Is Sticky Blood Bad for the Brain?

Hemostatic and Inflammatory Systems and Dementia in the Caerphilly Prospective Study

John Gallacher, Antony Bayer, Gordon Lowe, Mark Fish, Janet Pickering, Sofia Pedro, Frank Dunstan, James White, John Yarnell, Yoav Ben-Shlomo

Objective—Hemostasis and inflammation have been implicated in dementia. This study investigates the role of specific hemostatic and inflammatory pathways with incident vascular and nonvascular dementia.

Methods and Results—This was a prospective study of a population sample of men aged 65 to 84 years, with baseline assessment of hemostatic and inflammatory factors and cognition measured 17 years later. The sample included 865 men (59 had dementia and 112 had cognitive impairment, not dementia), free of vascular disease at baseline and for whom hemostatic and inflammatory marker data were available and cognitive status was known. A total of 15 hemostatic and 6 inflammatory markers were assessed. Factor analysis was used to identify hemostatic subsystems. The National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurologie criteria were used to identify vascular dementia. By using standardized (z) scores for hemostatic and inflammatory markers, and after adjustment for age and risk factors, vascular dementia was associated with fibrinogen (hazard ratio [HR], 1.68; 95% confidence interval [CI], 1.02–2.76), factor VIII (HR, 1.79; 95% CI, 1.09–3.00), and plasminogen activator inhibitor 1 (HR, 3.13; 95% CI, 1.73–5.70). For vascular dementia, the HR risk from high levels of all three hemostatic variables (fibrinogen, factor VIII, and plasminogen activator inhibitor 1) was 2.97 (P<0.001). Inflammatory factors were not associated with vascular dementia.

Conclusion—The associations of these hemostatic markers with vascular dementia may implicate clot formation as the primary mechanism and are consistent with a microinfarct model of vascular dementia. (Arterioscler Thromb Vasc Biol. 2010;30:599-604.)

Key Words: dementia • hemostasis • inflammation • cognition • aging

Hemostasis and the inflammatory response are complex and interrelated processes that are associated with a variety of phenotypes, including cardiovascular diseases.1 There is limited case-control evidence associating markers of hemostasis and inflammation with dementia.2–6 Limited prospective data come from the Rotterdam Study, which found that fibrinogen, but not C-reactive protein (CRP), was associated with incident dementia at the age of 6 years.7 Therefore, further studies of hemostatic and inflammatory markers and risk of dementia (both vascular and nonvascular) are required.

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Hemostasis involves a delicate balance of several closely related subsystems or pathways. It is possible, therefore, that associations with these responses reflect the impact of specific pathways rather than of individual biomarkers. One area of interest is whether hemostatic markers can be analyzed within the context of the coagulation pathways that they represent and whether these pathways can be used to identify more closely the mechanisms associated with cognitive impairment. In the Caerphilly Prospective Study, a wide range of available hemostatic markers allows the comparative influence of several pathways to be assessed.8

Methods

The Study Population

Between 1979 and 1983, all men aged 45 to 59 years within the locality of Caerphilly in South Wales, England, were invited to participate. Of the 2818 men found eligible, 2512 (89.1%) were recruited. For the second examination (1985), the original cohort was supplemented with all men of a similar age who had moved into the
area since the first examination. A total of 2398 men were seen and provided blood samples. Data on hemostatic and inflammatory markers were available for 2318 men. Not all the hemostatic and inflammatory markers were assessed for all men, because of progressive depletion of stored plasma samples. At the third (1993), fourth (1996), and fifth (2004) examinations, cognition was assessed. At the fifth examination, when the men were aged 65 to 84 years, cognitive assessment was used to identify men eligible for neurological examination to ascertain dementia. Informed consent was obtained from every participant, and the study was approved by the Gwent Research Ethics Committee.

Hemostatic and Inflammatory Markers

A fasting blood sample was obtained during the second examination. In a sample anticoagulated with potassium EDTA, fibrinogen was measured using heat precipitation nephelometry; plasma viscosity, with a Coulter-Harkness capillary viscometer; white blood cell count, in an automated cell counter; and α2-macroglobulin and α1-antitrypsin, as previously described.

