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VITREAL LEVELS OF ERYTHROPOIETIN ARE INCREASED IN PATIENTS WITH RETINAL VEIN OCCLUSION AND CORRELATE WITH VITREAL VEGF AND THE EXTENT OF MACULAR EDEMA

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Abstract

Purpose—This study compares vitreal levels of erythropoietin (EPO) in patients with retinal vein occlusion (RVO) with control subjects. In addition, it investigates different RVO disease parameters (time of vein occlusion, patient age, vitreal vascular endothelial growth factor (VEGF) levels, and extent of central macular edema) for possible correlations with vitreal EPO levels.

Methods—Serum and vitreal EPO were measured from 6 patients with branch retinal vein occlusion, 6 patients with central retinal vein occlusion, and 12 control subjects (10 macular puckers and 2 macular holes).

Results—Serum EPO levels (9.8 ± 4.9 mU/mL) did not differ between the RVO and control groups and were significantly lower than vitreal EPO levels in all groups. Vitreal EPO was elevated both in branch RVO (91 ± 59 mU/mL) and central RVO (182 ± 70 mU/mL) compared with controls (35 ± 24 mU/mL). Increased vitreal EPO correlated with higher vitreal VEGF ($r = 0.64$, $P = 0.0008$) and more pronounced central macular edema ($r = 0.66$, $P = 0.001$).

Conclusion—The results from this study indicate that EPO is locally expressed in the retina and that it is upregulated together with VEGF in RVO eyes. Because of its role both in neuroprotection and angiogenesis, ocular EPO might represent an interesting target to investigate in patients with RVO, especially in light of the current anti-VEGF treatments.

Keywords

erythropoietin; EPO; retinal vein occlusion; VEGF; macular edema; CME

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Retinal vein occlusion (RVO) is one of the most frequently occurring retinal vascular disorders. Occlusion of either the central retinal vein or one of its branches leads to disruption of retinal blood flow and subsequent tissue hypoxia. The disease mechanisms underlying RVO are not fully understood. One seminal study by Green et al¹ has found venous thrombi in postmortem eyes of patients with RVO. However, it is not fully established whether thrombus formation is the cause or rather a consequence of RVO. The main presenting symptom in patients with RVO is painless vision loss that usually develops over the course of hours to days. The vision loss perceived by patients with RVO is partially the result of central macular edema (CME) that develops secondary to the venous occlusion. Central macular edema is thought to result from a combination of increased intraluminal pressure in occluded veins and increased amounts of the permeability factor vascular endothelial growth factor (VEGF) that is expressed as a result of tissue hypoxia in retinas with impeded circulation.² The extent to which CME affects visual acuity in patients with RVO is illustrated by numerous studies reporting a decline in CME with a concomitant rise in visual acuity after intravitreal injection of anti-VEGF antibodies.^{3–12} Inversely, visual acuity often deteriorates during phases of CME rebound, when intravitreal VEGF inhibition ceases to sufficiently block VEGF signaling.¹³

Vascular endothelial growth factor expression is known to be regulated through the hypoxia-sensitive transcription factor Hif1 α .¹⁴ Erythropoietin (EPO) is similarly induced by Hif1 α in a hypoxia-dependent fashion.¹⁵ In addition to its well-established hematopoietic effects, EPO has neuroprotective properties both in the retina¹⁶ and in models of ischemic brain injury¹⁷ in which EPO has been shown to limit the extent of secondary brain edema.¹⁸ With regard to retinal EPO expression in patients with RVO, the data published to date are still fragmentary. One study by Inomata et al¹⁹ found a significant 12-fold EPO increase in the vitreous of 12 patients with branch RVO. Another study by Garci-Arumi et al²⁰ reported a fourfold increase in vitreal EPO in a cohort of nine patients with central RVO and three patients with branch RVO. However, this increase was not statistically significant. The aim of our study was to measure vitreal EPO in patients with RVO and control subjects without vascular disease and to identify parameters that correlate with vitreal EPO concentrations and could thus account for the reported differences.

