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A new insight into retinal vein occlusion pathogenesis

Nowe spojrzenie na patogenezę niedrożności naczyń żylnych siatkówki

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Abstract:

Aim: To evaluate (*ex vivo*) the characteristic of fibrin clotting in patients with retinal vein occlusion.

Material and methods: Fifty nine patients with a history of retinal vein occlusion were enrolled in the study. The diagnosis of retinal vein occlusion was based on the typical fundus appearance, supplemented by digital photography, fluorescein angiography, and optical coherence tomography.

The control group consisted of 59 subjects matched for age, sex, body mass index, medications, and cardiovascular risk factors.

The *ex vivo* fibrin clots obtained from citrate plasma samples from all patients were used for the measurement of clot permeation, expressed as the permeability coefficient, Ks (Darcy constant). The turbidity of fibrin clot formation, reflected by the "lag phase" of the turbidity curve and maximum absorbance *at plateau* (ΔAb_{max}), tissue-plasminogen activator (t-PA) – induced fibrinolysis characterized by maximum rates of increase in D-dimer levels ($D\text{-}D_{rate}$) and maximum D-dimer concentrations ($D\text{-}D_{max}$) were evaluated. The time required for 50% decrease in maximum clot absorption ($t_{50\%}$) was chosen as an additional marker of clot susceptibility to fibrinolysis.

Results: Patients with retinal vein occlusion were characterized by the unfavourable plasma fibrin clot properties. Clot permeability was 30% lower, as compared to the controls ($p<0.0001$), the "lag phase" was 11% shorter ($p<0.0001$) indicating faster fibrin formation, and the ΔAb_{max} was 19% higher ($p<0.0001$), indicating thicker fibrin fibers. The $D\text{-}D_{max}$ indicating thrombotic mass available for fibrinolytic agents was 22% higher in the RVO group ($p<0.0001$) and the t50% was 29% longer ($p<0.0001$) compared with controls. Only the $D\text{-}D_{rate}$ was similar in both groups ($p = 0.223$). The differences remained statistically significant after adjustment for fibrinogen, glucose, and platelet count.

Conclusion: The results indicate that in patients with retinal vein occlusion, less porous plasma fibrin clots composed of thicker fibrils with the reduced permeability and susceptibility to lysis are found, as compared to controls. Plasma fibrinogen and C-reactive protein levels are recognized as the most important modulators of fibrin function.

Key words: retinal vein occlusion, pathogenesis.

Streszczenie:

Cel: ocena struktury i czynności sieci fibrynowej ocenianej *ex vivo* u pacjentów z przebytą niedrożnością naczyń żylnych siatkówki.

Materiał i metody: badaniami objęto 59 pacjentów z niedrożnością naczyń żylnych siatkówki. Rozpoznanie niedrożności naczyń żylnych siatkówki ustalono na podstawie charakterystycznego obrazu dna oka, udokumentowanego fotografią cyfrową, wyniku angiografii fluoresceinowej i optycznej koherentnej tomografii siatkówki. Grupa kontrolna obejmowała 59 osób dobranych pod względem wieku, płci, indeksu masy ciała oraz przyjmowanych leków i czynników ryzyka chorób sercowo-naczyniowych. We wszystkich przypadkach badano *ex vivo* przepuszczalność skrzepów fibrynowych z osocza cytrynianowego, wyrażając ją współczynnikiem przepuszczalności Ks (stałą Darcy'ego). Wykonano analizę turbidimetryczną polimeryzacji fibryny, mierząc opóźnienie wzrostu absorbancji („lag phase") i maksymalną absorbancję w fazie *plateau* (ΔAb_{max}), oraz indukowaną tkankowym aktywatorem plazminogenu fibrynolizę, ocenianą na podstawie szybkości narastania stężenia dimeru D ($D\text{-}D_{rate}$), a także, a także maksymalne jego stężenie ($D\text{-}D_{max}$). Czas potrzebny do zmniejszenia absorbancji o 50% ($t_{50\%}$) wartości maksymalnej przyjęto jako dodatkowy marker podatności skrzepu na fibrynolizę.

