ARTICLE

Abnormalities in haemorheological factors and lipoprotein (a) in retinal vascular occlusion: implications for increased vascular risk

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Abstract

Background **The pathogenesis of retinal vascular occlusion (RVO), which includes patients with retinal vein or artery occlusions, may be associated with abnormalities of rheology and coagulation. These abnormalities have previously been linked with an increased risk of cardiovascular disease and stroke.**

Aim, patients and methods **To investigate changes in haemorheological factors (plasma viscosity, haematocrit, haemoglobin, white cell count (WCC)), plasma fibrinogen (CLAUSS), soluble adhesion molecule P-selectin (associated with platelet activity and atherosclerosis; ELISA), von Willebrand factor (vWf, an index of endothelial dysfunction; ELISA), fibrin D-dimer (ELISA), lipoprotein(a) (Lp(a), immunoturbidometric assay) and serum lipids, we conducted a cross-sectional case-controlled study of 49 patients (37 men; mean age 66.9 years, SD 12.1 years) with RVO; 34 patients had retinal vein occlusion, whilst 15 had retinal artery occlusion. Their results were compared with those in 36 healthy controls (21 men; mean age 63.7 years, SD 14.8 years).**

Results **Patients with retinal vein occlusion and retinal artery occlusion had higher systolic and diastolic blood pressures compared with controls (both $p < 0.0001$). These patients also had significantly elevated levels of plasma viscosity, haematocrit, haemoglobin, plasma fibrinogen, PAI, fibrin D-dimer and serum Lp(a) compared with controls. Apart from a reduction in blood pressure, there were no significant differences in the indices measured in patients with retinal vein occlusion when levels measured during their first and second visits were compared. In patients with retinal artery occlusion mean plasma PAI levels were significantly lower at visit 2 compared with visit 1. Plasma viscosity was significantly correlated with fibrinogen ($r = 0.63$, $p < 0.001$), systolic blood pressure ($r = 0.33$, $p = 0.03$) and cholesterol ($r = 0.32$, $p = 0.04$), while P-selectin was correlated with Lp(a) levels ($r = 0.38$, $p = 0.03$).**

Conclusion **This study suggests that abnormalities in haemorheological factors, fibrinogen and Lp(a) are present in patients with retinal vein occlusion and retinal artery occlusion. These abnormalities appear to persist even at follow-up examination 4–6 weeks later. Abnormalities in haemorheological factors, fibrinogen and Lp(a) may have a role in the pathogenesis of retinal vein occlusion and retinal artery occlusion, perhaps acting synergistically with clinical risk factors such as blood pressure. In addition, as haemorheological factors, fibrinogen and Lp(a) are associated with vascular disease, these findings in patients with RVO may potentially contribute to an increased risk of cardiovascular disease and stroke.**

Key words Retinal vein occlusion, Retinal artery occlusion, Haemorheological factors, Lipoprotein (a), Fibrinogen

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Retinal vascular occlusion (RVO), which includes patients with retinal vein or artery occlusions, is a common cause of visual loss. Although it is commonly associated with systemic disease, RVO occasionally occurs in otherwise healthy patients with no known systemic disease or ocular problem; the precise reasons for RVO in these patients is therefore uncertain. However, abnormalities of the haemostatic system or acquired abnormal haematological factors can produce a hypercoagulable state that accounts in general for 15–25% of unexplained systemic vascular

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thrombosis, especially in young patients; similar abnormalities have also been found in some patients with RVO.[1]

The process of thrombus formation (thrombogenesis) is generally associated with abnormalities of blood flow (rheology), abnormal blood constituents (especially haemostatic factors) and blood vessel abnormalities (including endothelial dysfunction or damage) (Virchow's triad). Improved biochemical techniques have allowed the quantification of some plasma factors associated with thrombogenesis and atherogenesis. Conditions such as stroke, myocardial infarction, hypertension and atrial fibrillation have been well recognised to be associated with haemorheological abnormalities, suggesting an association with a prothrombotic or hypercoagulable state.[2–10] Blood rheology is closely related to coagulation factors, such as fibrinogen, and haemostasis.[2,3] Furthermore, plasma fibrinogen has close epidemiological associations with cardiovascular disease and stroke,[4,5] whilst von Willebrand factor (vWf) is a marker of endothelial dysfunction[6] and fibrin D-dimer levels are an index of fibrin turnover/thrombogenesis.[7] Plasminogen activator inhibitor (PAI) levels are an index of impaired fibrinolysis, and are suggestive of increased thrombogenesis.[7] Lipoprotein (a) (Lp(a)) is a lipid factor associated with thrombogenesis and atherosclerosis.[8] Other factors such as soluble leucocyte adhesion molecular P-selectin are associated with platelet activation and atherosclerosis,[9,10] whilst soluble thrombomodulin (sTM) may be important in atherosclerosis and has been suggested as a marker of endothelial function.[11]