Patients and Methods

Patients, Study Design, and Ethics

Twelve consecutive patients with RVO and 12 control subjects were included in the study. Inclusion and exclusion criteria are outlined in Table 1. It must be noted that only patients with RVO with the need for vitreoretinal surgery were included. This criterion represents a selection bias for the more severe cases of RVO. This caveat applies to all studies involving vitreal samples from patients with RVO. The findings may not apply to patients with milder forms of RVO who usually do not require vitreal surgery.

Ethics

The study was approved by the hospital's ethics committee at the University of Freiburg, Germany, and was performed in accordance with the ethical standards in the 1964

Declaration of Helsinki. All patients gave their informed consent before their inclusion in the study.

Study End Points

Primary study end points were vitreous EPO levels in patients with RVO versus the control group. Secondary study end points were serum EPO levels and correlations between vitreous EPO levels and RVO disease parameters (e.g., patient age, vitreal VEGF levels, type and duration of occlusion, and CME). The extent of CME was determined by manually measuring the vertical extent of retinal edema centered on the macula using optical coherence tomography (Zeiss Stratus OCT 3, Jena, Germany).

Measurement of Erythropoietin and Vascular Endothelial Growth Factor Concentrations

Vitreous samples were obtained at the beginning of vitrectomy before opening the infusion port. Samples were immediately transferred on ice to the laboratory. Blood-tinged samples were excluded from the study. Samples were centrifuged at 4,000 *g* for 5 minutes at 4°C to remove cellular debris, and the supernatant was stored at –80°C. After thawing, EPO concentrations were measured using the Immulite 2000 chemiluminescent immunometric assay (Siemens Medical Solutions Diagnostics, Eschborn, Germany). Serum EPO was analyzed from venous blood samples using the same technique. Vitreal VEGF levels were measured using a VEGF enzyme-linked immunosorbent assay (R&D, Wiesbaden, Germany). Pearson correlation coefficients (*r* values) were calculated in Excel (Microsoft Inc., Redmond, WA), and the significance of *r* values was determined using an online statistics calculator (www.danielsoper.com).

Results

Vitreal Erythropoietin Is Increased in Retinal Vein Occlusion

We measured vitreal and serum levels of EPO in 12 consecutive patients with RVO and 12 nonvascular disease control subjects. The RVO group consisted of six patients with branch retinal vein occlusion and six patients with central retinal vein occlusion. Patient characteristics of all 24 patients are summarized in Table 2.

In all groups, EPO serum concentrations were within normal limits and without significant differences between RVO and control groups. Vitreal EPO levels were 4- to 16-fold higher compared with serum levels in all groups (RVO and control) indicating local EPO production in the eye as opposed to a transudation of EPO from the serum into the vitreous. Both in branch RVO and central RVO, vitreal EPO levels were significantly elevated compared with the nonvascular disease control group (Figure 1; *P* = 0.02 and *P* = 0.00001, respectively).

Vitreal Erythropoietin Levels Correlate With Vitreal Vascular Endothelial Growth Factor and the Extent of Macular Edema

Previous studies reported variable results regarding vitreal EPO levels in patients with RVO. Therefore, we investigated several RVO parameters that might be associated with different vitreal EPO levels. We found no correlation for vitreal EPO with time of RVO (*r* = –0.38, *P*

= 0.22) or patient age ($r = -0.39$, $P = 0.34$). However, vitreal EPO correlated positively with vitreal VEGF levels ($r = 0.64$, $P = 0.0008$) and the extent of macular edema ($r = 0.66$, $P = 0.001$; Figure 2).

Discussion

This study investigated EPO levels in serum and vitreous of patients with RVO. Our results show no change in serum EPO but significantly increased vitreal EPO levels in patients with RVO. In all groups (RVO and control), vitreal EPO levels were 4- to 16-fold higher than serum levels. This finding points to a constitutive ocular EPO production that is significantly upregulated after RVO (Figure 1). Because we were interested in identifying RVO disease parameters that might influence vitreal EPO levels, we correlated vitreal EPO concentrations with several RVO disease characteristics. We found increased vitreal EPO levels to be correlated with higher vitreal levels of the angiogenic growth factor VEGF and with more severe CME (Figure 2).