Activated partial thromboplastin time, activated protein C ratio, fibrinogen, factor VII, and factor VIII (FVIII) were assayed in an MDA-180 coagulometer (Organon Teknika, Cambridge, England). Fibrin formation time and reaction clotting time were measured by thromboelastography. Activated factor XII, prothrombin fragment 1+2 (Frag1 +2), thrombin-antithrombin complexes, tissue plasminogen activator antigen, von Willebrand factor antigen (VWF), and fibrin D-dimer were assayed by enzyme-linked immunosorbent assay; and plasminogen activator inhibitor 1 (PAI-1) was assayed using a chromogenic assay. High-sensitivity CRP was assayed by immunonephelometry. Interleukin 6 (IL-6) was assayed using a high-sensitivity enzyme-linked immunosorbent assay.

Ascertainment of Dementia

Cognitive screening at the fifth examination was used to identify men eligible for a neurological examination. The criteria were as follows: all men whose Cambridge Cognitive Examination score was lower than 83 or whose decline in Cambridge Cognitive Examination score between any two cognitive assessments was greater than 10 points or who were unable to complete the CAMCOG were eligible for a neurological examination. For nearly all men, the neurological examination occurred within two months of cognitive screening.

The criteria for dementia and cognitive impairment not dementia (CIND) are detailed elsewhere. Briefly, the neurological examination included the Cambridge Mental Disorders of the Elderly Examination, a cardiovascular and neurological examination; the Rosen-Modified Hachinski Ischaemic Score (HIS);14 the Frontal Assessment Battery;12 and the Clinical Dementia Rating.16 With the subject’s consent, someone who knew him or her well (usually the next of kin) was identified and approached to complete an Informant Questionnaire on Cognitive Decline in the Elderly and the modified Cambridge Mental Disorders of the Elderly Examination informant interview. Additional questions were asked when appropriate about symptom onset and progression. All available general practitioner and hospital records were reviewed and summarized, with particular attention given to mention of patients’ mental state and relevant investigations. All subjects who had died were identified by “flagging” at the National Health Service Central Register in Southport, and their cause of death was noted. Further information was sought on those with a cause of death recorded as dementia or Alzheimer’s disease (AD). Subjects with vascular dementia were required to fulfill National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l’Enseignement en Neurologie criteria for possible or probable vascular dementia. Subjects not meeting the full dementia criteria and with an HIS of 3 or higher (including history of cerebrovascular disease or consistent lateralizing neurological signs) were classified as having vascular CIND. Subjects who fulfilled the National Institute of Neurological and Communicative Disorders–Alzheimer’s Disease and Related Disorders Association criteria for probable AD and who had no clinical features suggestive of cerebrovascular disease (HIS ≤2, and absence of vascular disease on available neuroimaging) or other causative disorder were classified as having AD. Subjects with a presentation or clinical course in keeping with AD and features to suggest cerebrovascular disease (operationalized as an HIS ≥3 or neuroimaging evidence of infarction) were diagnosed as having mixed dementia. Subjects fulfilling the standardized diagnostic criteria for other dementia-like conditions were categorized accordingly. Subjects with CIND were classified by cause only if likely cause was apparent. Because of small numbers, all nonvascular conditions were combined for the purpose of analysis.

Statistical Analysis

Hemostatic and inflammatory markers were log transformed where appropriate, and all markers were standardized (ie, z scores were calculated). Associations of individual biomarkers with dementia and CIND were performed by Cox regression (STATA 10 software; Statacorp, Tex). Adjustment was made for age, social class, systolic blood pressure, body mass index, smoking status (never smoked, ex-smoker, or current smoker), total cholesterol level, and alcohol consumption. Men with previous vascular disease, intermittent claudication, or stroke were not included. Analyses were repeated adjusting for premorbid cognitive function using the National Adult Reading Test score obtained at the third examination. The Registrar General’s classification of social class is a definition of socioeconomic status widely used in England. Social class was modeled as a 4-level indicator variable composed of these levels: I and II, III nonmanual, III manual, and IV and V. To investigate the possibility of a prodromal effect of dementia, Cox regressions were repeated, not including men with evidence of early cognitive decline. Evidence of early cognitive decline was defined as cognitive scores declining consistently from the first cognitive examination. This is a strong test of the prodromal hypothesis; however, it excludes men whose decline began soon after baseline (second) examination and men whose decline is not the result of a dementing process.

To test the hypothesis that associations with individual biomarkers reflect the operation of specific coagulation pathways on vascular dementia, structural equation modeling (SEM) was used. SEM allows variables to act dependently and independently and enables the putative causal pathway to be modelled. A two-step procedure was used. First, specific coagulation pathways were identified by exploratory factor analysis. Structural modelling (using EQS software) was then used to estimate the association between the latent variables representing specific coagulation pathways and dementia. The fit statistics used to evaluate the fit of the data to the hypothesized coagulation pathways and dementia were the comparative fit index (CFI), the root mean square error of approximation (RMSEA), and the standardized root mean square residual (SRMR). The SEM glossary describes the coefficients that are shown (Figure).