To investigate changes in haemorheological factors (plasma viscosity, haematocrit, haemoglobin, white cell count (WCC)), plasma fibrinogen, soluble adhesion molecule P-selectin, vWf, PAI, fibrin D-dimer, Lp(a) and serum lipids, we conducted as a prospective study of patients presenting acutely with retinal vein or artery occlusions. We hypothesised that the pathogenesis of RVO may be associated with the abnormalities of rheology and coagulation; some of these abnormalities have previously been linked with an increased risk of cardiovascular disease and stroke.

Patients and methods

We conducted a prospective cross-sectional study of consecutive patients presenting acutely with RVO to the Accident and Emergency Department of the Wolverhampton and Midland Counties Eye Infirmary between August 1994 and July 1995 (12 months). All patients with the confirmed diagnosis of retinal vein occlusion or retinal artery occlusion who were in sinus rhythm were included in the study. The diagnosis of RVO was usually made on clinical grounds, with subsequent fundus fluorescein angiography only if there was an element of doubt.

The clinical history and details of antihypertensive therapy were carefully documented. As many patients usually presented after a imprecise period of non-specific visual loss, the time of the actual RVO could not be ascertained. However, we only included patients in whom the onset of symptoms had occurred within the preceding 72 h. Patients were studied on acute presentation (visit 1) and again 4–6 weeks later (visit 2). Blood pressures were measured after sitting and 10 min rest in a quiet room by a trained observer using a standard mercury sphygmomanometer. The study protocol was approved by the Wolverhampton hospitals ethics committee and informed consent was obtained from patients entered in the study.

Patients with significant systemic illness such as renal failure, liver impairment (defined as abnormal liver function tests with aspartate transaminase (AST) or alanine transaminase (ALT) levels more than twice the upper limit of normal), chronic infections, collagen disease or neoplastic disease were excluded. We also excluded patients with recent (within 2 months) myocardial infarction, unstable angina or stroke – to avoid the effect of any acute-phase response in haemostatic tests – those with limited venous access, or requiring transfusion or actively bleeding. Blood pressures and blood test results in patients with retinal vein or artery occlusions were compared with those derived from age- and sex-matched healthy subjects in sinus rhythm attending a non-acute pre-operative ophthalmological clinic for evaluation of eye conditions (mainly cataract).

Blood samples and assay procedures

Plasma viscosity and haematological indices (haematocrit, WCC, haemogobulin and platelet count) were measured on a blood sample anticoagulated with potassium EDTA. Blood samples for other haemostatic markers were drawn from the antecubital vein by careful venepuncture, anticoagulated with trisodium citrate (0.11 M, 9:1 v:v) and centrifuged. Blood samples for lipid measurements were taken in a plain tube without anticoagulant and centrifuged. The platelet-free plasma and serum samples were immediately separated and frozen at −80 °C.

Plasma fibrogen was assayed by the Clauss assay, using a KC10 coagulometer and Baxter/dade reagents and standards (Baxter Diagnostics, IL). Plasma soluble P-selectin, fibrin D-dimer, vWf and PAI levels were measured by enzyme-linked immunoabsorbent assays (ELISA) using established commercial reagents kits by Takaro Shuzo (Shiga, Japan), Agen (Parsippany, NJ), DAKO (Copenhagen, Denmark), Technoclone and Asserachrom (Diagnostica Stago, France) respectively. Lp(a) was assayed using an immunoturbidometric method (Incstar). The sensitivity of these assays allowed measurement of plasma soluble P-selectin, fibrin D-dimer, fibrinogen, vWf, PAI, sTM levels and Lp(a) to a minimum of 40 ng/ml, 30 ng/ml, 0.5 g/l, 10 IU/dl,

3 ng/ml, 5 ng/ml and 5 ng/ml, respectively. The reproducibility of all methods allowed inter-assay coefficients of variation of less than 10%.