Both EPO and VEGF are known to be regulated by the oxygen-sensitive transcription factor Hif1 α .^{14,15} The combined upregulation of EPO and VEGF in RVO eyes might reflect this shared hypoxia-inducible transcription mechanism. The differing degrees of EPO and VEGF upregulation in individual patients with RVO might thus point toward different degrees of retinal hypoxia in these patients and might partially explain the differing findings published so far: RVO patients with less severe retinal hypoxia might have almost normal vitreal EPO levels²⁰ while more hypoxic RVO eyes would show significantly elevated vitreal EPO levels.¹⁹

Although our results strongly suggest ocular EPO production and not serum EPO as the main contributor to increase vitreal EPO levels in patients with RVO, our clinical study cannot address the source of local EPO production in the eye. However, earlier studies have shown EPO gene expression in various layers of the neurosensory retina and in the retinal pigment epithelium.²¹ In the mouse model of oxygen-induced retinopathy, EPO protein predominantly localizes to the inner, hypoxic layers of the retina.²²

In this study, upregulation of ocular EPO and VEGF correlated with the extent of CME. Considering that VEGF is one of the main determining factors for CME in patients with RVO,^{2,13} the extent of CME can be regarded as a secondary factor that reflects the amount of hypoxia-induced VEGF. Whether EPO positively or negatively affects CME in this context cannot be answered from our study. However, EPO has repeatedly been found to limit the extent of brain edema in experimental brain injury models,^{23,24} and EPO has similarly been found to improve diabetic macular edema when administered for treatment of anemia in patients with diabetes and renal failure.²⁵ It could thus be speculated that EPO might have beneficial effects in the retina during the disruption of the neurovascular architecture associated with CME. However, when speculating on the possibly beneficial effects of ocular EPO during vasoproliferative diseases, the role of EPO as an angiogenic factor must be taken into account.^{22,26,27} Although ocular EPO might have beneficial effects during the early stages of retinopathy because of its well-documented properties in limiting permeability of the blood-brain barrier, increasing neuronal survival, limiting inflammation,

and recruiting endothelial progenitor cells,²¹ it may have detrimental effects during the proliferative stages of retinopathy by augmenting pathologic neovessel growth.²⁶ With regard to patients with RVO, the net effect of increased ocular EPO might thus be dependent on the disease stage (vasoobliterative vs. vasoproliferative). At our current state of knowledge, EPO remains a double-edged sword with both potentially beneficial neuroprotective and potentially deleterious proangiogenic properties in patients with RVO.

Interestingly, EPO shares similarities with VEGF regarding possibly opposing effects during different phases of proliferative retinopathy; increasing the levels of VEGF before the onset of active neovascularization in the oxygen-induced retinopathy mouse model prevents loss of normal vessels and consequentially reduces later development of neovessels.²⁸ In addition, VEGF (like EPO) is considered neuro-protective in the retina.²⁹ However, VEGF is also the main cause of pathologic neovascularization during the active stages of proliferative retinopathy.^{30–32} Considering the possibly overlapping functions of VEGF and EPO, it is important to note that the current anti-VEGF strategies do not directly affect EPO signaling. In theory, VEGF inhibition could lead to an EPO increase through enhanced Hif1 α feedback or, alternatively, to an EPO reduction as a result of less neuronal and glial stress after reduction of CME.

In summary, the results from this study strongly indicate that EPO is locally expressed in the retina of patients with RVO and that it is upregulated in concert with VEGF. Therefore, ocular EPO represents an interesting target to investigate both in terms of natural disease mechanisms and with regard to the current anti-VEGF strategies in patients with RVO.

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Fig. 1.

Serum EPO levels (dark columns) did not differ significantly between patients with RVO and control subjects. In all groups, vitreal EPO levels (light columns) were higher than serum levels. In patients with branch RVO and central RVO, vitreal EPO levels were significantly elevated compared with control subjects.

