Association between arterial elasticity, C-reactive protein and maximal oxygen consumption in well-trained cadets during three days extreme physical load: a pilot study

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Received 11 October 2007, accepted for publication 14 February 2008
Published DD MMM 2008
Online at stacks.iop.org/PM/29/1

Abstract
Regular aerobic training has beneficial effects on inflammatory pathways and on arterial elasticity, which are both important cardiovascular risk factors. The aim of the present study was to evaluate the effect of extreme physical load on arterial elasticity and inflammatory markers in well-trained healthy men who participated in a high-ranking combat course. Seven well-trained male cadets were examined during an international military combat course of 3.5 days duration. Small (C2) and large (C1) artery elasticity was assessed using diastolic pulse wave analysis. Inflammatory markers and arterial elasticity measurement were performed before and after the competition. The extreme prolonged physical load caused a individually different responses in arterial elasticity, C-reactive protein (CRP) and creatine kinase in individual cadets. Maximal oxygen consumption ($\overline{V}O_2$ max kg$^{-1}$) correlated significantly with the change ($\Delta$-difference between baseline and 24 h recovery period) of creatine kinase ($r = -0.78; \ p = 0.04$) and $\Delta$C2 ($r = 0.78; \ p = 0.04$) and $\Delta$C1 ($r = 0.82; \ p = 0.02$). In multivariate analysis ($R^2 = 0.89, \ p = 0.01$) the $\Delta$C2 correlated strongly with $\overline{V}O_2$ max kg$^{-1}$ ($p = 0.005$) and with the $\Delta$CRP ($p = 0.03$). Whereas the $\Delta$C1 correlated only with $\overline{V}O_2$ max kg$^{-1}$ and did not correlate significantly with the $\Delta$CRP. Extreme physical load induced changes in small arterial elasticity were significantly related to $\overline{V}O_2$ max kg$^{-1}$ and $\Delta$CRP, whereas the change of large artery elasticity was only associated with $\overline{V}O_2$ max kg$^{-1}$. Our preliminary results indicate that acute
exercise-induced inflammation may affect small artery elasticity. However, further more extensive studies are needed in this area.

Keywords: pulse wave analysis, arterial elasticity, inflammation, exercise

Introduction

Regular physical training reduces cardiovascular morbidity and mortality in the general population (Schnohr et al 2000). It is well known that moderate physical activity has beneficial effects on inflammatory pathways (Siegel et al 2001) and on arterial function (Goto et al 2003), which are both important cardiovascular risk factors (Bonetti et al 2003, Ridker et al 1997). Inflammation plays a key role in the pathogenesis of atherogenesis (Ross 1999). The inflammatory process in the atherosclerotic artery leads to increased blood levels of inflammatory cytokines and other acute phase reactants. Epidemiological and clinical studies have shown a strong and consistent relationship between markers of inflammation and risk for cardiovascular events (Blake and Ridker 2001). To date, C-reactive protein (CRP) is the most promising of these biomarkers for prediction of cardiovascular risk in terms of clinical utility (Pearson et al 2003). Research has shown that CRP is significantly reduced following nine months of endurance training in moderately trained runners (Mattusch et al 1999). On the other hand, some data suggest that intense exercise may impair arterial function through decreased levels of antioxidant capacity (Bergholm et al 1999) and increased reactive oxygen species (Davies et al 1982).

Pulse wave analysis (PWA) using a modified Windkessel model of the circulation provides a convenient noninvasive technique to separately assess large (C1) and small (C2) artery elasticity (12). Measurements of PWA are important for predicting cardiovascular risk as well as for estimating vascular abnormalities in cardiovascular disorders (Glasser et al 1997, Grey et al 2003). Several authors have reported a link between endothelial function and C2 (Parvathaneni et al 2002, Tao et al 2004). Small artery elasticity may provide a possible link between endothelium-mediated arterial tone (McVeigh et al 2001) indicating a relation with the functional changes in the vasculature. Thus, measurement of arterial elasticity allows us to assess the impact of prolonged strenuous exercise on vascular function (Parvathaneni et al 2002). There is evidence that regular endurance training may have a systemic anti-inflammatory effect (Mattusch et al 1999). However, there are no available data on the effect of strenuous exercise on arterial elasticity and inflammation.

The aim of this study was to evaluate the effect of extreme physical load on arterial elasticity and inflammatory markers in well-trained healthy cadets who participated in a 3.5 day international military combat course.

