Hypertension, hyperlipidaemia and thrombophilia as the most common risk factors for retinal vein occlusion in patients under 50 years

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Background and Aims. Cardiovascular (CV) diseases are the most common risk factors (RFs) for retinal vein occlusion (RVO) development in general. The aim of this study was to identify the most frequent causes of RVO in patients under 50.

Methods. We retrospectively evaluated a group of patients with RVO under 50 years. The parameters of interest included age and sex, RVO type, presence of arterial hypertension (HT), hyperlipidaemia (HLD), diabetes mellitus (DM), congenital thrombophilic disorder (TD), obstructive sleep apnoea syndrome (OSAS), thyroid eye disease (TED), use of hormone contraception (HC) or hormone replacement therapy (HRT), glaucoma and other potential RFs. Patients with central RVO (CRVO), hemi-central RVO (HRVO), branch RVO (BRVO), impending CRVO and combined arterial-venous (AV) occlusion were included.

Results. The group consisted of 110 eyes of 103 patients. CV disease was the most common systemic abnormality. 55.3% patients had HT, 17.5% had HLD. TD was the third most frequent RF (12.6%). The cohort also included patients with DM (6.8%), glaucoma (6.8%) and women using HC/HRT (26.2% of female patients). There were isolated cases of RVO due to retinal vasculitis, intense exercise, antiphospholipid syndrome and COVID-19 pneumonia. None of the patients had OSAS, TED or a haemato-oncological disease. The etiology remained unexplained in 20.4% patients. No difference was observed in RF occurrence between patients with CRVO and HRVO and those with BRVO.

Conclusion. The most common systemic abnormality in our cohort was CV disease, especially HT and HLD. The risk factors for central, hemi-central and branch RVOs were similar.

Key words: retinal vein occlusion, risk factors, younger patients, systemic comorbidities, arterial hypertension, hyperlipidaemia, congenital thrombophilic disorder

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INTRODUCTION

Retinal vein occlusion (RVO) is the second most common retinal vascular disease, preceded by diabetic retinopathy[1-6]. The classification distinguishes between central retinal vein occlusion (CRVO), where the main retinal vein stem is occluded; and branch retinal vein occlusion (BRVO), where a branch is occluded. Some authors define hemi-central retinal vein occlusion (HRVO) as a separate clinical unit[3,7,8]. The precursor of CRVO is impending CRVO with tortuous and dilated veins on the ocular fundus, a small amount of haemorrhage and the absence or presence of a tiny macular oedema; visual acuity (VA) is normal or only slightly reduced in this condition[1-3].

RVO pathogenesis is complex and is associated with Virchow's triad – damage to the vessel wall endothelium, blood stasis and hypercoagulability[9]. Different pathogenesis of BRVO and CRVO has been described in the literature[10]. A common feature of all RVOs is an increase of intraluminal venous pressure, leading to blood stagnation and retinal hypoxia. This results in capillary endothelial damage, extravasation of blood components and release of mediators. The most important mediator is the vascular endothelial growth factor (VEGF) (ref.[2,3]). VEGF induces macular oedema and retinal neovascularization, substantially affecting the VA of the eye.

RVO diagnosis is based on biomicroscopic fundus examination and optical coherence tomography. Fluorescence angiography is used to detect oxygenation in the retina. Automatic retinal oximetry has recently been in the spotlight as a method enabling blood oxygen saturation to be measured in RVO based on the amount of oxyhaemoglobin and deoxyhaemoglobin in the blood vessels[11-15].

The most important risk factor (RF) for RVO develop-

ment is age; 50% patients are over 65 years of age[3,8]. The main causes of RVO in such patients are systemic cardiovascular (CV) diseases – arterial hypertension (HT), hyperlipidaemia (HLD) and diabetes mellitus (DM) (ref.[16,17]). Younger patients are not fully protected from RVO – e.g. venous thrombosis may be associated with other RFs. The aim of this study was to identify the most common causes of RVO in younger patients under 50 years, to compare RFs between groups by age and between groups of patients with CRVO and HRVO versus group of patients with BRVO.