Wyniki: właściwości sieci fibryny były niekorzystnie zmienione u chorych, którzy przebyli niedrożność naczyń żylnych siatkówki. Przepuszczalność skrzepu fibryny u pacjentów z niedrożnością naczyń żylnych siatkówki w porównaniu z jego przepuszczalnością u osób z grupy kontrolnej była o 30% mniejsza ($p<0{,}0001$). Pacjenci z rozpoznaną niedrożnością naczyń żylnych siatkówki, w porównaniu z grupą kontrolną, charakteryzowali się krótszym o 11% czasem „lag phase" niedrożności naczyń żylnych siatkówki ($p<0{,}0001$), świadczącym o szybszym powstaniu fibryny, oraz większą o 19% ΔAb_{max} ($p<0{,}0001$), wskazującą na tworzenie grubszych fibryli. Pacjenci z niedrożnością naczyń żylnych siatkówki wykazywali większe o 22% $D\text{-}D_{max}$ ($p<0{,}0001$), wskazujące na zwiększoną masę sieci fibryny poddanej fibrynolizie i dłuższy o 29% $t_{50\%}$ ($p<0{,}0001$) w porównaniu z tymi parametrami u osób z grupy kontrolnej. Jedynie wartość $D\text{-}D_{rate}$ była podobna w obu grupach ($p = 0{,}223$). Różnice między grupami pozostały istotne statystycznie po uwzględnieniu stężenia fibrynogenu, stężenia glukozy i liczby płytek krwi.

Wnioski: wyniki badań wskazują, że u pacjentów z niedrożnością naczyń żylnych siatkówki stwierdza się tendencję do powstawania zbitych sieci fibryny o grubszych i słabo poddających się lizie włóknach. Stężenie fibrynogenu i C-reactive protein CRP okazały się najważniejszymi modulatorami właściwości sieci fibryny.

Słowa kluczowe: niedrożność naczyn żylnych siatkówki, patogeneza.

Introduction

Large population studies indicate that retinal vein occlusion (RVO) affects 16 million people worldwide (1). Although RVO constitutes, after diabetes, the second most common retinal cause of vision loss, the underlying causes have not been fully understood and its exact pathogenesis remains unclear. Numerous publications attribute RVO to disturbances in the coagulation system. Fibrin dysfunction and particularly fibrinolysis, occur in several diseases (2). Decreased permeability of the fibrin clot due to the tightly woven, rigid fibrin network is typical of individuals who develop coronary artery disease at a young age (3, 4). Interestingly, quicker fibrin polymerization and thicker fibers with reduced permeability of the clot are also detected in healthy relatives of such patients (5). Thromboembolic complications are observed more frequently in patients with chronic heart failure than in the general population (6). Similar changes have been reported in patients with the acute coronary syndrome (7). Unfavorable properties in the fibrin network detected in long-term dialysis patients and those with end-stage renal disease may contribute to the increased risk of cardiovascular death in such cases (8, 9). In both conditions, fibrin clotting showed decreased permeability and reduced susceptibility to fibrinolysis, while faster fibrin protofibril formation and increased thickness of the fibers were also observed in hemodialysed patients (9). Altered properties of fibrin clot have also been described in patients with active rheumatoid arthritis (10), cryptogenic ischemic stroke (11), acute ischemic stroke diagnosed within 72 hours after onset (12) and in patients with chronic obstructive pulmonary disease (13). There has only been one report on the features of fibrin clotting in patients with RVO (14).

The aims of this study were to evaluate the structural and functional properties of fibrin clot in patients with RVO, to determine the relationship between the stage and type of RVO and assess functional changes in the fibrin clot *ex vivo*.

Material and methods

Fifty nine patients (33 men and 26 women; aged 18–70, mean age 54.95 $\pm$ 11.04) with either branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO) were included in this study.

Inclusion criteria

1. Diagnosis of RVO based on characteristic clinical features, supplemented by digital photography, fluorescein angiography (FA) and optical coherence tomography (OCT).
2. The time from diagnosis to enrolment in the study ranged from 5 to 36 months.
3. Signed informed consent.
4. Age 18–75 years.

Exclusion criteria

1. Signs and symptoms of acute infection – C-reactive protein (CRP) >10 mg/L.
2. Cancer or autoimmune disease.
3. Cardiovascular event within 6 months preceding the study.
4. Severe concomitant hepatic or renal failure with the estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 or serum creatinine >177 μmol/l, and alanine aminotransferase (ALT) activity 1.5-fold above normal values.
5. Diabetes.
6. Anticoagulant therapy.
7. Venous thromboembolic event within 12 months preceding the study.
8. History of hemorrhagic diathesis.
9. Age above 75 years.

