Haemodynamic responses and changes of haemostatic risk factors in cold-adapted humans

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Summary

Epidemiological studies have shown an increase in acute myocardial infarctions or deaths due to myocardial infarction in colder weather; the mechanisms most likely involve increased blood levels of haemostatic risk factors, and increases in arterial blood pressure and heart rate. We studied the relationship between cold adaptation, haemostatic risk factors and haemodynamic variables. Cold adaptation was obtained by a programme of immersion of the whole body up to the neck in a water-filled bath, the temperature of which was gradually decreased from 22°C to 14°C, time of exposure being increased from 5 to 20 min over a period of 90 days. We studied 428 patients (44% men) and measured blood levels of fibrinogen, plasminogen activator inhibitor 1 (PAI-1), tissue plasminogen activator antigen (t-PA), plasma viscosity, von Willebrand factor, D-dimer and platelet count, both at baseline and after 90 days of daily immersion. There were significant reductions in von Willebrand factor (−3%; p<0.001), and plasma viscosity (−3.0 s; p<0.001), and a mild but significant increase in PAI-1 (+0.3 IU/ml; p=0.02). The pressure product (systolic blood pressure × heart rate) was also significantly lower after cold adaptation (−310; p=0.004). Cold adaptation, compared with exposure to cold weather, induces different haemodynamic responses and changes of blood levels of haemostatic risk factors.

Introduction

Recently, a marked increase has been reported in the number of acute myocardial infarction (AMI) cases during winter. Approximately 53% more cases were reported in winter than during summer. The mechanism or mechanisms by which abrupt rupture of atherosclerotic plaques could occur during cold exposure has been associated with an increased sympathetic tone, causing increased blood pressure, heart rate and cardiac workload. Furthermore, fibrinogen, plasma viscosity, von Willebrand factor, factor VII, and platelet count have all been shown to increase with cold weather. Woodhouse et al. studied 96 men and women, aged 65–74 years, living in their own homes, to examine seasonal variation in plasma fibrinogen and factor VII clotting activity (FVIIc). Both fibrinogen and FVIIc plasma values were greater in winter, with estimated winter-summer differences of 0.13 g/l for fibrinogen and 4.2% of standard for FVIIc. These seasonal variations in the cardiovascular risk factors fibrinogen and FVIIc might explain the marked seasonal variation in cardiovascular deaths in the elderly. Several mechanisms have been suggested whereby raised plasma fibrinogen could produce vascular disease, including involvement in early atherosclerotic plaque formation, the response to endothelial damage, platelet aggregability, and increased plasma viscosity. Keatinge et al. found increases in platelets, red cells, blood viscosity, and plasma cholesterol in healthy individuals exposed to 6 h mild surface cooling in moving air at 24°C, with little fall in core temperature (0.4°C). Meade et al. suggested that elevated fibrinogen may be due to increased winter infections, as evidenced by raised
neutrophil count and C-reactive protein in the elderly. On the other hand, Stout found that white cell count and smoking status did not significantly change in winter, suggesting that temperature change itself played an important role in cardiovascular mortality. Different and consecutive cardiovascular adjustments appear when humans are exposed to a cold environment. Peripheral vasoconstriction is one immediate response, secondary to an ortho-sympathetic stimulation initiated by the cutaneous thermo-and nociceptors activation. Heart rate also increases, due to the same phenomenon, but is not maintained during the exposure. A rise in blood pressure and heart rate, and an increase in cardiac output, are observed from the beginning of the cold exposure. This increased heart rate seems to be related to the nervous control of the nodal system, as judged by the chronology of events.

The aim of this study was to investigate the relationship between cold adaptation, blood levels of several haemostatic risk factors, and several haemodynamic variables.

Methods

We studied 428 males (44%) and females (56%) attending the Research Institute as part of a health screening programme. All were euthyroid by clinical and laboratory examination, and none had a goitre. None was on medication. All underwent physical examination and laboratory work-up, measuring height, weight, tympanic temperature, pulse rate, heart rate, and blood pressure. Body mass index (BMI) was calculated as weight/height squared. Standardized historical and physical examination data were obtained. An extensive self-administered questionnaire examined present health, physical activity, and dietary habits. Blood pressure and heart rate were measured with an automatic sphygmomanometer and electrocardiogram throughout the test.

Cold adaptation was by a programme of water immersion of the whole body up to the neck in a water-filled bath. The bath temperature was gradually decreased from 22 °C to 14 °C, and the time of exposure increased from 5 to 20 min, over a period of 90 days. Each immersion was in four stages: stage one, acclimatization of the feet to cold water and touch; stage two, acclimatization of the lower half of the body to cold water; stage three, total body immersion, varying from 5 to 20 min; stage four, re-warming phase.

