Research article

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Impact of cardiovascular risk factors on incidence and severity of Retinal Vein Occlusion

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Abstract

Purpose. Retinal Vein Occlusion (RVO) is a thrombotic process affecting retinal veins. The purpose of this research is to study demographic characteristics and prevalence of cardiovascular comorbidities among subjects affected by RVO. In addition, authors explore the role of each variable in determining occlusion type and severity.

Subjects, materials and methods. This was a prospective observational study recruiting subjects affected by RVO and secondary macular edema. Exclusion criteria included pre-existing macular edema, recent ocular surgery (<6 months), pregnancy, diagnosis other than RVO, diabetes mellitus type I, any systemic pathology that significantly reduced life expectancy. Each participant was studied through a comprehensive medical history, cardiovascular assessment, blood testing, ocular exam, and macular OCT imaging.

Results. A total of 145 eyes, 145 participants, thereof 80 males (55%) and 65 females. (45%) Mean age: 62.5 ± 14.3 SD. 61 eyes (42%) were affected by CRVO and 84 eyes (58%) by BRVO. No statistically significant differences were noted between genders. Hypertension was very prevalent (63%). Dyslipidemia was more associated with BRVO ($p = 0.044$). Subjects with hypertension had a mean central macular thickness (CMT) of 643 μm against a mean of 489 μm of those without hypertension. ($p < 0.05$). No other variable was associated with macular edema severity.

Conclusions. Older age and hypertension are strong risk factors for RVO. Dyslipidemia was strongly associated with BRVO. ($p=0.044$) Hypertension was not only associated with RVO incidence, but also with its severity. In fact, hypertensive subjects had significantly worse macular edema.***Clin Ter 2020; 171 (6):e534-538. doi: 10.7417/CT.2020.2269***

Key words: *Retinal Vein Occlusion, RVO, Branch Retinal Vein Occlusion, BRVO, Central Retinal Vein Occlusion, CRVO, Central Macular Thickness, CMT, Cardiovascular Risk Factors, Hypertension*

Introduction

Retinal Vein Occlusion (RVO) is the second most frequent cause of vision loss worldwide after diabetic retinopathy (1). It is a thrombotic phenomenon involving retinal veins and commonly presents as sudden, monocular vision loss. It generally occurs after the fourth decade of life, but no age group is spared. Its prevalence varies from 0.3% to 2.1% in populations older than 40 years. (2–5) RVO can occur in the central vein (CRVO) or any of its branches (BRVO). This manifests as retinal and vitreous hemorrhage and macular edema.

Several factors can predispose to RVO. (1,5–7,8) For example, older age is strongly associated with it. RVO rarely affects subjects younger than 40 years. No differences are present between males and females, but RVO seems to be more prevalent in some ethnicities, such as Asians and Hispanics. (2–4,9–11) Systemic comorbidities such as hypertension, dyslipidemia, diabetes mellitus, metabolic syndrome, SLE, and OSA also increase the risk. When they present together in the form of metabolic syndrome, risk is in fact even higher. (4, 11–23) Active smoking is another important risk factor. (3) Higher fasting levels of homocysteine, low levels of vitamin B12, factor V Leiden mutation, and anticardiolipin antibodies all increase the risk of RVO. (24) In fact, thrombophilia should be suspected in young subjects with RVO and no cardiovascular risk factors. Suspicion should be even higher in case of bilateral RVO, history of previous thrombosis, or family history of thrombosis. (25,26) Some ocular conditions such as glaucoma or ocular hypertension have been shown to increase the risk for CRVO. (5,27)

The purpose of this observational study is threefold. First, authors investigate the prevalence of systemic cardiovascular comorbidities among subjects with RVO. In addition, authors explore whether any of these variables is more strongly associated with a specific RVO sub-type or worse clinical outcome.

Materials and methods

This was a joint study between the Retina Clinic and the Thrombosis Unit of Policlinico Umberto I, University of Rome La Sapienza, in Rome, Italy (Trial registration: ClinicalTrials.gov Identifier: NCT02257333 on October 6, 2014). This study enrolled patients diagnosed with RVO between 2015 and 2018. No distinction was made between ischemic and non-ischemic types.