The control group consisted of 59 individuals matched for age, sex, body mass index (BMI) and cardiovascular risk factors, who did not have retinal vascular disease. The same exclusion criteria were applied to the controls.

All patients underwent ophthalmic examination as well as FA (Topcon fundus camera with IMAGEnet 2000 software, Japan) and OCT (Optovue Inc., Fremont, CA, USA).

Laboratory tests in all individuals included: complete blood count, ALT activity, lipid profile, CRP and fibrinogen, activated partial thromboplastin time (APTT), and prothrombin time (PT). Fibrin clot permeability was measured using the method described by Mills et al. (5) and modified by Undas et al. (7), turbidymetric analysis of fibrin polymerization was conducted using Perkin-Elmer Lambda 4B (Molecular Devices Corp., Menlo Park, CA, USA) while clot susceptibility to fibrinolysis was assessed based on lysis time measured according to the modified method described by Williams et al. (15). Kinetics of coagulation and clot lysis was monitored with spectrophotometry at the wavelength of 405 nm. The D-dimer concentration was measured in serial samples of the buffer with added recombinant t-PA (t-PA – tissue-plasminigen activator) (Boehringer Ingelheim, final concentration of 0.2 μmol/l) and 1 mg/ml of bovine albumin (Sigma). Buffer samples percolating through the gels were collected every 20 minutes according to the method described by Collet et al. (4).

The comparison of distribution of the variables between the groups was performed using Chi^2 test of independence. The Kolmogorov-Smirnov test was used to determine the normal distribution. Independent Student t-test was used when the distribution of the variables was normal; if not, the Mann Whitney test was used. Due to the lack of linear relationship between the analyzed variables the Kendall tau-B coefficient was used in order to measure the strength of the association between them. The $p < .05$ was considered statistically significant.

Results

Thirty six patients had BRVO and 23 CRVO. In 63.3% of BRVO patients, the occlusion affected superior temporal branch, and in 36.7% the inferior temporal branch. Two patients included in the CRVO group had occlusion involving half of the retina. Macular edema was detected in 86.4%.

No differences were observed between the RVO patients and controls with respect to total cholesterol, HDL and LDL cholesterol, triglycerides, creatinine, as well as ALT activity and CRP values above 3.36 mg/ml. In non-diabetic patients with RVO, a slight elevation of fasting glucose (by 4%), and of fibrinogen (by 17%) were found. Platelet counts in RVO patients were 10% lower than in controls.

Assessment of fibrin clot function

Table I summarizes the structural and functional analysis of fibrin clot. The differences were statistically significant after adjustment for fibrinogen, glucose and platelet counts.

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Parameter/ Parametr	RVO group/ Grupa pacjentów z RVO (n = 59)	Control group/ Grupa kontrolna (n = 59)	p value/ wartość
Ks (10^{-9} cm^2)	6.9 (5.9–8.0)	9.8 (8.5–10.5)	<0.0001
ΔAb^{max} (405 nm)	0.86 (0.80–0.94)	0,72 (0.66–0.77)	<0.0001
Lag phase (s)	41.42 ± 4.59	46.42 ± 4.12	<0.0001
$t_{50\%}$ (min)	9.3 (8.5–10.2)	7.2 (6.8–7.7)	<0.0001
D-D_{max} (mg/l)	4.04 (3.48–4.55)	3.32 (3.26–3.43)	<0.0001
D-D_{rate} (mg/l/min)	0.071 (0.063–0.074)	0.069 (0.063–0.073)	0.151

Data showed as mean values ± standard deviation or median (interquartile range)/ Dane podano jako średnie wartości ± odchylenie standardowe lub medianę (przedział międzykwartylowy)
p – after adjustment for fibrinogen, glucose and platelet count/ p – po uwzględnieniu stężenia fibrynogenu, glukozy i liczby płytek
Ks – clot permeability coefficient/ Ks – współczynnik przepuszczalności
ΔAb_{max} – maximum absorbance of fibrin clot at 405 nm/ ΔAb_{max} – maksymalna absorbancja żelu fibryny przy długości fali 405 nm
"lag phase" (s) – turbidity of fibrin clot formation/
$t_{50\%}$ – clot lysis time/ $t_{50\%}$ – czas fibrynolizy
D-D_{max} – maximum D-dimer concentrations percolating through a buffer containing fibrin clots/ D-D_{max} – maksymalne stężenie dimeru D w buforze przeciekającym przez skrzep fibrynowy
D-D_{rate} – maximum increase rates of D-dimer levels percolating through a buffer containing fibrin clots/ D-D_{rate} – szybkość narastania stężenia dimeru D w buforze przeciekającym przez skrzep fibrynowy