These are as follow: (1) standardized path coefficients (single-headed arrows) that are standardized regression coefficients and indicate the association between dependent and independent variables, (2) standardized residual covariances (double-headed arrows) indicating associations between independent variables not accounted for in the model, and (3) standardized residual variances (adjacent to independent variables) indicating measurement error for the observed independent variables. An introduction to SEM is provided as electronically available supplementary material (available online at http://atvb.ahajournals.org).

Results

Of the 2318 men with data on hemostatic and inflammatory markers, 750 were known to have died before the current phase of the study, leaving 1568 considered to be alive; 1429 of these men were eligible for follow-up, with 1137 (79.6%) successfully followed up and cognitively screened. Of these men, 71 were diagnosed as having dementia, 171 were diagnosed as having CIND, and 895 were cognitively healthy. A further 21 men were diagnosed as having dementia from medical records, resulting in the cognitive status being available for 1158 men. Of these men,
865 were free of vascular disease at baseline and available for analysis, of whom 112 had cognitive impairment and 59 had dementia. If men with evidence of early decline are omitted, 744 were available for analysis, of whom 85 were cognitively impaired and a further 42 had dementia. The maximum follow-up was 20 years; however, it averaged 17.3 years (SD, 1.3 years). For the exploratory factor analysis, 476 men had complete data for all hemostatic variables. For structural modeling, 602 men had complete data.

The baseline characteristics of the 1568 men who were alive at the beginning of the study show that men who were not followed up were more likely to be of manual social class (34.8% vs 62.0%; P<0.01) and more likely to be current smokers (44.5% vs 35.9%; P<0.01) and to have a lower cognitive function (National Adult Reading Test mean, 21 vs 25; P<0.01). They did not differ significantly in age or body mass index, and any differences in blood pressure were small. Regarding hemostatic markers, all differences were slight, with men who were not followed up having a longer activated partial thromboplastin time (mean, 33.4 vs 32.9 seconds; P=0.04) and higher levels of D-dimer (mean, 82.2 vs 78.0 ng/mL; P=0.05), factor XIA (mean, 3.23 vs 3.02 ng/mL; P=0.04), and tissue plasminogen activator antigen (mean, 11.9 vs 11.2 ng/mL; P<0.01). Men who were not followed up also had slightly higher levels of the inflammatory markers α2-macroglobulin (mean, 15.7 g/100 g vs 15.2 g/100g; P=0.03) and α1-antitrypsin (mean, 16.7 g/100 g vs 16.1 g/100 g; P<0.01) and substantially higher levels of IL-6 (mean, 4.91 vs 2.20 pg/mL; P<0.01). The following markers required log transformation for the analysis: D-dimer, Frag1+2, thrombin-antithrombin complex, VWF, plasma viscosity, CRP, IL-6, and α2-macroglobulin.

Associations with cognitive impairment (CIND and dementia) were investigated in 865 men free of vascular disease at baseline (Table 1). After adjustment for age, social class, systolic blood pressure, body mass index, smoking status, total cholesterol level, and alcohol consumption, an association with vascular impairment was found for fibrinogen. Evidence of association was also found for PAI-1. There was no evidence of association with any of the inflammatory markers. For nonvascular impairment, there was no evidence of increased risk with any of the hemostatic markers or inflammatory markers, although factor VII appeared to have a protective effect.

The analysis was repeated for dementia. For the hemostatic markers, vascular dementia was associated with fibrinogen, FVIII, and PAI-1. The analysis was repeated, excluding men with evidence of early cognitive decline. The smaller numbers reduced the power of the analysis, but the point estimates were closely comparable to those found in the sample as a whole, with the strongest associations being found for fibrinogen (hazard ratio [HR], 1.79; 95% confidence interval [CI], 0.98–3.28; P=0.06), FVIII (HR, 1.77; 95% CI, 0.88–3.57; P=0.11), and PAI-1 (HR, 2.68; 95% CI, 1.22–5.88; P=0.04).

For nonvascular dementia, evidence of a protective association was found for the hemostatic marker Frag1+2 and for the inflammatory marker plasma viscosity.