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Inclusion criteria:
- 18 years of age or above
- Diagnosis of CRVO/BRVO between 2015 and 2018
- Macular edema secondary to RVO
- CMT of ≥ 285 µm

Exclusion criteria:
- Diagnosis of RVO prior to 2015
- Pre-existing macular edema
- Pregnancy
- Dense cataracts
- Diagnosis other than RVO
- Ocular surgery in the 6 months prior
- Diabetes mellitus type I
- Any systemic pathology that significantly reduces life expectancy

All subjects signed written consent prior to being enrolled in this study. This study adheres to the Declaration of Helsinki. Upon recruitment, each study participant was investigated as follows:
- Past and current medical history
- Current medications and/or therapies
- Comprehensive eye exam
- OCT of the macula and biometry
- Screening for cardiovascular risk factors
- Complete Blood Count and Basic Metabolic Panel
- Cardiologic evaluation
- Screening for thrombophilias

CMT was obtained with Spectralis HRA-OCT of Heidelberg Engineering with the following acquisition settings: volumetric scan of 512 x 49 lines; scanning area of: 6 x 6 mm; acquisition time for each scan: 15,0 seconds. On average, OCT imaging of the macula was generally performed 2 weeks following the occlusive episode.

Statistical Analysis

Categorical variables are reported as percentages, whereas continuous variables are reported as mean ± SD, or alternatively as median and interquartile range. Differences between percentages have been calculated using Chi-square Test or Fisher's Test. Student's T test or ANOVA analysis were used for continuous variables normally distributed. Non-parametric tests (Mann-Whitney e Kruskal-Wallis test) were used for the other variables. The statistical analysis was computed using the following software: SPSS (IBM) v. 25. Statistical significance was declared at a p-value ≤ 0.05.

Results

Demographic characteristics

The study sample consisted of 145 Caucasians subjects (145 eyes), 80 males and 65 females, all affected by RVO. (Table 1) The primary occlusive event occurred between January 2015 and March 2018. Mean age ± SD of participants was 62.5 ± 12.3 years. 18 subjects were younger than 50 years. Males were slightly more affected than females: 55.2% vs 44.8% (80 male patients, 65 female patients), but this difference was not significant. Subjects were stratified on RVO type and hypertensive status.

Table 1. Demographic characteristics of study participants

Eyes	145
Subjects	145
Age (mean ±SD)	62.5 ± 14.3
Males	80 (55.2%)
Females	65 (44.8%)
CRVO type	61
BRVO type	84

Prevalence of cardiovascular comorbidities

As shown in Table 2, hypertension was the most prevalent risk factor: 91 subjects (62.8%) had hypertension (>140/90 mmHg). 72 (79%) were on medications, while the remaining 19 (21%) were not taking any medication or were not aware of their hypertensive status. Dyslipidemia was the second most prevalent risk factor among RVO patients. It was present in 44 subjects (30%). 30 subjects (21%) were active smokers. Ex-smokers (25) were not counted. Ex-smokers include those who have smoked for 10 years or more in their lives but stopped at least 5 years prior to the RVO episode. The fourth most common cardiovascular risk factor was carotid artery stenosis (CAS), defined as stenosis of 70% or more in at least one vessel. CAS was present in 22 patients (15.2%). Diabetes Mellitus type II had a similar prevalence to that of CAS (14.5%). The other comorbidities listed in Table 2 were not as prevalent and statistical significance was hard to determine. In terms of eye comorbidities, glaucoma was present in12 (8%) of our subjects.

Comparison of demographic characteristics and cardiovascular comorbidities between BRVO and CRVO

As shown in Table 3 and Figure 1, the only variable associated with a specific RVO-subtype was dyslipidemia. Dyslipidemia was present in 36.9% of subjects with BRVO, while in only 21.3% of subjects with CRVO.