Tab. I. Fibrin clot properties in patients with RVO and in the control group.
Tab. I. Właściwości sieci fibryny u pacjentów z RVO i u pacjentów z grupy kontrolnej.

Permeability of fibrin clots

Fibrin clot permeability, expressed as the permeation coefficient Ks, was 30% lower in RVO patients as compared to controls (Fig. 1.), indicating that fibrin clots produced in RVO patients are denser.

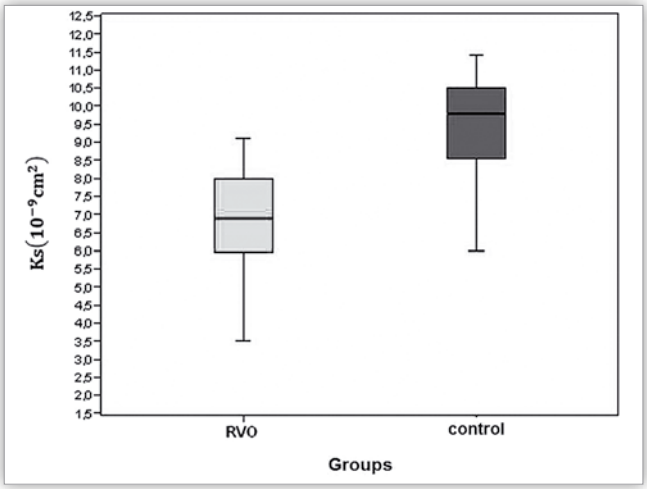

Fig. 1. Fibrin clots permeability in the RVO group (n = 59) and control group (n = 59) presented as permeability coefficient (Ks) (±SD), p <0.001. Horizontal line – median; upper and lower margin of rectangle – interquartile range, vertical line – observations away from 1.5 quartiles.
Ryc. 1. Przepuszczalność skrzepów fibrynowych u pacjentów z grupy RVO (n = 59) i z grupy kontrolnej (n = 59) wyrażona wartością współczynnika przepuszczalności (Ks) (±SD), p <0,001. Pozioma linia – mediana, dolny i górny brzeg prostokąta – przedział międzykwartylowy, wąsy – obserwacje odstające o 1,5 rozstępu kwartylowego.

A negative correlation between Ks and concentration of fibrinogen was observed in RVO patients (r = –0.414, p = 0.000).

Turbidimetric analysis

RVO correlated with 19% higher maximal absorbance of fibrin gel (Fig. 2.) and 11% shorter "lag phase" (Fig. 3.) as compared to controls. These findings suggest faster fibrin protofibril formation and generation of thicker fibres.

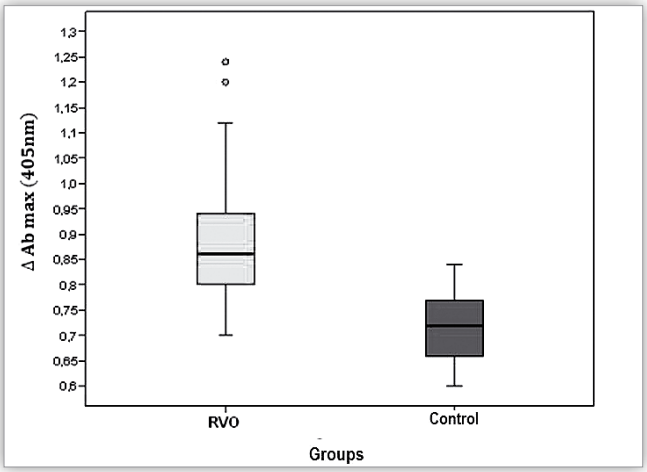

Fig. 2. Maximum fibrin clot absorbency – ΔAb_{max} in the RVO group and control group, p <0.001. ° – values away from not more than 3 quartiles. Rest designations see Fig. 1.
Ryc. 2. Maksymalna absorbancja skrzepu – ΔAb_{max} u pacjentów z grupy RVO i z grupy kontrolnej, p <0,001. ° – wartości odstające od kwartyli o nie więcej niż 3 rozstępy kwartylowe. Pozostałe oznaczenia na rycinie: patrz rycina 1.