MATERIALS AND METHODS

We retrospectively evaluated a group of patients under 50 years who were diagnosed as RVO at the Department of Ophthalmology of the University Hospital Olomouc and the Faculty of Medicine and Dentistry, Palacky University in Olomouc during the period from September 2004 to February 2021. The parameters of interest included age and sex, RVO type, presence of HT, HLD, DM, congenital thrombophilic disorder (TD), obstructive sleep apnoea syndrome (OSAS), thyroid eye disease (TED), use of hormone contraception (HC) or hormone replacement therapy (HRT), glaucoma and other potential RFs described in literature (see below). Patients with CRVO, HRVO, BRVO, impending CRVO and combined arterial-venous (AV) occlusion were included.

We compared the incidence of the various RVO types between the male and female patients, one male patient with CRVO in one eye and impending CRVO in the other eye was excluded from this comparison. We divided the patients into two groups by their age to compare the prevalence of the RVO type and the RVO causes – under 40 years (46 eyes) and 41–50 years (64 eyes). We compared the RVO causes in the group of patients with CRVO and HRVO with the group of patients with BRVO.

IBM SPSS Statistics version 23 (Armonk, NY: IBM Corp.) was used for data analysis. The Chi-square test or Fisher's exact test were used to assess the association between RVO type and age, sex and the presence of RF. The significance level was corrected according to Bonferroni for multiple comparisons. The tests were performed at a significance level of 0.05. The study protocol was approved by the local Ethics Committee and the study was performed in accordance with the tenets of the Declaration of Helsinki.

RESULTS

The group consisted of 117 patients, we had to exclude 14 patients due to missing data. The final study included 110 eyes of 103 patients: 61 (59.2%) men and 42 (40.8%) women, the mean age was 41.2 years (median 43 years, min-max: 16–50 years). The average follow-up period was 29 months (median 19 months, min-max: 1–129 months), mean baseline best-corrected VA 0.516 decimal (median 0.400).

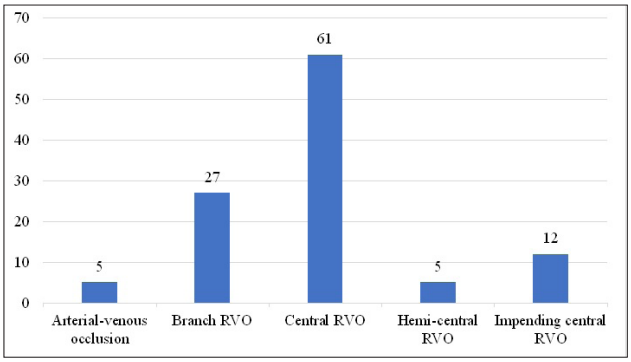

Fig. 1. Proportions of the various retinal vein occlusion (RVO) types in the cohort (n=110).

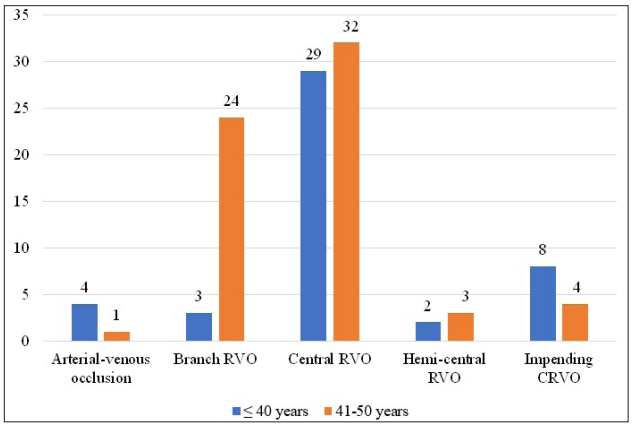

Fig. 2. Proportions of the retinal vein occlusion (RVO) types in the two age categories (n=110).

The proportions of the RVO types are shown in Fig. 1. Seven patients had bilateral RVO. No significant difference was observed in the incidence of the various RVO types between the male and female patients. A statistically significant difference in the RVO number was found between the two age categories (P=0.001). A significant difference in the proportions of BRVO was found between the two age categories – BRVO was more frequent in the group of 41–50 years than in the group under 40 years (Fig. 2).

The final evaluation of the RF incidence is presented in Table 1. Congenital TD was detected in 13 patients (12.6%), 5 of them had multiple TDs. Mutations in the 5,10-methylenetetrahydrofolate reductase (MTHFR) gene and mutations in the plasminogen activator inhibitor (PAI-1) gene were the most common (Table 2).