Table 2. Prevalence of cardiovascular comorbidities among study participants

Cardiovascular Risk Factors	Prevalence
Atrial Fibrillation	8 (5.5%)
Hypertension	91 (62.8%)
Diabetes Mellitus Type II	21 (14.5%)
Dyslipidemia	44 (30.3%)
Active smoker	30 (20.7%)
Myocardial Infarction	9 (6.2%)
Heart Failure	6 (4.2%)
Stroke	9 (6.2%)
Carotid Stenosis	22 (15.2%)
Peripheral Arterial Disease	4 (2.8%)
DVT or Pulmonary Embolism	5 (3.4%)

Table 3. Distribution of demographic characteristics and cardiovascular comorbidities for each RVO sub-type

Variables	CRVO (n=61)	BRVO (n=84)	P
Age (mean ±SD)	60.9 ± 15.7	63.8 ± 12.9	0.264
Male gender	49.2%	59.5%	0.216
Female gender	51.8%	40.5%	0.174
Atrial Fibrillation	6.6%	4.8%	0.640
Hypertension	65.6%	60.7%	0.550
Diabetes Mellitus	16.4%	13.1%	0.577
Dyslipidemia	21.3%	36.9%	0.044
Active smoker	18.0%	22.6%	0.501
Myocardial Infarction	1.6%	9.5%	0.052
Heart Failure	1.6%	6.0%	0.198
Stroke	6.6%	6.0%	0.882
Carotid Artery Stenosis	9.8%	19.0%	0.127
PAD	3.3%	2.4%	0.745
DVT/PE	3.3%	3.6%	0.924

CMT comparison between hypertensive and non-hypertensive subjects

CMT was available for 95 subjects only. As shown in Figure 2, hypertensive patients had a mean CMT of 642.74 ± 214.33 µm, against 489.49 ± 202.35 µm of subjects without high blood pressure. This difference was highly statistically significant ($p < 0.001$).

Discussion and conclusions

In this study, authors quantified the prevalence and the impact of demographic characteristics and cardiovascular comorbidities on the incidence and severity of RVO.

Our study sample showed that RVO is more prevalent among middle-aged adults and the elderly. Mean age was in fact 62.5 years with a standard deviation of 14.3 years. No significant differences were noted between males and females. These findings confirm those of a large pooled data analysis by Rogers et al. in 2010. (4) The prevalence ratio between BRVO and CRVO in our sample (about 1.4:1) differs from that reported in other studies. (14) This might be attributable to the fact that BRVO generally has a milder clinical presentation and more self-limiting course. Consequently, patients who are bedridden, in nursing homes or with some degree of cognitive impairment might be less prone to present to our Emergent Eye Clinic for an evaluation. For what concerns risk factors, our results confirmed a high prevalence of cardiovascular comorbidities in our subjects. Hypertension was indeed the most prevalent systemic comorbidity, present in 62% of participants. Other cardiovascular conditions, such as atrial fibrillation, diabetes mellitus, dyslipidemia, myocardial infarction, heart failure,

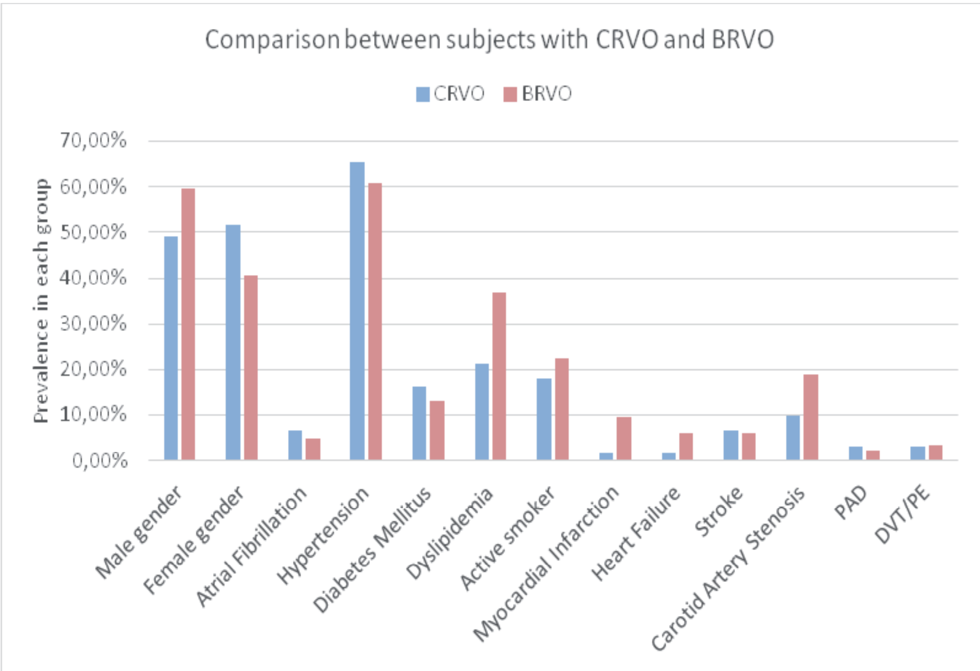

Fig. 1

PAD: peripheral artery disease; DVT: deep venous thrombosis
PE: pulmonary embolism