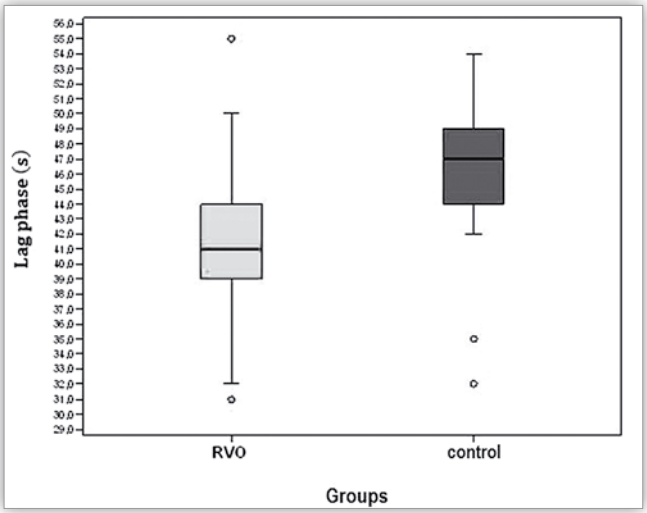

Fig. 3 "Lag phase" values in the RVO group and control group, p <0.001. Rest designations see Fig.1 and 2.
Ryc. 3. Wartości „lag phase" u pacjentów z grupy RVO i grupy kontrolnej, p <0,001. Pozostałe oznaczenia na rycinie: patrz ryciny 1. i 2.

ΔAb_{max} correlated positively with fibrinogen both in RVO ($p = 0.002$) and in the control group ($p < 0.0001$) in contrast to "lag phase", for which a negative correlation was detected in both groups (RVO: $p < 0.0001$, controls: $p = 0.001$).

Clot susceptibility to lysis

The $t_{50\%}$ in patients with RVO was 29% longer than in the control group (Fig. 4.). When a different laboratory technique was used for the assessment fibrinolysis efficiency, the maximum concentration of D-dimer was 22% higher in RVO patients, indicating an increase in the clot mass undergoing fibrinolysis (Fig. 5.).

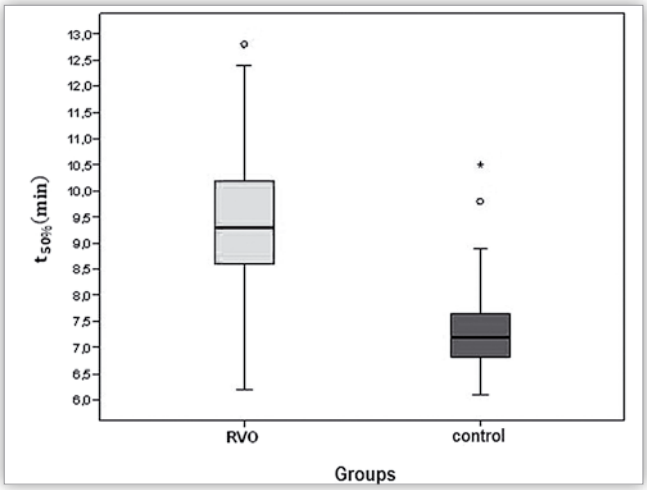

Fig. 4. Clot lysis time measured as $t_{50\%}$ in the RVO and control group, $p < 0.001$. ° – values outliers /away from not more than 3 quartiles, * – extreme elements, away from more than 3 quartiles. Rest designations see Fig. 1 and Fig. 3.

Ryc. 4. Czas lizy skrzepu wyrażony wartością $t_{50\%}$ u pacjentów z grupy RVO i grupy kontrolnej, $p < 0{,}001$. Grupa *– wartości odstające od kwartyli o więcej niż 3 rozstepy. Pozostałe oznaczenia na rycinie: patrz rycinya 1. i 3.