The comparison of the RVO causes in two age categories is shown in Table 3. Of the parameters of interest, a significant difference was demonstrated only in the occurrence of HT and HLD (they were more frequent in the group over 40 years of age). There was no statistically significant difference in the RFs between patients with CRVO and HRVO versus group of patients with BRVO (Table 4).

Table 1. Incidence of the risk factors in the cohort.

	Total	
	Number	Percentage
Arterial hypertension	57	55.3%
Hyperlipidaemia	18	17.5%
Congenital thrombophilic disorder	13	12.6%
Hormonal contraception or hormone replacement therapy	11	10.7% (26.2% of women)
Diabetes mellitus	7	6.8%
Glaucoma	7	6.8%
Vasculitis	2	1.9%
Intense exercise	1	1.0%
Catastrophic antiphospholipid syndrome	1	1.0%
Coronavirus disease 2019	1	1.0%
Haemato-oncological disease	0	0%
Obstructive sleep apnoea syndrome	0	0%
Thyroid eye disease	0	0%
Unexplained	21	20.4%

Table 2. Congenital thrombophilic disorder (- negative, + positive, ++ homozygous, ± heterozygous; n=13).

	1	2	3	4	5	6	7	8	9	10	11	12	13
Leiden mutation	+	±	+	+	-	-	-	-	-	-	-	-	-
Methylenetetrahydrofolate reductase (MTHFR) C677T	-	-	-	-	±	±	-	±	-	-	-	-	±
MTHFR A1298C	-	-	-	-	-	-	±	-	-	-	-	-	-
MTHFR – unspecified	-	-	-	-	-	-	-	-	-	-	-	±	-
Plasminogen activator inhibitor-1 (PAI-1) 4G/4G	-	-	-	-	-	-	-	-	++	-	-	-	-
PAI-1 4G/5G	-	-	-	-	-	-	-	±	-	±	±	±	-
Prothrombin 20210 G/A	-	-	-	-	-	-	-	-	-	-	-	-	±
Hyperhomocysteinaemia	-	-	-	-	-	-	-	-	-	-	±	±	-
Glycoprotein (GP) Ia	-	-	-	-	-	-	-	-	-	±	±	-	-
GPIII	-	-	-	-	-	-	-	-	-	-	±	-	-
Factor XIII	-	-	-	-	-	-	-	-	-	-	±	-	-

DISCUSSION

RVO prevalence increases with age. It is a confirmed fact that in the elderly BRVO is 4 times more common than CRVO (ref.[2,18]). On the other hand, young CRVO is more common than BRVO but the reason for this discrepancy is unknown[4]. This is also confirmed by our data – BRVO was more frequent in patients in the older age group while the proportion of CRVO patients was higher in the group under 40 years.

The RVO etiology is multifactorial. The most common systemic abnormality was CV diseases, especially HT and HLD, which are also RFs for CRVO, HRVO and BRVO. In our cohort, 55.3% RVO cases were associated with HT, 17.5% with HLD and only 6.8% with DM, which is consistent with the results published by O'Mahoney et al., who published a meta-analysis of 21 studies comparing the incidence of HT, HLD and DM in patients with RVO and in healthy controls. They confirmed a statistically significantly higher incidence of HT and HLD in all RVO types. The association of DM and RVO was less pronounced. They reported that 47.9% of RVO cases are associated with HT, 20.1% with HLD and 4.9% with DM (ref.[19]). However, the age of the patients enrolled in these studies was not stated.

Chen TY et al. performed a retrospective evaluation of CRVO RFs in patients under 40 years, comparing 95 patients with healthy controls. The most significant RFs for CRVO in younger adults were primary open-angle glaucoma, retinal vasculitis, pseudotumor cerebri, hypercoagulable state, history of deep vein thrombosis/pulmonary embolism and HLD, whereas HT and DM did not pose significant risks[20]. We demonstrated that HLD is also very frequent RF in young adults under 50 years and the incidence increases with age. There were also some cases of retinal vasculitis, hypercoagulable states and glaucoma in our cohort. In contrast to the study mentioned, HT was very common RF in our patients. Furthermore, there were many women with HC or HRT as potential RF for RVO development.