Table 1**Inclusion and Exclusion Criteria**

Inclusion Criteria	Exclusion Criteria
For the RVO group: central RVO or branch RVO with need for vitreoretinal surgery (radial optic neurotomy or arteriovenous dissection)	Systemic conditions potentially affecting serum EPO levels (e.g., diabetes mellitus, pregnancy, anemia, malignancy)
For the control group: patients with macular pucker or macular hole with need for vitreoretinal surgery	Ocular conditions potentially affecting retinal EPO levels (e.g., wet age-related macular degeneration, glaucoma, previous ocular surgery)
For all patients: age > 18 years and able to provide informed consent	

Table 2

Patient Characteristics of All 24 Patients Included in the Study

Patient (ID)	Sex (M/F)	Pathology (CRVO/BRVO)	Patient Age (Years)	Time After Occlusion (Weeks)	Macular Edema (μm)	EPO (Serum) (mU/mL)	EPO (Vitreous) (mU/mL)	VEGF (Vitreous) (pg/mL)
RVO 1	F	BRVO	70	3	780	8.1	199	2,229
RVO 2	F	BRVO	65	7	481	12.8	65.8	323
RVO 3	F	BRVO	79	29	614	11.7	20.4	0
RVO 4	F	BRVO	80	7	522	8.4	40.6	0
RVO 5	M	BRVO	56	9	217	16.1	113	3,230
RVO 6	F	BRVO	60	17	ND	18	110	11,938
RVO 7	M	CRVO	49	10	946	17	216	>50,000*
RVO 8	M	CRVO	75	11	402	13.3	84.3	2,535
RVO 9	F	CRVO	57	2	857	11.6	121	20,471
RVO 10	M	CRVO	72	5	635	10	252	47,888
RVO 11	M	CRVO	47	12	767	8.4	278	4,540
RVO 12	M	CRVO	80	10	439	17.7	146	>50,000*
CTR 1	F	Macular pucker	77	N/A	447	6.7	35	0
CTR 2	F	Macular pucker	62	N/A	231	11.3	33	15
CTR 3	M	Macular pucker	79	N/A	244	4	41.2	6
CTR 4	F	Macular hole	61	N/A	N/A	9.7	96.2	0
CTR 5	M	Macular pucker	57	N/A	355	10.8	25.4	0
CTR 6	M	Macular pucker	75	N/A	571	13.4	51.2	0
CTR 7	F	Macular pucker	78	N/A	184	9.7	19.1	0
CTR 8	F	Macular hole	75	N/A	N/A	4.9	12.2	0
CTR 9	F	Macular pucker	69	N/A	427	8.9	18.9	0
CTR 10	F	Macular pucker	76	N/A	473	23.6	63.6	18
CTR 11	F	Macular pucker	69	N/A	457	7.1	17.5	0
CTR 12	M	Macular pucker	65	N/A	340	7.4	12.3	0
		Mean $\pm$ SD (BRVO)	68 $\pm$ 9	12 $\pm$ 8.7	522 $\pm$ 184	12.5 $\pm$ 3.7	91.4 $\pm$ 58.6	2,953 $\pm$ 4,197
		Mean $\pm$ SD (RVO)	63 $\pm$ 13	8.3 $\pm$ 3.6	674 $\pm$ 203	13 $\pm$ 3.4	182 $\pm$ 70.5	29,238 $\pm$ 20,856

Patient (ID)	Sex (M/F)	Pathology (CRVO/BRVO)	Patient Age (Years)	Time After Occlusion		Macular Edema (µm)	EPO (Serum) (mU/mL)	EPO (Vitreous) (mU/mL)	VEGF (Vitreous) (pg/mL)
				(Weeks)	(Years)				
		Mean ± SD (CTR)	70 ± 7.2	N/A		373 ± 118	9.8 ± 4.9	35.5 ± 23.8	3.26 ± 6.15

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Vitreous levels for both EPO and VEGF are elevated in both patients with BRVO and CRVO compared with control subjects.

* Above saturation of enzyme-linked immunosorbent assay (50,000 pg/mL).

M, male; F, female; CTR, control; CRVO, central RVO; BRVO, branch RVO; SD, standard deviation; ND, not done; N/A, not applicable.