Methods

Subjects and study protocol

Seven well-trained male army cadets aged 21–29 years were examined during an international military combat course (ERNA, Estonia) of 3.5 days duration (in total 84.5 h). The course involved walking, jogging and special military combat activities (approximate total distance 135 km). During the race, the cadets had to avoid the reconnaissance patrol who were assigned the task of making the race as difficult as possible. The sleeping time during the race was...
limited to 240 min per night. A participant carried a backpack with special equipment and an automatic rifle with a combined weight of 25 kg. Food and drinks were provided during the race as part of the equipment and additional drinks were available at each checkpoint. The covered distance and the precise location of each subject were monitored using a global positioning system (GPS). Heart rate was monitored continuously and stored at 60 s intervals using the telemetry system (Sporttester Polar S810, Finland). Mean heart rate during the race (including resting time) ranged from 48–57% of the maximal pulse rate. The study protocol was approved by the Ethics Committee, University of Tartu. Informed written consent was obtained from each participant.

All subjects passed a routine medical examination 48 h before the competition, including a complete history and physical examination, electrocardiography, PWA, blood tests and an exercise test on treadmill. None of the participants showed any signs or symptoms of cardiovascular disease. The subjects reported that they had not used any vasoactive, vitamin or anti-inflammatory medication within the previous two months. Blood samples were collected between 8:00 a.m. and 10:00 a.m. following an overnight fast and abstinence from tobacco, alcohol, tea and coffee, for measurements of the plasma CRP, glucose, creatine kinase, white blood cell count, red blood cell count, haematocrit, haemoglobin and platelets.

Laboratory assays

White blood cell count and red blood cell count, haematocrit, haemoglobin and platelets were measured using a Sysmex XE 2100 autoanalyser (Sysmex Corporation, Japan). CRP was determined by a validated high-sensitivity assay using a latex particle-enhanced immunoturbidimetric assay (Roche Diagnostics GmPh, Germany) with the automated analyser Hitachi 912.

Pulse wave analysis

After 15 min of rest in a supine position in a quiet temperature-controlled room, peripheral blood pressure and the arterial waveform were measured in the dominant arm by the Cardiovascular Profiling Instrument (HDI/Pulse Wave CR-2000, Hypertension Diagnostics Inc., USA). Briefly, the tonometer was applied to the patient’s radial artery at the wrist overlying the radial bony prominence. The blood pressure measurement cuff was placed on the contralateral arm and inflated concurrently with pulse waveform recording calibration. The elasticity indices of the arteries (C1 and C2) were quantified during the diastolic portion of the cardiac cycle (mean of 30 s recording). According to the modified Windkessel model of circulation, C1 is a marker for large artery elasticity and C2 is a marker for small artery elasticity. Heart rate, mean arterial pressure and stroke volume were also calculated from the radial pressure waveform using the HDI/Pulse Wave CR-2000 software. Haemodynamic and PWA recordings were made in duplicate. The full method has been previously validated and described in detail (Zimlichman et al 2005).

Incremental running exercise test

The incremental running exercise test on the treadmill was performed according to a standard protocol test using the ParvoMedics Truemax 2400 metabolic measurement system (ParvoMedics, USA). Prior to testing, the gas analyser was calibrated with standard gas mixture containing 16.0% of O₂ and 4.0% of CO₂ before each subject was tested. The accuracy of the oxygen analyser was 0.03%, for CO₂ analyser 0.1% and for pneumotach flow
Table 1. Baseline characteristics of the study subjects.

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Age (years)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>BMI (kg m(^{-2}))</th>
<th>(\text{VO}_2) max (l min(^{-1}))</th>
<th>(\text{VO}_2) max kg(^{-1}) (ml kg(^{-1}) min(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>24</td>
<td>188</td>
<td>81.5</td>
<td>23.5</td>
<td>5.08</td>
<td>62.3</td>
</tr>
<tr>
<td>2</td>
<td>27</td>
<td>171</td>
<td>62.2</td>
<td>21.2</td>
<td>3.58</td>
<td>57.6</td>
</tr>
<tr>
<td>3</td>
<td>27</td>
<td>186</td>
<td>77.1</td>
<td>22.0</td>
<td>5.96</td>
<td>77.3</td>
</tr>
<tr>
<td>4</td>
<td>29</td>
<td>175</td>
<td>67.9</td>
<td>22.2</td>
<td>4.55</td>
<td>67.0</td>
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<td>182</td>
<td>81.4</td>
<td>24.5</td>
<td>5.20</td>
<td>63.9</td>
</tr>
<tr>
<td>6</td>
<td>29</td>
<td>176</td>
<td>72.9</td>
<td>23.6</td>
<td>4.31</td>
<td>59.1</td>
</tr>
<tr>
<td>7</td>
<td>21</td>
<td>183</td>
<td>67.7</td>
<td>20.2</td>
<td>5.05</td>
<td>74.6</td>
</tr>
</tbody>
</table>

((x ± SD) 26.0 ± 2.9 180.1 ± 6.3 73.0 ± 7.7 22.5 ± 1.5 4.8 ± 0.8 66.0 ± 7.5)

Table 2. Biochemical markers before and after the race.