The retrospective design of our study without a control group is more similar to the recent study of Chen J et al., who examined RFs in RVO patients up to 45 years of age in a group of 15 patients. The most prevalent systemic RFs were the use of oral medications known to cause hyperviscosity or hypercoagulability (33%), CV diseases

Table 3. Comparison of the risk factors by age category (n=103, for hormonal contraception or hormone replacement therapy n=42).

	Age category				*P*
	≤40 years		41–50 years		
	Number	Percentage	Number	Percentage	
Arterial hypertension	14	**34.1%**	43	**69.4%**	**0.0004**
Hyperlipidaemia	2	**4.9%**	16	**25.8%**	**0.006**
Diabetes mellitus	2	4.9%	5	8.1%	0.700
Hormonal contraception or hormone replacement therapy	6	31.6%	5	21.7%	0.504
Congenital thrombophilic disorder	7	17.1%	6	9.7%	0.269
Intense exercise	1	2.4%	0	0.0%	0.398
Vasculitis	1	2.4%	1	1.6%	1.000
Catastrophic antiphospholipid syndrome	1	2.4%	0	0.0%	0.398
COVID-19	0	0.0%	1	1.6%	1.000
Glaucoma	2	4.9%	5	8.1%	0.700
Unexplained	12	29.3%	9	14.5%	0.083

Table 4. Comparison of the risk factors between central retinal vein occlusion (CRVO) and hemi-central retinal vein occlusion (HRVO) versus branch retinal vein occclusion (BRVO) (n=88, for hormonal contraception or hormone replacement therapy n=42).

	BRVO		CRVO + HRVO		*P*
	Number	Percentage	Number	Percentage	
Arterial hypertension	19	73.1%	34	54.8%	0.111
Hyperlipidaemia	2	7.7%	16	25.8%	0.055
Diabetes mellitus	0	0.0%	5	8.1%	0.316
Hormonal contraception or hormone replacement therapy	3	21.4%	7	35.0%	0.467
Congenital thrombophilic disorder	3	11.5%	7	11.3%	1.000
Vasculitis	0	0.0%	2	3.2%	1.000
COVID-19	1	3.8%	0	0.0%	0.295
Glaucoma	1	3.8%	6	9.7%	0.669
Unexplained	2	7.7%	14	22.6%	0.134

(26.7%), infection or inflammation (26.7%), intense exercise (20%) and increased platelet count (20%). More than half of the young patients had multiple RFs (ref.[21]). Our results may differ due to the discrepancy between the sizes of the cohorts (15 versus 103 patients). However, 48.5% patients had multiple RFs in this cohort.

The role of thrombophilic RFs in RVO is controversial and there is no consensus as to in which patients to look for the TD. Previous studies proposed that TD play a significant roles in the development of RVO in young patients[22-24]. The meta-analysis of Rehák et al. confirmed a statistically significantly higher incidence of Leiden mutation (LM) in RVO compared to healthy controls. However, the real impact of LM presence on the development of RVO could not be assessed because of the small size of the cohorts used in the studies[25]. Many authors agree that the development of RVO is affected by hyperhomocysteinaemia, LM and antiphospholipid syndrome (APS) (ref.[6,23-28]). The current study, however, demonstrated that such disorders are not so common in young RVO patients. Only 13 patients had congenital TD; in three of them, it was an independent RF. These findings agree well with the study of Ahluwalia et al., who concluded that thrombophilic RFs were not commonly associated with RVO in young patients[29]. The results of Rehák's analysis show a statistically significantly higher prevalence of APS in RVO compared to healthy controls[26]. Janssen et al. have similarly shown an association between the presence of anticardiolipin antibodies and RVO (ref.[23]).

HC and HRT is important RF for vascular occlusions especially in young women. Although it was not clearly identified how use of HC or HRT leads to RVO, there are many studies suggesting that it increases RVO risk[30,31].

Glaucoma is another RF for RVO. The meta-analysis of Yin et al. confirmed that primary open-angle glaucoma is significant RF for RVO development. There was a plausible relationship between primary angle closure glaucoma and RVO risk. Glaucoma should be kept in mind when investigating patients with RVO in the clinic[32].