Blood was sampled following a 12 h fast, at 0900 h. Plasma fibrinogen was measured by a prothrombin time (PT)-based assay, using rabbit brain thromboplastin as the PT reagent. FVII coagulant (FVII:C) activity was determined by an indirect PT assay using FVII-deficient plasma. These assays used an automated coagulation analyser (ACL 300 Research) and reagents, standards and controls from Instrumentation Laboratory. The levels of tissue plasminogen activator (t-PA) were measured by a bioassay that captured t-PA using a specific antibody coated on the wells of microtitre plates, prior to amidolytic assay. The assay of biologically active PAI-1 was by immunoassay. PAI-1 was bound to t-PA coated on the wells of microtitre strips, and detected using a specific monoclonal antibody. The reagents, calibrators and controls for t-PA and PAI-1 assays were from Biopool. The plasma levels of D-dimer were estimated by ELISA using reagents, calibrators and controls from Chromogenix.

The levels of von Willebrand factor (Diagnostica Stago) were also estimated by ELISA. Plasma viscosities were determined using a miniature falling-ball viscometer (Microviscometer) which measures the falling time of a ball through a microcolumm of a Newtonian fluid (e.g. blood plasma), this being proportional to the viscosity. The inter-assay coefficients of variation were 2.0% and 1.6% for pooled human plasma and distilled water, respectively.

The study was approved by the ethics committee of Beatrice Research Centre, and written informed consent was obtained from every patient.

Statistical analysis used the SAS statistical package. Statistical comparisons were performed Wilcoxon’s paired test. The null hypothesis was rejected when \( p < 0.05 \). Data are shown as medians (1st–3rd quartile).

Results

The clinical details of the study subjects are described in Table 1.

The rate pressure product (systolic blood pressure × heart rate) was significantly lower after 90 days of intermittent head-out cold-water immersion (8700) compared with baseline data (8880) (\( p = 0.004 \)) (Table 2).

Analysis of haemostatic factors at baseline and after 90 days of head-out cold water immersion is

<table>
<thead>
<tr>
<th>Table 1 Clinical details for 428 subjects</th>
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<tbody>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Male gender</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
</tr>
<tr>
<td>systolic</td>
</tr>
<tr>
<td>diastolic</td>
</tr>
<tr>
<td>Heart rate (l/min)</td>
</tr>
</tbody>
</table>

Data are medians (1st–3rd quartile).
Cold adaptation and the heart

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Haemodynamic variables at baseline (A1) and after 90 days of cold water immersion (D1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>D1</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>71 (65–80)</td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td></td>
</tr>
<tr>
<td>systolic</td>
<td>125 (110–140)</td>
</tr>
<tr>
<td>diastolic</td>
<td>80 (70–90)</td>
</tr>
<tr>
<td>Pressure rate product</td>
<td>8880 (7700–10500)</td>
</tr>
</tbody>
</table>

Data are medians (1st–3rd quartile).

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Blood levels of haemostatic risk factors at baseline (A1) and after 90 days of cold water immersion (D1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>D1</td>
</tr>
<tr>
<td>Factor VII:c (%)</td>
<td>103 (91–121)</td>
</tr>
<tr>
<td>Fibrinogen (g/l)</td>
<td>3.26 (2.85–3.77)</td>
</tr>
<tr>
<td>Plasminogen activator inhibitor-1 (IU/ml)</td>
<td>4.09 (0.6–8.9)</td>
</tr>
<tr>
<td>Tissue type plasminogen activator antigen (IU/ml)</td>
<td>1.63 (1.06–2.33)</td>
</tr>
<tr>
<td>D-dimer (IU/ml)</td>
<td>33.3 (13.3–61.9)</td>
</tr>
<tr>
<td>Plasma viscosity (s)</td>
<td>616.67 (603–633.33)</td>
</tr>
<tr>
<td>Platelets (10³ × ml)</td>
<td>229 (201–266)</td>
</tr>
<tr>
<td>Von Willebrand factor (%)</td>
<td>96 (83–106)</td>
</tr>
</tbody>
</table>

Data are medians (1st–3rd quartile).

shown in Table 3. There was a significant reduction in von Willebrand factor (−3%; p < 0.001), and plasma viscosity (−3.0 s; p < 0.001), and a significant increase in PAI-1 (+0.3 IU/ml; p = 0.02).

Blood levels of fibrinogen (+0.07; p = 0.1), t-PA (−0.05 IU/ml; p = 0.4), D-dimer (p = 0.4), factor VII:c (+2%; p = 0.06) and platelet count (p = 0.84) were not significantly different at the end of the 90 days, compared with baseline results (Table 3).

