrate gels during the race).

Although runners exhibited a significant decrease in body weight, our calculations based on changes in hematocrit and hemoglobin (9) indicate that plasma volume did not substantially change (−0.31 ± 1.25%). Furthermore, dehydration and associated changes in plasma volume cannot explain our femoral FMD data since shear rate was in fact larger postrace in the femoral artery, not smaller as would be expected in the presence of reduced FMD. Any increase in viscosity that may have occurred would have further increased the shear stimulus to FMD, yet the FMD we observed was diminished. It is also unlikely that hemoconcentration explains the changes we observed in troponin concentrations, primarily because cTnI is undetectable and does not circulate under normal conditions. Although several previous studies indicated that cardiac function (44) and troponins (30) return to prerace baseline within 24–48 h of completion of the event, future studies will be required to ascertain the time course of impairment and return to baseline of vascular function. Finally, although there are numerous studies of the association between upper limb conduit artery function and coronary function (2, 38), there are no extant studies to our knowledge that have correlated lower limb conduit artery function and coronary function. Associations between our femoral FMD impairment and possible coronary impairment should, therefore, be made with caution.

In conclusion, in the current cohort of nonelite subjects running a marathon, we observed reductions in indexes of conduit (femoral) artery vasodilator function, left ventricular diastolic function, as well as the widespread appearance of cTnI. This combination of changes, in a healthy cohort of runners, suggests a period of increased cardiovascular risk in the aftermath of such prolonged and intense exertion. The clinical consequences and underlying mechanisms of these changes in runners have yet to be elucidated. Although these findings suggest a period of relative increase in risk immediately following prolonged intense exercise, the possibility also exists that such changes also provide a potent stimulus to adaptation. In this sense, the changes we observed may be seen as physiological and beneficial, while simultaneously exposing the individual to a temporary period of enhanced risk. This paradigm provides some support for previous epidemiological evidence regarding the “exercise paradox” (17). We suggest that future studies should focus on collecting measures of oxidative stress or inflammation and recruiting larger numbers of subjects to validate correlational analysis.
ACKNOWLEDGMENTS

We thank CRY for runners and organizational support, and GE UK for loan of equipment. We thank George Robinson, Keymed, and Terson for provision of the vascular ultrasound equipment.

REFERENCES