Retinal vasculitis, excessive physical activity, haemato-oncological diseases and TED are rare causes of RVO. Retinal vasculitis is vision-endangering retinal vessel inflammation, it can be either primary (idiopathic) or secondary (sarcoidosis, Crohn's disease, systemic lupus erythematosus, tuberculosis, syphilis) (ref.[33]). It can lead to the RVO development due to the inflammatory infiltration in the vessel wall. In case of intense exercise, associated dehydration leads to increased haematocrit, i.e. hyperviscosity. This results in a decreased blood flow, especially in the area of the lamina cribrosa[34]. A similar mechanism can explain RVO development in patients with leukaemia, multiple myeloma or polycythemia[35]. In TED, RVO is caused by increased orbital pressure and venous congestion[36]. These four RFs have been mentioned in isolated case reports only[30,35-38] and were rare in our cohort as well.

Thrombotic complications associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection are currently a hotly debated topic. The increased number of systemic thrombosis episodes in patients with coronavirus disease 2019 (COVID-19) is explained by an increased D-dimer level, prolonged prothrombin time, activated partial thromboplastin time and increased fibrinogen and cytokine levels, together leading to a hypercoagulable state and RVO development even in the absence of systemic RFs (HT, HLD, DM). In addition, intermittent hypoxia in patients with pneumonia can lead to a release of the tissue factor from endothelial cells and activate the external haemocoagulation cascade[39]. A relationship between RVO and the presence of COVID-19 was described in some case reports[39-41]. One case of BRVO was in time coincidence with left-sided pneumonia in a patient with COVID-19 in our cohort. Because the patient had no other systemic RFs and the fundus finding regressed substantially after the resolution of pneumonia, we considered the ocular finding to be a consequence of microangiopathy in COVID-19.

Some authors believe that OSAS may be associated with RVO. Agard et al. prospectively compared limited polygraphy results in 69 OSAS patients with a group of 45 healthy controls and confirmed a statistically significantly higher prevalence of RVO in OSAS patients than in healthy controls (82.6% vs. 55.6%, P=0.005). All RVO patients underwent polysomnography to confirm the diagnosis. However, only a small fraction of the healthy controls underwent this procedure, and so the groups could not be compared[42]. Glacet-Bernard et al. studied a cohort of 30 RVO patients with 2 out of 3 RFs – an associated CV disease (especially HT), snoring or increased daytime sleepiness. They performed limited polygraphy in patients and found that 23 patients (77%) had OSAS. This way they confirmed a strong association between RVO and OSAS (ref.[43]). No patients in our cohort suffered from OSAS. In our opinion, OSAS is not considered as a potential RF in RVO patients and so they are underdiagnosed. This is documented by the paper by Young, who estimates that 93% women and 82% men with moderate to severe OSAS are not diagnosed at all[44].

The causation of RVO is unclear or no obvious RF is found in 60% patients under 50 years[2]. In our cohort, this concerned 21 patients (21.4%). It is not clear if, and to what extent, the development of RVO could be contributed to by vasospasm of the retinal vessels, e.g. during increased mental stress, as sometimes seen in young patients[45], or if it was due to some other RFs, undiscovered by us.

The limitation of the study is incompleteness and missing data due to its retrospective nature. The large size of the cohort is a strong point of the study. The data was collected over a period of almost 17 years. To the best of our knowledge, this is the only study to date which has examined the difference between RF in the group of CRVO and HRVO patients compared to BRVO patients under the age of 50.

A prospective study comparing the presence of congenital TDs between all age groups with RVO and healthy controls might be of great benefit in the future. It would be appropriate to include the level of CV disease control among the data monitored.

CONCLUSION

RVO is a frequent cause of VA loss not only in elderly patients but also in patients of productive age in developed countries. In our cohort, we confirmed that the most common abnormalities leading to RVO in patients under 50 years are systemic CV diseases, particularly HT and HLD. RVO is frequently associated with congenital TDs, although their role in RVO development is not fully understood yet.

Comprehensive patient care must include the search for all of the above-mentioned RFs. An ophthalmologist may be the first physician to detect a serious general illness. Interdisciplinary cooperation between the ophthalmologist, an internal medicine specialist and a haematologist is of great importance to investigate and compensate for systemic diseases.

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