<table>
<thead>
<tr>
<th>Subjects</th>
<th>CRP (mg L(^{-1}))</th>
<th>Creatine kinase (U/L)</th>
<th>WBC (x10(^9) l)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td>Before</td>
</tr>
<tr>
<td>1</td>
<td>1.17</td>
<td>7.7</td>
<td>282</td>
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<tr>
<td>2</td>
<td>0.62</td>
<td>44.3</td>
<td>80</td>
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<td>3</td>
<td>1.42</td>
<td>1.39</td>
<td>424</td>
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<td>4</td>
<td>1.05</td>
<td>1.91</td>
<td>190</td>
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<tr>
<td>5</td>
<td>1.97</td>
<td>2.73</td>
<td>253</td>
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<tr>
<td>6</td>
<td>1.18</td>
<td>4.34</td>
<td>102</td>
</tr>
<tr>
<td>7</td>
<td>0.71</td>
<td>0.84</td>
<td>165</td>
</tr>
</tbody>
</table>

((x ± SD or IQR) 1.17 (0.71; 1.42) 2.73 (1.39; 7.70)\(^{a}\) 213.7 ± 118.1 507.6 ± 101.6\(^{b}\) 6.1 ± 1.3 5.7 ± 2.1)

\(^{a}\) \(p = 0.03\).

\(^{b}\) \(p = 0.002\) compared with the baseline values.

measurement and water trap ±2% of reading. The subjects were required to meet two of the three standard criteria for having achieved \(\text{VO}_2\) max (heart rate \(\geq\) age-predicted maximum heart rate, respiratory exchange ratio \(\geq 1.10\), rating of perceived exertion \(\geq 19\)).

Twenty-four hours after the competition (24 h recovery period), all blood tests and PW A were repeated under the conditions described previously.

Statistical analysis

Statistical analysis was performed using the SPSS version 11.0. Data were expressed as the mean ± standard deviation (SD) and non-normally distributed data were presented as the median with the inter-quartile range (IQR). The data were analysed using the paired-samples \(t\)-test and the Wilcoxon paired test. To examine the associations between the clinical parameters, the Pearson correlation analysis and multiple regression analysis were used. One sample \(t\)-test for statistical power analysis was used. Statistical significance was defined as \(p < 0.05\).

Results

Due to the nature of this team-based endurance study, an individual’s physical performance in the competition could not be distinguished from that of their team. The individual and mean values of the biochemical markers for the cadets before and after the race are presented in tables 1 and 2. There was a 58% increase in plasma creatine kinase \((p = 0.002; \text{statistical power 0.9})\) and a 57% increase in CRP \((p = 0.03; \text{statistical power 0.25})\) after the competition in
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Comparison with baseline values. The post-race values of glucose, haemotocrit, haemoglobin, red blood cell count and platelets did not significantly differ from the baseline values (data not shown). The circulating level of white blood cell count remained unchanged after the race (table 2). Systolic blood pressure, diastolic blood pressure, pulse pressure, mean arterial blood pressure and heart rate did not change significantly when compared with the baseline and the post-race data (table 3). Our data revealed that mean C1 of the subjects was unaffected after the competition, while mean C2 decreased by 23%, but the decrease was statistically nonsignificant ($p = 0.09$, statistical power 0.65) (table 3).

Descriptive analysis revealed that two cadets with maximal oxygen consumption ($V_O2$ max kg$^{-1}$) $> 70$ ml kg$^{-1}$ min$^{-1}$ (mean $V_O2$ max kg$^{-1}$, 75.95 ml kg$^{-1}$ min$^{-1}$) showed a considerable increase in C1 (30%) and C2 (12%), whereas there were no remarkable changes in CRP (4.5%) after the competition. Subjects with $V_O2$ max kg$^{-1}$ $< 70$ ml kg$^{-1}$ min$^{-1}$ (mean $V_O2$ max kg$^{-1}$, 62.0 ml kg$^{-1}$ min$^{-1}$) revealed a significant decrease in C2 (34.3%, $p = 0.02$) and considerable decrease in C1 (9.7%). At the same time, among cadets with $V_O2$ max kg$^{-1}$ $< 70$ ml kg$^{-1}$ min$^{-1}$, CRP increased significantly (73%, $p = 0.04$) after the competition in comparison with the pre-race data.