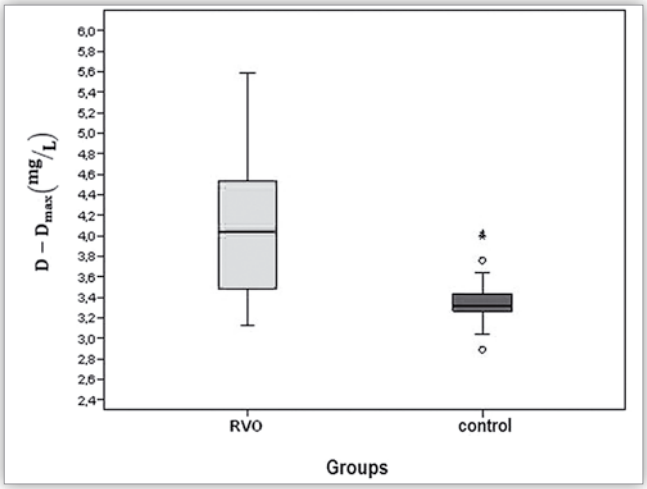

Fig. 5. Maximum D-dimer concentrations (D-D_{max}) in RVO and control group, $p < 0.001$. ° – values not more than 3 quartiles, away from. Rest designations see Fig. 1, and Fig. 3.

Ryc. 5. Wartości maksymalnego stężenia D-dimerów (D-D_{max}) u pacjentów z grupy RVO i grupy kontrolnej, $p < 0{,}001$. Oznaczenia na rycinie: patrz ryciny 1., 2. i 3.

In contrast, there was no difference between the groups with respect to the ratio of D-dimer concentration increase in the subsequent buffer samples percolating through the clot.

In the RVO group, $t_{50\%}$ correlated positively with fibrinogen ($r = 0.350$, $p < 0.0001$).

D-D_{max} correlated positively with fibrinogen ($p < 0.0001$), while D-D_{rate} correlated negatively ($p < 0.0001$). Such correlations were not observed in the control group.

No differences were observed in the fibrin-related parameters in various patient populations with BRVO or CRVO, with or without neovascularization, macular oedema, ischaemic or non-ischaemic CRVO. These findings indicate a lack of correlation between the severity of RVO and alterations in fibrin clotting. Importantly, the results indicate that the CRP concentration significantly influenced the fibrin clot parameters in both RVO and the control group. We detected higher maximum fibrin clot absorbance, longer clot lysis time and higher maximal D-dimer concentration as well as lower ratio of the D-dimer concentration increase in RVO patients with levels of CRP ≥3.36 mg/l as compared to the patients with CRP levels < 3.36 mg/l. The controls with CRP values ≥3.36 mg/l had lower K_s (8.5 [7.1–9.7] vs. 10.0 [8.9–10.6] 10^{-9} cm, $p = 0.004$), higher ΔAb_{max} (0.77 [0.73–0.81] vs. 0.70 [0.65–0.75] 405 nm, $p = 0.003$) and shorter "lag phase" (44.0 ± 4.5 vs. 47.11 ± 3.8 s, $p = 0.015$) than RVO patients.

Discussion

The results show that several parameters of plasma – derived fibrin clot are unfavourably altered in patients with RVO. We demonstrated that RVO is associated with more rapid formation of fibrin protofibrils and their faster lateral aggregation, as well as generation of a compact fibrin clot consisting of thicker fibres as compared to the matched control group. At the same time, fibrin clot in RVO patients is characterized by reduced susceptibility to t-PA – mediated lysis when compared to controls. Furthermore, the differences between the groups remained statistically significant when adjusted for small, but statistically significant differences in fibrinogen and glucose levels as well as platelet count. To our knowledge, it is the first report assessesing the structure and function of fibrin – the key component of coagulation process in patients with RVO. Interestingly, the results indicate that the comparable pro-thrombotic phenotype of fibrin as observed in RVO has also been reported in venous thromboembolism (16) as well as in atherosclerosis (2). For example, fibrin clots in RVO patients were characterized by 30% lower permeability than in respective controls.

Our results show that unfavorable alterations in fibrin clot properties do not depend on the type of RVO (CRVO or BRVO). Indeed, both local and systemic risk factors for CRVO and BRVO are similar and include hypertension, hyperlipidemia, type 2 diabetes, obesity, tobacco use and haematological disorders (17, 18). Nevertheless, they contribute variably to the pathogenesis of CRVO and BRVO. For example, hyperopia, atherosclerosis and hypertension are more commonly associated with BRVO, whereas the increased intraocular pressure and diabetes are more frequently linket to CRVO (19). Most studies on the pathogenesis of RVO consider it to be a single clinical entity, and our results strongly support this concept. The independent assessment of fibrin clotting properties in these two types of RVO in this study shows that these features do not account for the differences in clinical manifestation, but rather constitute a common denominator for all cases of RVO.