Other measurements

The haematocrit, WCC and platelet count were obtained using a Technetium H2 auto-analyser (Bayer, Basingstoke, UK) and the plasma viscosity measured using a Coulter viscometer II (Coulter Electronics, Luton, UK). Serum cholesterol and triglycerides were measured using an enzymatic method (Olympus AU5223 Analyser, Olympus, Japan).

Statistical analysis

Values of blood pressures, rheological and haemostatic indices, plasma fibrinogen and serum lipids (cholesterol and triglycerides) are expressed as the mean ± standard deviation (SD). As levels of Lp(a), soluble P-selectin and fibrin D-dimer were known to be non-parametrically distributed, values are expressed as the median (IQR, interquartile range). Comparisons between cases and controls were made using one-way analysis of variance (ANOVA) for parametric distributions and the Kruskal–Wallis test for non-parametric distributions. Comparisons between mean or median levels of various indices at visit 1 and visit 2 were performed using a paired *t*-test and paired Wilcoxon test; the null hypothesis was that visit 1 levels of measured indices were greater than visit 2 levels due to an acute-phase effect.

Data were correlated by Pearson's method and linear regression analysis. Stepwise multiple regression analysis was used to ascertain significant clinical determinants (that is, age, sex, blood pressures, vascular history, smoking status, RVO type (vein/artery)) for levels of different variables. All statistical calculations were performed on a microcomputer using a commercially available statistical package (MINITAB v8, Minitab INC, PA). A probability of <0.05 was considered statistically significant.

Results

We studied 49 patients (37 men; mean age 66.9 years, SD 12.1 years) with RVO; 34 patients had retinal vein occlusion, whilst 15 had retinal artery occlusion. Their results were compared with 36 healthy controls (21 men; mean age 63.7 years, SD 14.8 years). There was no significant difference in sex ratio between the three groups ($\chi^2 = 9.92$; d.f. = 2, $p = 0.14$) (Table 1). Patients were studied on acute presentation (visit 1) and 4–6 weeks later (visit 2) (Table 2).

Table 1. *Patients with retinal vein occlusion or retinal artery occlusion compared with healthy controls*

	Vein occlusion ($n = 34$)	Artery occlusion ($n = 15$)	Controls ($n = 36$)	p
Males:females	24:10	13:2	21:15	0.15
Smokers				
Yes	6	3	8	
No	14	7	23	
Ex	14	5	5	0.15
Past history				
IHD	9	7	(Healthy)	
CVA	3	2	—	
HBP	15	5	—	
PVD	2	2	—	
DM	5	1	—	
Mean (SD)				
Age (years)	65 (13)	72 (9)	64 (15)	0.102
Systolic BP (mmHg)	162.4 (12.7)	159.3 (8.9)	129.0 (17.8)*	<0.001
Diastolic BP (mmHg)	91.2 (13.9)	93.7 (12.7)	78.4 (8.7)*	<0.001
Cholesterol (mmol/l)	5.61 (1.27)	5.86 (1.08)	5.97 (1.48)	0.591
Triglycerides (mmol/l	2.23 (0.21)	1.92 (0.37)	2.11 (0.11)	0.91
Plasma viscosity (mPa)	1.74 (0.12)	1.73 (0.14)	1.63 (0.08)*	0.001
Haematocrit (%)	44.2 (4.2)	43.3 (2.7)	41.3 (3.4)*	0.009
Haemoglobin (g/dl)	14.7 (1.4)	14.4 (1.0)	13.6 (1.3)*	0.006
Fibrinogen (g/l)	4.1 (1.2)	4.0 (1.4)	3.0 (0.5)*	<0.001
WCC ($\times 10^9$/l)	6.76 (1.62)	6.83 (1.22)	6.39 (1.62)	0.54
vWf (IU/dl)	104 (21)	109 (33)	100 (28)	0.589
sTM (ng/ml)	49.3 (15.3)	40.1 (9.8)	44.4 (14.1)	0.103
PAI (ng/ml)	39.9 (17.6)	47.6 (22.9)	19.0 (13.5)*	<0.001
Median (interquartile range)				
Lp(a) (ng/ml)	188 (117–312)	203 (36–414)	56 (28–188)+	0.009
Soluble P-selectin (ng/ml)	180 (138–270)	245 (195–334)	185 (150–355)	0.109
Fibrin D-dimer (ng/ml)	430 (345–590)	630 (290–720)	95 (105–280)+	<0.001