Correlation analysis revealed that $V_O2$ max kg$^{-1}$ correlated significantly with the change ($\Delta$-difference between baseline and 24 h recovery period) $\Delta$C2 and $\Delta$C1 and with the $\Delta$creatinine kinase (figures 1 and 2). The association between $V_O2$ max kg$^{-1}$ and $\Delta$CRP remained statistically nonsignificant (figure 2).

In multiple regression analysis ($R^2 = 0.89$, $p = 0.01$), $\Delta$C2 as the dependent variable correlated strongly with $V_O2$ max kg$^{-1}$ ($p = 0.005$) and $\Delta$CRP ($p = 0.03$) (table 4). At the same time, $\Delta$C1 as the dependent variable correlated only with $V_O2$ max kg$^{-1}$; no significant correlation was revealed for the $\Delta$CRP.

Discussion

The major finding of the present study is that extreme prolonged physical stress in well-trained young men caused a different responses in CRP and creatine kinase and changes in small and
Table 3. Arterial elasticity indices and haemodynamics before and after the race.

<table>
<thead>
<tr>
<th></th>
<th>C1 (mL mmHg(^{-1}) x 10)</th>
<th>C2 (mL mmHg(^{-1}) x 100)</th>
<th>MAP (mmHg)</th>
<th>Pulse pressure (mmHg)</th>
<th>Heart rate (x min(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td>Before</td>
<td>After</td>
<td>Before</td>
</tr>
<tr>
<td>1</td>
<td>20.1</td>
<td>22.6</td>
<td>13.5</td>
<td>6.4</td>
<td>69.5</td>
</tr>
<tr>
<td>2</td>
<td>16.9</td>
<td>14.6</td>
<td>12.7</td>
<td>10.8</td>
<td>92.5</td>
</tr>
<tr>
<td>3</td>
<td>21.1</td>
<td>35.9</td>
<td>12.2</td>
<td>13.5</td>
<td>74.5</td>
</tr>
<tr>
<td>4</td>
<td>21.9</td>
<td>19.9</td>
<td>11.6</td>
<td>10.2</td>
<td>75.0</td>
</tr>
<tr>
<td>5</td>
<td>18.9</td>
<td>16.1</td>
<td>14.2</td>
<td>9.3</td>
<td>70.0</td>
</tr>
<tr>
<td>6</td>
<td>25.0</td>
<td>17.2</td>
<td>15.7</td>
<td>8.0</td>
<td>70.0</td>
</tr>
<tr>
<td>7</td>
<td>22.0</td>
<td>25.6</td>
<td>9.9</td>
<td>11.6</td>
<td>74.0</td>
</tr>
<tr>
<td>x ± SD</td>
<td>20.8 ± 2.6</td>
<td>21.7 ± 7.3</td>
<td>12.8 ± 1.9</td>
<td>9.9 ± 2.3</td>
<td>75.1 ± 8.0</td>
</tr>
</tbody>
</table>
Arterial elasticity, maximal oxygen consumption and inflammation

large arterial elasticity in individual subjects. Extreme physical load-induced changes in small arterial elasticity significantly depended on VO$_2$ max kg$^{-1}$ and on the change of CRP, while the change of large artery elasticity was rather associated with VO$_2$ max kg$^{-1}$.

This study was designed as a pilot study to investigate the acute effect of systemic inflammation on arterial elasticity in young men. Prolonged physical stress was used as a model of acute inflammation. It is well known that intensive physical exercise is associated with acute inflammatory reaction (Liesen et al 1977). Physical exercise produces microinjuries and local inflammatory reaction in the musculature increases CRP concentration. Several studies have suggested that regular aerobic physical training generates anti-inflammatory reaction and enhances antioxidative defence mechanisms (Criswell et al 1993, Ji et al 1998). Sports disciplines that are associated with excessive and long-term exertion do not always increase inflammatory reaction in the blood. It has been demonstrated that nine months of endurance training was associated with the reduction of plasma CRP in moderately trained runners (Mattusch et al 1999).