stroke, carotid artery stenosis, peripheral artery disease, deep venous thrombosis, and pulmonary embolism, were all present in our sample, though with less frequency. These variables likely play a role in the pathogenesis of RVO and might have a synergistic effect, as in the case of arterial thromboembolic events.

Authors of this study found that dyslipidemia was strongly associated with BRVO. In fact, BRVO is believed to result from a combination of mechanical compression and endothelial dysfunction in retinal venules at arteriovenous (A/V) crossing sites. As initially noted in 1928 by Koyanagi, then confirmed by Duker et al and Zhao et al (28), retinal arteries are often anterior to retinal veins at A/V crossing sites, which are the sites where BRVO occurs most frequently. Mechanical compression of the underlying venule by the overlying artery was believed to lead to the sequence of venous compression, turbulent flow, upstream venous dilation, blood stasis, and ultimately thrombosis. (3, 21, 29–32) However, Zhao et al found the same anatomical relationship also in A/V crossing sites not affected by BRVO. (28) This meant that mechanical compression could not be the sole mechanism leading to venous occlusion and other factors must be involved. A few years later, Jefferies P et al and Seitz R et al (33) investigated the histological changes of vessel walls at the A/V crossing sites and found an alternative explanation. They noted alterations of the endothelium and intima media in affected veins. Seitz concluded that changes in venous endothelium and intima media were in fact responsible for venous thrombosis. Therefore, one unifying theory was that mechanical compression of the overlying artery caused turbulent flow which promoted endothelial damage and hypertrophy of the intima media layer, eventually leading to thrombus formation. (28) (33) The presence of turbulent blood flow was indeed confirmed by Christoffersen et al with fluorescein angiography. (32) In the pathophysiology of BRVO, the role of dyslipidemia might be two-fold. First, dyslipidemia might facilitate arterial arteriosclerosis, which leads to greater mechanical compression of the arteriole on the underlying venule. The second explanation could be that dyslipidemia might directly cause epithelial damage and intima media hypertrophy in retinal venules.

The other novel finding of this study was the quantitative effect of hypertension on macular edema. As shown in Figure 2, macular edema was more severe among hypertensive subjects. ($p=0.001$) The explanation for this quantitative association is probably directly related to the pathophysiology of macular edema in BRVO. In fact, edema is hypothesized to be caused by efflux of fluid from the affected vessels (Starling's law) (34,35), due to breakdown of the blood-retinal barrier (BRB) as a result of damage to the tight junctions between capillary endothelial cells (36–39), vitreoretinal adhesion and traction on the macula (40, 41), and secretion into the vitreous of vaso-permeability factors such as VEGF (6) produced by retinal cells. In this regard, high intraluminal pressure could facilitate the efflux of fluid from permeated vessels.

In conclusion, authors found a high prevalence of cardiovascular comorbidities among subjects affected by RVO. A strong association was present between dyslipidemia and BRVO. Authors believe that dyslipidemia might facilitate arterial arteriosclerosis and venous endothelial dysfunctions, which are two root processes in the pathophysiology of venous occlusion. Future studies will characterize the type of dyslipidemia in each participant and explore how RVO subjects respond after treating dyslipidemia with systemic medications. A small sample size is a limitation of this study. Future studies will include more participants.

Furthermore, authors described a quantitative relationship between hypertension and macular edema. In this regard, high intraluminal pressure likely promotes fluid efflux from permeated vessels. As a result, in these patients, blood pressure control might increase the effectiveness of current interventions for the management of macular edema.

Ethics declarations

Conflict of interest

The authors declare no conflict of interest.

Ethical approval

All procedures performed in studies involving human participants were inaccordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included inthe study.

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