Discussion

The association of cold weather with coronary heart disease may be explained in many ways. One possibility is that cold weather could precipitate arteriosclerosis or its complications over weeks or months.14–18

The acute effects of cold on the heart and circulation may explain some of the cold complications associated with a cold environment.19 The stimulation of the cold receptors of the skin, in particular, induces stimulation of the sympathetic nervous system, as indicated by increased levels of catecholamines in the blood.20 A seasonal variation in norepinephrine and epinephrine excretion has also been reported in men, higher levels being found in winter, suggesting an increase in the activity of the sympatoadrenal system.9 This results in vasoconstriction in the skin, increased systolic blood pressure, and increased central blood volume.21 Cardiac filling pressure, left ventricular end-diastolic pressure and volume, and stroke volume are also increased.22 These factors add to the workload of the heart and its oxygen requirement. Increased sympathetic stimulation and a large end-diastolic volume increase the oxygen requirement of the heart more than the increased product of the increased heart rate and systolic blood pressure alone would suggest.23 These phenomena increase the oxygen requirement in the myocardium while impeding its access to oxygen.13,14

This chain of events may explain a variety of cold-induced functional abnormalities in some of the coronary patients: decreased stroke volume and abnormal myocardial contraction; reduction of anginal threshold and physical performance capacity; ECG changes indicating myocardial ischaemia occurring at lower loads; and possibly increased frequency of cardiac arrhythmias. In our cold-adapted volunteers, we observed a significant reduction in the rate pressure product, which could indicate a decline in autonomic stimulation. These haemodynamic responses are similar to those reported by Muza et al.23 in a group of males who showed increased blood pressure during the first cold water exposure, but not during the last cold water immersion. These observations can be explained by the short
intermittent adaptation described by Radomski et al., who observed that non-pre-adapted healthy volunteers showed significant increased norepinephrine excretion in the urine when suddenly exposed to cold, which was not evident in the pre-adapted group. As with physical training, repeated exposure to severe cold may result in a diminution of the sympathetic response to cold, and an enhancement of the vagal response.

We suggest that the decreased sympathetic activity during short intermittent adaptation is related to habituation, repeated exposures to a stress producing a decline in autonomic stimulation.

Epidemiological studies leave little doubt of the link between thrombo-atherogenesis and fibrinogen, and clinical studies have demonstrated the importance of thrombosis in ischaemic heart disease. Seasonal variation in fibrinogen in people aged 75 years and over has been shown by Stout et al., and by several large cross-sectional studies. The increase in plasma fibrinogen concentration that occurs in the cold is of particular interest. Fibrinogen aggregates platelets, once agents such as adenosine or granulocyte elastase have exposed binding sites on their surface, as well as being as substrate for fibrin production. Several other mechanisms have been suggested whereby raised plasma fibrinogen could produce vascular disease, including involvement in early atherosclerotic plaque formation, the response to endothelial damage, and increased plasma viscosity. Yeh et al. observed a short temporal relation between temperature drop and mortality in Taiwan, where ambient temperature fluctuates greatly, supporting the hypothesis that temperature drop may be a major factor in the mortality change in winter, partly due to changes of haemostatic factors.

In our volunteers, after 90 days of short intermittent cold water immersions, we observed a mild increase in PAI-1, and a decrease of von Willebrand factor and plasma viscosity, with no significant changes in fibrinogen, factor VIIc, t-PA, platelet count, or D-dimer.

An increase in circulating PAI-1 can attenuate physiological fibrinolytic activity and the rate of clot lysis. However, measurement of PAI-1 has produced conflicting results, possibly because its concentration varies depending on age, sex, risk factors and the degree of atherosclerosis in an individual. Increase plasma concentrations of von Willebrand factor derived from endothelial cells have been reported in various vascular disorders. Thus increases in the concentration of this factor in patients at high risk for coronary thrombotic occlusion may reflect endothelial perturbation. The results of our study, contrasting with past observations that cold weather can induce increases in blood viscosity, fibrinogen, platelet count, and arterial blood pressure, suggest that cold adaptation does not increase the risk of vascular thrombosis.

We have previously demonstrated a significant reduction of total and LDL-cholesterol in a group of patients with hypercholesterolemia after 90 days of cold adaptation. On the other hand there is little doubt of the link between cold weather and increased level of serum lipid levels, fibrinogen, factor VII, platelet count, and plasma viscosity and myocardial infarction. This study demonstrates that cold adaptation induces different haemodynamic responses and changes in blood levels of haemostatic risk factors than does exposure to cold weather. Further work is required to investigate the effects of acute cold stress on cardiovascular risk factors in adapted and non-adapted humans to determine the possible protective effect of cold adaptation.

Acknowledgements
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