Seasonal Changes in Haemostatic Factors in Young and Elderly Subjects

R. W. STOUT, V. L. S. CRAWFORD, M. J. McDERMOTT, M. J. ROCKS, T. C. M. MORRIS

Summary
Morbidity and mortality from cardiovascular disease are more common in colder seasons, especially in elderly people. Previous studies have shown higher fibrinogen levels in old people in the winter months. The present studies of haemostatic factors in relation to age and season have shown that fibrinogen, tissue plasminogen activator (tPA), protein S and protein C levels are higher in old (aged 75 years and over) than young (aged 25–30 years) subjects while antiplasmin levels are lower in old people. Antiplasmin and protein C levels are lower in winter in both young and old while plasminogen activator inhibitor (PAI) is higher, and tPA higher in old people only. This study illustrates the complex interrelationships of the haemostatic system and may suggest that in 'successful' elderly people the fibrinolytic system may alter to maintain the delicate balance between thrombogenic and fibrinolytic activity. Nevertheless, the results presented here suggest that both old age and cold weather may increase the risk of atherothrombotic disease.

Introduction
There is a marked seasonal variation in morbidity and mortality, particularly in elderly people in the United Kingdom [1]. The main cause of this seasonal effect is cardiovascular disease, especially coronary heart disease and stroke [2]. In general the seasonal changes in mortality correlate with changes in environmental temperature. In a previous study we showed that fibrinogen levels were significantly higher in the colder months than the warmer months in people aged 75 and over and the changes in fibrinogen correlated with changes in ambient temperature [3]. Viscosity and HDL cholesterol were also higher in the colder months. In the present study measurements were made of haemostatic factors in young and elderly subjects living in the community in the winter and summer.

Subjects and Methods
One hundred people living in their own homes were studied. Fifty were aged 25–30 years and 50 were aged 75 years and over, the proportion of the males being 44% in the young and 36% in the elderly. The study was approved by The Queen's University of Belfast Research Ethical Committee. A research nurse visited each subject on four occasions—during two colder months (January and February) and two warmer months (June and July) of 1992. Blood samples were taken and the blood was rapidly returned to the laboratory where coagulation studies were carried out. The methods used were as follows: fibrinogen was measured by the Clauss method [4]; protein S activity was measured using the IL Test™, an assay based on the prolongation of prothrombin time; protein C activity, tissue plasminogen activator (tPA), antithrombin III (AT III), plasminogen activator inhibitor (PAI) and antiplasmin were measured photometrically using chromogenic techniques (Chromogenix™ kits). Fibrinogen levels were measured immediately and were subject to daily quality assurance using Immuno 'control normal plasma' which is assayed for fibrinogen using the Clauss method; one batch of control plasma was used throughout. All the other variables were analysed in large batches on frozen plasma according to the test-kit manufacturer's protocol. In all cases, all tests for a given variable were analysed using reagents from the same batch; in each case a full calibration was included with every analysis.

The results were compared between the young and the elderly subjects by independent \( t \) tests and within the young and elderly groups, the paired results in the cold and warm months were compared by paired \( t \) tests. Repeated measures analysis of variance was computed to confirm significant seasonality.

Results
The temperature, both in the home and in the external environment, was higher in the summer months (Table). The mean minimum environmental temperatures were 3.5°C in the winter months and 10.6°C in the summer; the mean maximum environmental temperatures were respectively 9.5°C and 17.9°C. In the home the winter/summer differences were smaller—minimum 12.4/18.1°C and maximum 17.6/21.6°C. The data for the haemostatic variables are shown in the Table. Fibrinogen, protein S, tPA and protein C were higher in the old than the young while antiplasmin was higher in the
increased levels of protein C, a coagulation inhibiting molecule in the coagulation process before the deposition of fibrin, has again been shown to be higher in older subjects protein C and antiplasmin were again lower in the colder months than the warmer months while PAI was higher and there was no significant difference in the other measurements. In the older subjects protein C and antiplasmin were again higher in the warmer months whereas PAI and tPA were higher in the colder months. There was no seasonal effect on fibrinogen, AT III or protein S.

Discussion

Epidemiological studies leave little doubt of the link between thrombo-atherogenesis and fibrinogen [5] and clinical studies have demonstrated the importance of thrombosis in ischaemic heart disease [6]. Seasonal variation in fibrinogen in people aged 75 years and over has been shown by the present authors [3] and confirmed by another longitudinal study in people aged 65–74 [7], and by several large cross-sectional studies [8, 9]. A seasonal effect on fibrinogen was not found in the present study. This may be because of the relatively small number of observations but the difference in temperature between winter and summer was also less than in the previous study [3]. It would have been desirable to make observations monthly throughout the year and to use larger numbers of subjects in order to identify time trends as in the previous study [3], but the complexity and expense of some of the assays precluded this. An increase in factor VIIc in colder weather has been reported in one longitudinal study [7] but not confirmed in a large cross-sectional study [8] while raised levels of α2-macroglobulin have also been found in the coldest months [8].