The associations of FVIII, fibrinogen, and PAI-1 with vascular dementia may either reflect a general effect of the coagulation cascade or identify specific coagulation pathways that confer increased risk. These alternatives were investigated by including FVIII, fibrinogen, and PAI-1 in the same analysis to show whether their effects were independent of one another. The presence of a general hemostatic effect would be indicated by the absence of independent associations. The analysis was consistent with each biomarker making some independent contribution to the association: fibrinogen, HR, 2.11 (95% CI, 0.88–5.04; P=0.09); FVIII, HR, 2.09 (95% CI, 1.02–4.31; P=0.04); and PAI-1, HR, 4.39 (95% CI, 1.97–9.77; P<0.001). The combined independent effects of these biomarkers on risk for vascular dementia was 2.97 (95% CI, 1.38–4.56; P<0.001).

The SEM was used to further investigate the relative contribution to risk of vascular dementia of the coagulation pathways represented by the available hemostatic markers. Exploratory factor analysis found four statistical factors corresponding to components of the coagulation pathway (Table 2). The high loadings on statistical factor 1 of FVIII (0.88) and VWF (0.82) were interpreted to represent the FVIII/VWF complex (indicating potential for platelet and fibrin plug formation). High loadings on statistical factor 2 of PAI-1 (0.80) and tissue plasminogen activator antigen (0.75) were interpreted to represent the potential for impaired fibrinolytic activity. High loadings on statistical factor 3 of fibrinogen (0.81) and D-dimer (0.69) were interpreted to represent clotting activity. High loadings on statistical factor four of thrombin-antithrombin complexes (−0.75) and Frag1+2 (−0.77) were interpreted to represent thrombin generation. These statistical factors were used as latent variables for the purposes of structural modeling.

The four-factor structural model (Figure), using the two highest loading biomarkers per latent variable as identified in the exploratory factor analysis (Table 2, boldface), provided a poor fit to the data (N=524, χ²=83.46, P<0.001).
In this 17-year prospective study, hemostatic rather than inflammatory markers have been shown to predict vascular cognitive impairment and vascular dementia. Specifically, fibrinogen, FVIII, and PAI-1, representing the coagulation pathways of clotting activity, platelet and fibrin plug formation, and fibrinolytic potential, were identified as increasing the risk of vascular dementia.

**Strengths and Limitations**
High levels of participation have been achieved throughout the study, although the sample was composed of men only. The sample used herein reflects an 80% response rate. Diagnosis of cognitive status was obtained through examination of participants and medical records using standard criteria. Hemostatic factors were assayed using standard techniques, and internal laboratory quality assurance was evaluated.\(^8,11\) Adjustment for a wide range of potential confounding variables was made. Cognitive status was not available at baseline, but adjustment was made for premorbid cognitive function assessed within 5 years of baseline. Men who were not followed up were more likely to have higher levels of some biomarkers and were more likely to be manual social class, to be current smokers, and to have lower cognitive function. These
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fibrinolytic potential with vascular dementia implicates fibrin-
olysis. Whether this is the result of inhibition of fibrinolysis
by PAI-1 or is a response to higher coagulation levels is
unknown.

Our findings may be attributed to residual confounding.
However, the fact that robust associations are found with some hemostatic markers and not others, and with vascular
and nonvascular dementia, argues against this conclusion.
Associations with the hemostatic markers are unlikely to
reflect reverse causality because attenuation by adjustment
for premorbid cognitive function was generally slight and in
some cases the association was strengthened. However, all
three hemostatic markers associated with vascular dementia
are also acute-phase protein reactants.1,25 Therefore, it is
possible that the associations of fibrinogen, FVIII, and PAI-1
with vascular dementia simply reflect associations with other
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of vascular dementia on hemostatic factors is unlikely to
account for the associations found.

These data present a picture of vascular dementia being
related to clot formation as the primary mechanism. These
data are consistent with a microinfarction model of vascular
dementia. The small amount of longitudinal data on cognitive
decline supports this conclusion, with some evidence that
D-dimer and fibrinogen are associated with decline in global
function26 and fluid intelligence.27 The clinical implication of
these findings is that reducing clot formation through antico-
agulation is likely to result in greater cognitive benefit than
just the established benefit of a reduction in ischemic stroke,
as suggested in a study of patients with atrial fibrillation.28
However, many of the hemostatic factors identified are

with vascular dementia but not nonvascular dementia. Previ-
ous prospective evidence has shown that fibrinogen, but not
CRP, was associated with vascular dementia.7 Our findings
extend this evidence to FVIII, PAI-1, and the inflammatory
marker plasma viscosity.

