

Editorial Focus

Retinal vein occlusion disease and platelet activation: Will antiplatelet therapy be a promising therapeutic strategy for patients with retinal vein occlusion disease in the future?

Suzanne Fateh-Moghadam¹, Meinrad Gawaz²

¹Medizinische Klinik mit Schwerpunkt Kardiologie, Campus Virchow-Klinikum, Charite-Universitätsmedizin, Berlin, Germany; ²Medizinische Klinik III, Universitätsklinikum Tübingen, Tübingen, Germany

Retinal vein occlusion (RVO) is the second most common retinal vascular disorder after diabetic retinopathy and represents an important cause of permanent visual loss (1). The prevalence of RVO has been reported to be between 0.7% and 1.6% and increases with age (1). Overall, 90% of patients who develop vein occlusion disease are over 50 years of age (2). Retinal vessels are affected to a different extent, from central retinal vein occlusion (CRVO), to hemicentral retinal vein occlusion (HCRVO) and branch retinal vein occlusion (BRVO) (3). The precise mechanism leading to thrombosis in RVO has not been clearly elucidated. The most frequent site of occlusion is the tract of the central retinal vein passing through the lamina cribrosa (3). Several reasons have been discussed for this localisation. Collagen tissue of the lamina cribrosa becomes thicker and stiff with age causing compression of the vascular wall, and degenerative processes of the central retinal artery with positive arterial remodelling may cause compression of the adjacent venous wall resulting in the formation of an endoluminal thrombus (3). Others favour the hypothesis that open-angle glaucoma predisposes to RVO due to increased intra-ocular pressure and compromised venous outflow (4).

Many of the acquired and inherited risk factors and conditions associated with deep venous thrombosis have been sought in subjects with RVO. Over the last years literature has accumulated on the possible role of different haemostatic factors in the pathogenesis of RVO. Some studies state an association between thrombophilic risk factors such as deficiency of antithrombin, protein S or protein C, elevated levels of PAI-1, activated protein C resistance, different polymorphisms of the prothrombin gene or of the PAI-1 gene, whereas other studies do not (5). Most of these data are predominantly based on retrospective retrieval of information from case records with small sample sizes. Prospective randomized studies on this subject, however, are missing. One meta-analysis (5) on this issue shows that there is only evidence for an association between hyperhomocysteinemia and anticardiolipin antibodies, factors that are known as risk factors for venous thrombosis as well as for arterial thrombotic

disease. The minor effect of the factor V Leiden mutation and the prothrombin gene mutation (risk factors for venous thrombosis only) suggest that atherosclerosis might be the more important condition in the development of RVO (5). This hypothesis is supported by other studies showing an association between RVO and classical risk factors such as arterial hypertension, diabetes mellitus, hypercholesterolemia and hyperhomocysteinemia (6). The anatomy of retinal arteries and veins could be an explanation for this. RVO occurs at crossing sites where the retinal artery is passing anterior to the vein. During systemic atherosclerotic disease the retinal artery could thicken and hence cause compression of adjacent veins, because artery and vein are confined within a common adventitial sheath. Platelets play a pivotal role in atherosclerotic disease, but the role of platelets in the pathogenesis of RVO has been poorly evaluated so far.

In this issue of *Thrombosis and Haemostasis* Leoncini et al. (7) (see article beginning page 218) studied platelet response to collagen and signal transduction steps involved in platelet activation in a selected group of patients (n=38) with RVO. In resting and activated platelets isolated from these patients p72syk phosphorylation, phospholipase γ 2 phosphorylation, protein kinase C activation, intracellular calcium levels and nitric oxide (NO) formation were measured. The study group consisted of 18 patients with CRVO, 20 patients with BRVO and a control group comprising 40 age-matched healthy subjects. Platelets derived from patients with CRVO/BRVO were more responsive to collagen in comparison to the healthy controls in regard to phosphorylation of p72syk, activation of phospholipase γ 2 and protein kinase C. Furthermore, platelets from RVO patients showed enhanced rise in intracellular calcium and less formation of the antithrombotic mediator NO than healthy control subjects. Thus, the authors convincingly show that the increased platelet response to collagen might contribute substantially to thrombogenesis in RVO patients.