This study extends the range of haemostatic factors studied in elderly people in warm and cold months and underlines the complexity of examining single variables from a highly complex system. Fibrinogen, the final molecule in the coagulation process before the deposition of fibrin, has again been shown to be higher in old people [10–13]. Older individuals, however, have increased levels of protein C, a coagulation inhibiting factor, but the levels of protein C were found to be reduced in cold weather in both old and young people. Neil et al. [14] have suggested that protein C may leave the plasma during the period of haemoconcentration that occurs in acutely cooled subjects.

Opposing this cold-induced atherothrombogenic effect, protein S and tPA were both found to be higher in our elderly group, the latter only in the colder months. Although protein S did not vary with the season, tPA was elevated in the elderly people in cold weather. Higher tPA in elderly people [15, 16] and an exercise induced reduction in tPA in old but not in young people has been reported [15]. It seems that in old people tPA is sensitive to both cold and exercise but does not respond to these challenges in young people. The increase in tPA produced by physical activity has been proposed as one of the mechanisms by which habitual physical activity might reduce the risk of cardiovascular disease. The fibrinolytic system also has its antagonists, and antiplasmin and PAI were found to have different relationships to age and cold, antiplasmin being reduced in elderly subjects and in cold weather in both old and young, while PAI was increased in cold weather but not altered by age as previously shown [16, 17].

The role of haemostatic factors in coronary artery disease has become better understood in recent years [18]. As already mentioned, fibrinogen is an independent risk factor for cardiovascular disease [5]. There is also a strong independent relation between impaired fibrinolytic activity and the development of coronary artery disease [18]. Thus elevated PAI activity and reduced fibrinolytic activity and the development of coronary artery disease [18]. The fibrinolytic system also has its antagonists, and antiplasmin and PAI were found to be reduced in cold weather in both old and young, while PAI was increased in cold weather but not altered by age as previously shown [16, 17].

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**Table. Levels of haemostatic variables (mean with 95% CI) in young and old subjects in cold and warm months**

<table>
<thead>
<tr>
<th></th>
<th>Cold</th>
<th>Warm</th>
<th>p†</th>
<th>Cold</th>
<th>Warm</th>
<th>p†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.3 (2.2–2.4)</td>
<td>2.3 (2.3–2.4)</td>
<td>0.394</td>
<td>3.0 (2.9–3.2)*</td>
<td>3.0 (2.9–3.1)*</td>
<td>0.810</td>
</tr>
<tr>
<td>Fibrinogen (g/l)</td>
<td>84.5 (80.9–88.0)</td>
<td>87.6 (83.7–91.4)</td>
<td>0.009</td>
<td>93.4 (88.2–98.6)*</td>
<td>99.5 (94.0–104.9)*</td>
<td>0.000</td>
</tr>
<tr>
<td>Protein C (%)</td>
<td>1.2 (1.1–1.3)</td>
<td>1.2 (1.2–1.3)</td>
<td>0.537</td>
<td>1.6 (1.3–1.8)*</td>
<td>1.2 (1.2–1.3)</td>
<td>0.014</td>
</tr>
<tr>
<td>tPA (iu/ml)</td>
<td>104.5 (101.8–107.1)</td>
<td>121.9 (119.1–124.8)</td>
<td>0.000</td>
<td>98.6 (95.6–101.6)*</td>
<td>117.3 (113.1–121.4)*</td>
<td>0.000</td>
</tr>
<tr>
<td>Antiplasmin (%)</td>
<td>17.2 (15.7–18.6)</td>
<td>14.3 (12.7–16.0)</td>
<td>0.002</td>
<td>17.6 (15.9–19.3)</td>
<td>15.7 (13.8–17.6)</td>
<td>0.016</td>
</tr>
<tr>
<td>PAI (au/ml)</td>
<td>102.1 (98.3–105.9)</td>
<td>100.4 (96.2–104.6)</td>
<td>0.362</td>
<td>97.6 (93.3–102.0)</td>
<td>100.7 (96.5–104.9)</td>
<td>0.084</td>
</tr>
<tr>
<td>Protein S (%)</td>
<td>90.9 (86.6–95.2)</td>
<td>89.5 (85.4–93.6)</td>
<td>0.434</td>
<td>99.6 (95.7–103.3)*</td>
<td>101.0 (97.1–104.8)*</td>
<td>0.381</td>
</tr>
</tbody>
</table>

† Significant differences between cold and warm months within each age group. *p < 0.05, young vs. old group within each season.

tPA tissue plasminogen activator; PAI plasminogen activator inhibitor; AT III antithrombin III.
The present results illustrate the complex inter-relationship of the thrombotic and fibrinolytic systems and their inhibitors, making it difficult to predict the overall effect. Interpretation of results in the elderly group may also be seen as more complex in as much as these are survivors in whom the haemostatic mechanism has been particularly successful in avoiding both excessive haemorrhage and thrombosis.

References

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