Of particular interest are the mechanisms by which hemostatic factors affect risk of vascular dementia. SEM indicated
that coagulation pathways (represented by latent variables)
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### Interpretation

These analyses address two basic mechanisms that may be
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nonvascular dementia is anomalous and likely to be a chance
effect.

The hypothesis that hemostasis affects vascular dementia
was strongly supported. Our findings confirm those of several
case-control studies showing that hemostatic markers are
related to vascular dementia in particular.4,6 and dementia in
general.2 Our findings extend this evidence to show prospectively over 17 years that hemostatic markers are associated

### Table 2. Varimax-Rotated Factors From 476 Men With Complete Hemostatic Marker Data

<table>
<thead>
<tr>
<th>Hemostatic Marker</th>
<th>(Platelet Plug Formation)</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen</td>
<td>0.05</td>
<td>0.13</td>
<td>0.81</td>
<td>0.05</td>
</tr>
<tr>
<td>Factor VII</td>
<td>0.01</td>
<td>0.58</td>
<td>0.09</td>
<td>0.13</td>
</tr>
<tr>
<td>Factor VIII</td>
<td>0.88</td>
<td>0.05</td>
<td>0.09</td>
<td>−0.01</td>
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<tr>
<td>von Willebrand factor antigen</td>
<td>0.82</td>
<td>−0.05</td>
<td>0.18</td>
<td>0.07</td>
</tr>
<tr>
<td>Factor Xlla</td>
<td>0.06</td>
<td>0.36</td>
<td>−0.17</td>
<td>−0.48</td>
</tr>
<tr>
<td>Activated partial thromboplastin time</td>
<td>−0.69</td>
<td>−0.06</td>
<td>0.27</td>
<td>0.14</td>
</tr>
<tr>
<td>Activated protein C ratio</td>
<td>−0.41</td>
<td>−0.20</td>
<td>−0.06</td>
<td>0.22</td>
</tr>
<tr>
<td>Reaction clotting time</td>
<td>−0.13</td>
<td>−0.13</td>
<td>0.35</td>
<td>0.01</td>
</tr>
<tr>
<td>Fibrin clotting time</td>
<td>−0.01</td>
<td>0.06</td>
<td>−0.25</td>
<td>−0.04</td>
</tr>
<tr>
<td>Fragment 1 + 2</td>
<td>−0.01</td>
<td>0.04</td>
<td>0.11</td>
<td>−0.77</td>
</tr>
<tr>
<td>Thrombin-antithrombin complex</td>
<td>0.02</td>
<td>−0.13</td>
<td>0.03</td>
<td>−0.75</td>
</tr>
<tr>
<td>Tissue plasminogen activator</td>
<td>0.12</td>
<td>0.75</td>
<td>0.09</td>
<td>0.04</td>
</tr>
<tr>
<td>Plasminogen activator inhibitor</td>
<td>−0.05</td>
<td>0.80</td>
<td>0.02</td>
<td>0.05</td>
</tr>
<tr>
<td>D-dimer</td>
<td>0.17</td>
<td>−0.01</td>
<td>0.69</td>
<td>−0.28</td>
</tr>
</tbody>
</table>

Biases indicate that the current analysis is likely to be conserva-
tive. The use of SEM to explore the effect of specific hemostatic
pathways is limited to the variables available to the study and
does not represent the influence of the coagulation cascade as a
whole. Although SEM generated a biologically plausible anal-
ysis, the analysis requires confirmation elsewhere. Although
sufficiently powered for its intended purpose, the study is small
for the present purpose. Despite this, consistent and robust
associations were found. However, much larger studies are
required for precise estimates of risk to be available.

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acute-phase reactant proteins; similar associations were observed for plasma viscosity and white blood cell count. Therefore, these associations may also reflect an association of systemic inflammation with vascular dementia.

In conclusion, specific hemostatic mechanisms, notably those related to clot formation and lysis, are related to increased risk of vascular dementia. Further studies are required, however, to confirm these findings and to establish whether there is any cognitive benefit from interventions targeting the clotting process.

Acknowledgements

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Source of Funding

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Disclosures

None.

References

Observed variables (haemostatic markers and dementia)

Latent variables (haemostatic pathways: from factor analysis)

Standardised path (regression) coefficient from independent to dependent variable

Standardised covariance between independent variables: double headed arrow

Standardised residual (error) variance for independent observed variables (adjacent to the observed variable)