IHD, ischaemic heart disease; CVA, cerebrovascular disease; HBP, hypertension; PVD, peripheral vascular disease; DM, diabetes mellitus (non-insulin-dependent); BP, blood pressure.
*One-way ANOVA, + Kruskal–Wallis test. Results from visit 1 are compared with healthy controls.

Table 2. *Blood pressures, haemorheological factors and lipoprotein (a) in patients with retinal vascular occlusion: visit 1 versus visit 2*

	Visit 2	Visit 1	*p* value (visit 1 vs visit 2)
(a) **Retinal vein occlusion**			
Mean (SD)			
Systolic BP (mmHg)	153.4 (27.3)	162.4 (30.8)	0.06
Diastolic BP (mmHg)	87.2 (11.4)	91.2 (13.9)*	0.034
Plasma viscosity (mPa)	1.79 (0.15)	1.74 (0.12)	0.80
Haematocrit (%)	43.9 (4.6)	44.1 (4.2)	0.22
Haemoglobin (g/dl)	14.6 (1.5)	14.7 (1.4)	0.18
Fibrinogen (g/l)	4.1 (0.8)	4.1 (1.2)	0.60
vWf (IU/dl)	101 (23)	104 (21)	0.33
sTM (ng/ml)	46.6 (14.1)	49.3 (15.3)	0.48
PAI (ng/ml)	36.4 (16.1)	39.9 (17.7)	0.16
Median (interquartile range)			
Lp(a) (ng/ml)	156 (95–240)	188 (117–312)	0.265
Soluble P-selectin (ng/ml)	220 (150–270)	180 (138–270)	0.51
Fibrin D-dimer (ng/ml)	450 (380–580)	430 (345–590)	0.64
(b) **Retinal artery occlusion**			
Mean (SD)			
Systolic BP (mmHg)	153.4 (26.9)	159.3 (23.7)	0.25
Diastolic BP (mmHg)	86.6 (10.2)	93.7 (12.7)*	0.05
Plasma viscosity (mPa)	1.79 (0.15)	1.73 (0.14)	0.97
Haematocrit (%)	43.5 (3.1)	43.3 (2.7)	0.67
Haemoglobin (g/dl)	14.5 (1.16)	14.4 (0.94)	0.64
Fibrinogen (g/l)	4.2 (1.3)	4.1 (1.4)	0.48
vWf (IU/dl)	118 (20)	109 (33)	0.65
sTM (ng/ml)	38.8 (9.6)	40.1 (9.8)	0.40
PAI (ng/ml)	39.4 (16.3)	47.6 (22.9)*	0.027
Median (interquartile range)			
Lp(a) (ng/ml)	281 (97–396)	203 (36–414)	0.104
Soluble P-selectin (ng/ml)	210 (156–294)	245 (195–333)	0.27
Fibrin D-dimer (ng/ml)	450 (440–660)	630 (290–720)	0.147

BP, blood pressure.
Paired *t*-test, visit 1 vs visit 2, $*p \leq 0.05$.

Patients with retinal vein occlusion and retinal artery occlusion had higher systolic and diastolic blood pressures compared with controls (both $p < 0.001$) (Table 1). Mean age and systolic blood pressures were slightly higher in those who had retinal vein occlusion, but there was no significant difference in mean diastolic blood pressure when patients with retinal vein occlusion were compared with those with retinal artery occlusion. In patients with retinal vein occlusion, blood pressures were higher at visit 1 compared with visit 2 (paired *t*-test; $p = 0.06$ for systolic blood pressure, $p < 0.05$ for diastolic blood pressure); in patients with retinal artery occlusion, there was also a non-significant trend towards lower blood pressures at visit 2 (Table 2). None of the patients had been started on antihypertensive therapy between visit 1 and visit 2.