The idea that activated platelets are involved in the pathogenesis of RVO is not entirely new. There have been a few studies performed focusing on platelet aggregation and RVO. Watson et

Correspondence to:

Suzanne Fateh-Moghadam, MD
Medizinische Klinik mit Schwerpunkt Kardiologie
Campus Virchow-Klinikum, Charite-Universitätsmedizin
Augustenburger Platz 1, 13353 Berlin, Germany
Tel.: +49 30 450653757, Fax: +49 30 450553957
E-mail: suzanne.fateh-moghadam@charite.de

Received January 5, 2007
Accepted January 5, 2007

Prepublished online January 8, 2007
doi:10.1160/TH07-01-0007

Thromb Haemost 2007; 97: 169–170

al. (8), Priluck et al. (9) and Houtsmuller et al. (10) support the findings by Leoncini et al. that platelets are hyperreactive in patients with RVO. Walsh et al. (11), on the contrary, did not report about enhanced ADP-, collagen- or epinephrine stimulated platelet aggregation in RVO patients.

The strength of the present work of Leoncini et al. is the comprehensive evaluation of platelet function including aggregometry, signal transduction mechanism and NO generation in a fairly appreciable number of patients.

Thus, the question arises whether antiplatelet therapy is beneficial in the treatment of RVO patients. This is a still controversial issue, because no prospective randomized study exists with an adequate sample size demonstrating clinical benefit of antiplatelet therapy with clear clinical endpoints, namely preventing visual loss. Hayreh et al. (12) promote the opinion that antiplatelet therapy might negatively influence visual outcome of these patients because of the risk of retinal hemorrhages, but this opinion is only based on some observations in the clinical routine and is not the result of a prospective clinical study. Yama-

moto et al. (13) reported a significant increase in the formation of small platelet aggregates in 68 RVO patients compared to control subjects (n=30). Furthermore he could demonstrate an inhibition of these small platelet aggregates by berabrost, an oral prostacyclin analogue, or ticlopidine. From these data Yamamoto et al. concluded that antiplatelet drugs may represent a possible therapeutic tool for treating patients with RVO. Houtsmuller et al. (10) studied in 35 CRVO and 54 BRVO patients the influence of ticlopidine on the natural course of RVO. Compared with placebo he observed significant improvement in visual acuity in the ticlopidine group. The effect of ticlopidine was most pronounced in patients with increased platelet aggregation.

Since we currently have no proven safe and effective treatment for RVO patients, there is urgent need of prospective interventional trials with greater sample size and clearly defined clinical endpoints to evaluate the role of antiplatelet treatment regimens in RVO patients. The present study by Leoncini et al. may stimulate clinicians to initiate such clinical trials.

References

1. Shahid H, Hossain P, Amoaku WM. The management of retinal vein occlusion: is interventional ophthalmology the way forward? *Br J Ophthalmol* 2006; 90: 627–639.
2. Cheru KC, Zegans ME. *Ophthalmology Review Manual*. Philadelphia, Lippincott Williams & Wilkins, 2000; 132–146.
3. Prisco D, Marcucci R. Retinal vein thrombosis: risk factors, pathogenesis and therapeutic approach. *Pathophysiol Haemost Thromb* 2002; 32: 308–311.
4. Vannas S, Tarkkanen A. Retinal vein occlusion and glaucoma: tonographic study of the incidence of glaucoma and of its prognostic significance. *Br J Ophthalmol* 1960; 44: 583–589.
5. Janssen MC, den Heijer M, Cruysberg JR, et al. Retinal vein occlusion: a form of venous thrombosis or a complication of atherosclerosis? *Thromb Haemost* 2005; 93: 1021–1026.
6. Vine AK. Hyperhomocysteinemia: a risk factor for central retinal vein occlusion. *Am J Ophthalmol* 2000; 129: 640–644.
7. Leoncini G, Bruzzese D, Signorello MG, et al. Platelet activation by collagen is increased in retinal vein occlusion. *Thromb Haemost* 2007; 97: 218–227.
8. Watson PG, Gordon JL, Kok D, et al. Platelet aggregation study in ischemic retinal vascular disease. *Trans Ophthalmol Soc UK* 1971; 91: 223–230.
9. Priluck IA. Impending central venal occlusion associated with increased platelet aggregability. *Ann Ophthalmol* 1979; 11: 79–84.
10. Houtsmuller AJ, Vermeulen JACM, Klomp M, et al. The influence of ticlopidine on the natural course of retinal venal occlusion. *Agents Actions Suppl* 1984; 15: 219–229.
11. Walsh PN, Goldberg RE, Tax RL, et al. Platelet coagulant activities and retinal vein thrombosis. *Thromb Haemost* 1977; 38: 399–406.
12. Hayreh SS. Management of central vein occlusion. *Ophthalmologica* 2003; 217: 167–188.
13. Yamamoto T, Kamei M, Yokoi N, et al. Comparative effect of antiplatelet therapy in retinal vein occlusion evaluated by the particle-counting method using light scattering. *Am J Ophthalmol* 2004; 138: 809–817.