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The concentration of fibrinogen in the RVO group was 17% higher than in controls. There was also a correlation between the decreased clot permeability, susceptibility to lysis, increased rate of protofibril formation and concentration of fibrinogen. The reports assessing the correlation of fibrinogen and RVO are scarce and contradictory. For example, Wong et al. established an odds ratio for CRVO development at the presence of the elevated fibrinogen concentration (defined as exceeding the 95th percentile) at 3.29 (95% CI 1.08–10.02), while Sofi et al. did not find such correlation when analyzing fibrinogen concentrations in 180 RVO patients and 180 matched healthy controls (only 4.5% higher in RVO group) (18, 20). Higher concentration of fibrinogen can certainly affect changes in the properties of fibrin in this group of patients; nevertheless, one has to bear in mind that variations in fibrinogen concentration contribute only to 18% of variations in the permeation coefficient Ks (21).

It appears that that even a slight elevation of CRP level (3.36 – 9.7 mg/ml) had an adverse effect on fibrin function in RVO. As initially postulated by Salonen et al., based on their *in vitro* studies, C-reactive protein was further characterized as the only independent predictor of permeability and the time of clot lysis in patients with stable angina and the acute coronary syndrome (7, 22, 23). Therefore, the effect of CRP on fibrin in low-degree chronic inflammation typical of both stable atherosclerosis and its acute phase is strong enough to be detectable in spite of simultaneous tendency for an increase in fibrinogen concentration. Our results in RVO patients clearly show that individuals with CRP ≥3.36 mg/l had higher ΔAb_{max}, longer $t_{50\%}$, higher D-D_{max} and lower D-D_{rate}, while the control group with CRP ≥3.36 mg/l had lower Ks, higher ΔAb_{max} and shorter "lag phase".

The described association between the slightly elevated CRP concentration and fibrin properties in both RVO and control group suggests that an ongoing inflammatory process may present a significant risk factor for RVO development, and that chronic and inflammatory diseases such as chronic obstructive pulmonary disease and rheumatoid arthritis may increase the risk of RVO in these patients.

It is important to point out a lack of correlation between any of the fibrin clot parameters as well as the interval between RVO onset and time of examination. This supports the concept of fibrin clot alterations being a constant and consistent finding in patients with this disease, and not merely a transient phenomenon of the thrombotic episode. It therefore questions the plausibility of "reverse cause and effect" relationship in this case.

Our results indicate that the total cholesterol, LDL, HDL and triglyceride levels did not influence the fibrin clot alterations in patients with RVO, while in the control group a correlation between higher triglyceride concentration and shorter "lag phase" was observed. Fatah et al. reported a negative correlation between triglyceride levels and clot permeability in healthy individuals who constituted a control group for patients with myocardial infarction (3). Nevertheless, the vast majority of reports published to date does not indicate any correlation between lipid profile, especially cholesterol, and fibrin clot properties. Most researchers agree that even in an experimental setting based on plasma analysis, the influence of lipids *per se* is usually overlooked, and it may be expressedonly as the increased oxidative stress due to significant hypercholesterolemia.

RVO patients had lower platelet counts as compared to controls, which suggests that platelets may alter the fibrin clot structure. Indeed, a recent study on patients with rheumatoid arthritis showed that some features of fibrin correlated with platelet counts in these patients (10). One can therefore speculate that an inferior quality of fibrin clotting in patients with RVO may be compensated by a decrease in the number of platelets, which constitute a source of several factors adversely affecting fibrin, e.g. platelet factor 4 (24).

Our study showed that in patients with RVO, regardless of the stage of the disease, such fibrin clot properties as decreased permeability and susceptibility to lysis as well more rapid formation of thicker fibres were altered. Unfavorably altered fibrin clot properties in RVO patients correlate with the increased concentration of fibrinogen and CRP. Our results shed new light on the poorly understood RVO pathogenesis and warrant further studies on larger groups of patients in order to confirm our findings and determine their importance in RVO risk assessment.

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