Patients with retinal vein occlusion and retinal artery occlusion had significantly elevated levels of plasma viscosity, haematocrit, haemoglobin, plasma fibrinogen, PAI, fibrin D-dimer and serum Lp(a) compared with controls. There were no significant differences in plasma vWf, soluble P-selectin, sTM, WCC, serum cholesterol or triglyceride levels between patients and controls at visit 1 (Table 1). Apart from a reduction in blood pressure, there were no significant differences in the indices measured in patients with retinal vein occlusion when levels measured at visit 1 and visit 2 were compared. In patients with retinal artery occlusion mean PAI levels were significantly lower at visit 2 compared with visit 1 (Table 2).

Significant correlations were found between some of the measured haemorheological and lipid indices. In the whole group of patients with RVO, plasma viscosity was significantly correlated with fibrinogen ($r = 0.63$, $p < 0.001$), systolic blood pressure ($r = 0.33$, $p = 0.03$) and cholesterol ($r = 0.32$, $p = 0.04$); while P-selectin was correlated with Lp(a) levels ($r = 0.38$, $p = 0.03$). Using stepwise multiple regression analyses, there were no significant clinical determinants (or confounding variables) for soluble P-selectin, vWf, fibrinogen and fibrin D-dimer levels. However, systolic blood pressure was a significant determinant for plasma viscosity levels, whilst diastolic blood pressure, RVO type (vein, artery) and sex were significant determinants for sTM levels ($F > 4.0$ stepwise, $p < 0.05$). Sex was also a significant determinant for Lp(a) levels.

Discussion

This study is limited by being a cross-sectional case–control study of a relatively small number of patients with retinal vein occlusion or retinal artery occlusion. In addition, the precise time of the actual retinal vascular occlusion was not ascertained, although

we have attempted to minimise late presentations by including only patients in whom the onset of symptoms had occurred within the preceding 72 h. Nevertheless, we have investigated a wide range of factors in both vein and artery occlusions, and demonstrated significant abnormalities in haemorheological factors, fibrinogen and Lp(a) levels. Abnormalities also appear to persist even when blood tests were repeated a second time, 4–6 weeks later. However, due to the small numbers in this study, we have not investigated the seasonal variation in RVO,[12] which may be relevant due to the small seasonal variation in haemostatic abnormalities, such as plasma fibrinogen.[13] In addition, patients with retinal artery occlusion were slightly older than patients with retinal vein occlusion; apart from minor differences in systolic blood pressure, there were no significant differences in other parameters. Age was, however, not a significant determinant for various indices using stepwise multiple regression analysis.

RVO can occur via multiple mechanisms. However, there are three basic pathological processes: degenerative changes of the vessel wall; abnormal haematological factors; and an abnormal perivascular status, such as an adjacent sclerotic vessels sharing a common adventitia.[1] The exact aetiology of retinal vein occlusion is unclear. Histological studies suggests two different principal factors in the mechanism of occlusion: firstly, primary endothelial degeneration and swelling with secondary intramural formation of thrombus and, secondly, extreme phlebosclerosis' with secondary endothelial degeneration.[14,15] By contrast, in patients with retinal artery occlusion, thromboembolism is considered to be commonest underlying cause, although the source is often undetected (in two-thirds), suggesting that an intrinsic prothrombotic or hypercoagulable state may exist; amongst those with thromboembolism, carotid artery disease can be present in 27%, whilst a cardiac origin is unusual (2%).[16] Hypertension is, however, a common associated systemic feature for both retinal artery and vein occlusion, especially in older patients (aged >50 years), whilst race, family history, diabetes, coronary artery disease or previous stroke were less significant.[16–19] It is well-recognised that hypertension is associated with abnormalities of rheology and coagulation.[3] The latter may in part explain why, despite the arterial tree being exposed to high pressures, the complications of hypertension are thrombotic rather than haemorrhagic.