Our study showed a strong association between physical load induced changes in C2, VO$_2$ max kg$^{-1}$ and ΔCRP levels, whereas a ΔC1 was associated only with VO$_2$ max kg$^{-1}$. Moreover, physical load caused a significant increase in CRP and a decrease in C2 in cadets with VO$_2$ max kg$^{-1} < 70$ ml kg$^{-1}$ min$^{-1}$. Interestingly, a progressively inverse relationship occurred between CRP and C2 in subjects with VO$_2$ max > 70 ml kg$^{-1}$ min$^{-1}$. The exact mechanism of the reduction in C2 in the conditions of strenuous exercise is probably multifactorial. Hence, we suggest that CRP may have an important role in the genesis of inflammation-induced

Figure 2. Correlation of VO$_2$ max kg$^{-1}$ and extreme physical load induced changes in C1 (left) and C2 (right).

Table 4. Multiple regression analysis for the extreme physical load induced changes in C2.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>β-values</th>
<th>Regression coefficient</th>
<th>Standard error</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO$_2$ max kg$^{-1}$, ml kg$^{-1}$ min$^{-1}$</td>
<td>1.15</td>
<td>0.58</td>
<td>0.10</td>
<td>0.005</td>
</tr>
<tr>
<td>ΔCRP, mg l$^{-1}$</td>
<td>0.65</td>
<td>0.16</td>
<td>0.05</td>
<td>0.03</td>
</tr>
</tbody>
</table>

$r^2 = 0.89, p = 0.01.$
vascular dysfunction as was recently demonstrated by Clapp et al (2004). Experimental models of induced acute inflammation have been associated with endothelial dysfunction (Hingorani et al 2000, Kharbanda et al 2002). Small artery elasticity index has been shown to correlate significantly with endothelial function (Parvathaneni et al 2002, Tao et al 2004) at least partly reflecting endothelium-mediated arterial tone (McVeigh et al 2001). In our study, no changes occurred in C1, while C2 decreased in response to increased CRP. It can be suggested that in healthy young men, acute inflammation affects NO mediated pathways in the smaller arteries, closer to the arterial branching points, rather than in the large arteries.

Another finding of the study is that the response of inflammatory and artery elasticity parameters to physical exercise was significantly related to the subjects’ VO2 max kg\(^{-1}\). It has been shown that endothelial function (Moyna and Thompson 2004) and arterial stiffness (Binder et al 2006) are directly related to maximal aerobic capacity. It seems that higher aerobic capacity may avoid or minimize inflammation response and prevent vascular and muscular damage. It has previously been shown that regular training improves antioxidative capacity (Banerjee et al 2003), decreases sympathetic tone (DeSouza et al 2000) and enhances endothelial function (Clarkson et al 1999). Moreover, physical activity and cardiorespiratory fitness have anti-inflammatory and antithrombotic effects that may favourably affect vascular function (Abramson and Vaccarino 2002).

The main limitation of the present study is the small number of study participants. However, the nature of this kind of competitions is unique due to the prolonged (84.5 h) physical and psychological strain. The military competition presumes that participants have a high aerobic fitness level and special preparation is required for the competition. The relatively high intensity of the long-lasting race is also indicated by the greatly elevated mean pulse rate of our subjects (48–57% of maximal pulse rate). PWA is a time-consuming procedure and it has to be performed 24 h after the race, which means that examiners were limited to performing a single measurement at a single time. The relatively low statistical power of the present study does not allow us to confirm with certainty the inflammation-induced impairment of small artery elasticity and its dependency on VO2 max kg\(^{-1}\). However, this unique inflammatory model may be useful in sports disciplines that involve strenuous conditions of physical stress. The study demonstrates that it is important to monitor not only inflammatory and oxidative stress markers, but also to take into account the role of individual maximal oxygen consumption and the parameters of arterial function. More extensive studies are definitely needed to confirm our preliminary study results.

In conclusion, the major finding of the present study is that extreme physical load induced changes in small arterial elasticity significantly depended on subjects’ VO2 max kg\(^{-1}\) and the change of CRP, whereas the change of large artery elasticity was only associated with VO2 max kg\(^{-1}\). Our preliminary results indicate that acute inflammation may affect small artery elasticity. However, further more extensive studies are needed in this area.

Acknowledgments

This work was supported by the grants nos 5833, 5496, 6588 and 7480 of the Estonian Scientific Foundation and by the target-financed theme nos PARBK 06906 and 1787 from the Ministry of Education and Research of Estonia.

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