Various factors leading to a hypercoagulable state or predisposing to thromboembolism can also be found in many patients with retinal vein occlusion or retinal artery occlusion, and this is often independent of hyperension and other coexisting vascular risk factors.[20–22] In the present study, there were some relationships between blood pressure and various haemorheological parameters on multivariate analysis, and mean blood pressure was significantly elevated in patients with retinal vein occlusion or retinal artery occlusion compared with controls. Mean blood pressures were also much higher at visit 1 compared with visit 2, especially in patients with retinal vein occlusion, perhaps suggesting a 'white coat' effect at initial presentation, or distress associated with the initial presentation with visual loss.

The presence of a hypercoagulable state in patients with retinal vein occlusion or retinal artery occlusion may in part account for the high morbidity and mortality from cardiovascular disease and stroke seen in such patients.[23,24] In an Edinburgh study of retinal artery occlusion, the absolute risk of death was 8% per year; of stroke 2.5% per year (7.4% in the first year); of coronary events 5.3% per year; and of stroke, myocardial infarction or vascular death 7.4% per year.[24] In the present study, we also confirm previous small cross-sectional studies of patients with RVD demonstrating such abnormalities of haemorheological factors and other markers of hypercoagulability, but we have investigated a wide range of factors. In addition, we show that these abnormalities persist even at 4–6 weeks follow-up. In the study by Bandello *et al.*,[25] for example, activated factor VII, with high levels of prothrombin fragment 1 + 2, fibrin D-dimer and Lp(a), were found in patients with retinal vein occlusion; these findings suggest increased thrombin formation with fibrin deposition and impaired fibrinolysis. Similar findings of abnormal haemostasis and abnormal fibrinolysis have been demonstrated by other workers.[1,26] Abnormal haemorheological factors, such as elevated blood viscosity, erythrocyte aggregation and high haematocrit, have been reported, and such abnormalities could perhaps be predictive of severity in this condition.[22,27–29] For example, increased blood viscosity may contribute to RVO by inducing stasis of blood flow, with thrombus formation in at-risk individuals who go on to develop iris neovascularisation.[29] In the study by Arend *et al.*,[22] the haemorheological abnormalities (raised haematocrit and plasma viscosity) were increased independently of associated cardiovascular risk factors. By contrast, other workers[30,31] did not find any significant haemorheological abnormalities in patients with RVO.

We have demonstrated high levels of fibrin D-dimer in patients with RVO, suggesting increased fibrin turnover and intravascular thrombogenesis in such patients.[7] Increased fibrin D-dimer is also seen in other conditions without overt thrombus formation (for example, coronary artery disease or hypertension) and may indicate that actual thrombus may not be required for this elevation, although subclinical thrombogenesis may still be occurring.[7] This is important as high levels of fibrin D-dimer have previously been shown to be highly predictive of mortality and cardiovascular events, even in healthy populations and in patients with peripheral arterial disease.[32–34] Its elevation in patients with retinal vein occlusion and retinal artery occlusion is therefore further evidence that such patients are at high vascular risk.

Lp(a) is another thrombogenic factor, through interaction with the fibrinolytic system, in view of the structural homology between apolipoprotein (a) (contained with Lp(a)) and plasminogen.[8] Previous

reports have found that RVO has been associated with raised Lp(a),[25,35,36] as confirmed in the present study. In addition, inherited plasminogen deficiency has also been reported in such patients.[36] However, other prothrombotic factors, such as antiphospholipid antibodies[37] and hyperhomocysteinaemia,[38] have been less commonly reported in retinal vein occlusion or retinal artery occlusion.

In the present study we did not find any significant elevation in vWf in patients compared with controls. This is contrast to previous work showing high vWf in patients with central vein occlusion compared with controls, which was independent of underlying systemic disease.[39] vWf is also well recognised as a marker of endothelial dysfunction in cardiovascular disease and stroke, and may have prognostic implications in some patients with vascular disease.[6] Further studies on various markers and their inter-relationships are therefore required in larger numbers of patients with RVO, who need to be followed-up prospectively to ascertain the predictive value of these abnormal haemorheological and prothrombotic markers for cardiovascular events and mortality.

In conclusion, this study suggests that abnormalities in haemorheological factors, fibrinogen, intravascular thrombogenesis and Lp(a) are present in patients with RVO, and that these persist even at follow-up. These abnormalities may contribute towards the pathogenesis of RVO and the increased risk of cardiovascular disease and stroke in these patients.

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