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Hypoxia tolerance and retinal vein occlusion: a pilot evaluation

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PURPOSE. *To determine if hypoxia tolerance in patients with retinal vein occlusion (RVO) following exposure to transient hypoxia is different from the hypoxia tolerance of healthy patients without retinal vein occlusion.*
METHODS. *Consecutive patients presenting with RVO following exposure to transient hypoxia (Group I) were compared with healthy subjects (Group II). In addition to cardiovascular and plasma tests, functional respiratory evaluation was performed at rest and during exercise at both normal oxygen levels (21% O_2) and in hypoxia (11.6% O_2). We used the Wilcoxon test for statistical analysis.*
RESULTS. *Both groups of eight males had similar mean ages: Group I, 47.5 years and Group II, 53 years. In Group I, three patients had glucose or lipid abnormalities, one had hypertension, and one minor thalassanemia. In Group II, one patient had hypertension. At rest in hypoxia, the oxyhemoglobinic desaturation was significantly different (p=0.03) in Group I in comparison with Group II (–13.8 versus –9.3). At exercise in hypoxia, the oxyhemoglobinic desaturation was similar in both groups but there was a statistically significant increase in both systolic (189 versus 155 mmHg; p=0.01) and diastolic (94 versus 77 mmHg; p=0.03) blood pressure in Group I. Ventilation rate and increased heart rate during hypoxia were higher in Group I compared with Group II but were not statistically significant.*
CONCLUSIONS. *In our pilot study, patients with RVO following exposure to transient hypoxia demonstrated intolerance to hypoxia and were significantly different from healthy subjects in their response to hypoxia. A larger study is required to confirm these preliminary results. (Eur J Ophthalmol 2009; 19: 86-90)*

KEY WORDS. *Air travel, Blood pressure, Hemoglobin oxygen saturation, High altitude, Hypoxia tolerance, Mountain ascent, Retinal vein occlusion*

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INTRODUCTION

Acute retinal venous occlusive disorders collectively constitute one of the major causes of blindness or seriously impaired vision (1). In normal patients, nutrition and oxygenation of the retina are maintained by vascular autoregulation (2, 3). However, patients with hypoxia intolerance have, in hypoxic conditions, a disturbance of their vascular autoregulation. This results in significant hemoglobin desaturation or abnormal increase of systemic blood pressure, or both.

High altitude pulmonary edema (4) is a life-threatening illness occurring in climbers or tourists ascending to altitudes higher than 2500 meters. This corresponds almost exactly to the air pressure in long distance flights that are currently taken by billions of people (5). Although there are many controversies regarding the pathogenesis, clinical features, and management of acute retinal venous occlusive disorders and high altitude pulmonary edema, they share the presence of impaired capillary permeability (6).

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High altitude disorders are more frequent and serious in patients with hypoxia intolerance which is represented by a decrease in ventilatory response to hypoxia as well as significant hemoglobin desaturation and increase of systemic blood pressure. Hypoxia intolerance occurs in 6% to 10% of the general population (7) and can be diagnosed by conducting specific tests (8). The exact origin of this condition is unknown but is probably multifactorial. We performed this study to determine if the hypoxia tolerance in patients with retinal vein occlusion (RVO) following a situation with transient hypoxia is different from the hypoxia tolerance of healthy patients without retinal vein occlusion.

METHODS

Consecutive patients presenting with ischemic or edematous form of RVO following exposure to transient hypoxia such as long distance air travel or mountain ascent above 2500 meters (Group I) were compared with healthy subjects (Group II) without RVO. The healthy subjects for this study had no known risk factors for acute mountain sickness and were recruited from subjects who presented for expert evaluation (medical examination, evaluation of physical condition, and hypoxia tolerance) before possible high altitude ascent. Our study followed the tenets of the Declaration of Helsinki. Informed consent was obtained from the subjects after explanation of the nature and consequences of this study.

Functional respiratory evaluation was performed in both groups, including the following functional tests at normal oxygen levels (21% O_2) and in simulated altitude (4800 meters: 11.6% O_2), at rest, and during exercise of moderate intensity (on a cycloergometer at 30% of max V O_2): hemoglobin oxygen saturation (SO_2) analysis, heart rate, ventilation parameters, and blood pressure. The SO_2 desaturation change in hypoxia is considered as correlated with hypoxia intolerance when greater than 15% at rest. The blood pressure increase during rest and exercise in hypoxia is considered as significant for hypoxia intolerance when higher than 20 mmHg. In addition, cardiovascular and plasma tests including blood count, sedimentation rate, glucose levels, lipid profile, homocystinemia evaluation, lipoproteinemia A, and coagulation tests were performed. We used the Wilcoxon test for statistical analysis of the observed results.

RESULTS

Both the groups of eight males had similar mean ages and were not statistically different: Group I (Tab. I): 47.5 years (range 24–69 years) and Group II (Tab. II): 53 years (range 15–68 years). In Group I, three patients had glucose or lipid abnormalities (one diabetes, one hyperlipoproteinemia A, one hypertriglyceridemia), one had hypertension, one had minor thalassanemia, one had pigmentary glaucoma with myopia, and one patient had a

TABLE I - CHANGES IN SO_2 AND BLOOD PRESSURE INDUCED BY HYPOXIA AT REST AND DURING EXERCISE IN GROUP I (patients with RVO)

Group I (patients)	Age, yr	Δ SO_2 at rest (%)	Δ SO_2 at exercise (%)	Systolic BP at rest, mmHg	Diastolic BP at rest, mmHg	Systolic BP at exercise, mmHg	Diastolic BP at exercise, mmHg
P1	62	20	17	156	93	173	106
P2	59	8	20	151	88	217	93
P3	24	11	18	137	75	199	66
P4*	49	17	—	121	70	—	—
P5	40	16	22	136	84	175	88
P6	27	16	26	106	86	154	85
P7	69	09	10	163	87	209	92
P8	50	13	10	103	87	197	127
Mean ± SE	47.5±5.7	13.8†±1.9	17.6±2.2	134±7.9	83±2.6	189‡±8.5	94†±7.1

*Patient 4 was not able to complete the required exercise.
† 0.05>p>0.01.
‡ 0.01>p>0.001.
RVO = retinal vein occlusion; ΔSO_2 = changes in hemoglobin oxygen desaturation; SE = standard error of the mean.

large nevus in the second eye as well as sleep apnea syndrome (SAS). In Group II, one subject had hypertension.

Two patients presented an ischemic form of CRVO: Patient 4 in one eye and Patient 6 in both eyes. Another patient (Patient 1) had an ischemic CRVO in one eye 2 years ago and at the time of this study had an edematous BRVO in the other eye. The other five patients had an edematous form of RVO. Six patients had one eye affected including Patient 5 who had recurrence of an edematous CRVO that had completely resolved in the same eye 18 months before. Two patients had both eyes affected (Patients 1 and 6). All the patients had a CRVO except Patients 1 (left eye) and 2 who had BRVO.

Changes in SO_2 and blood pressure induced by hypoxia at rest and during exercise in Group I (patients with RVO) and II (healthy subjects) are shown in Tables I and II, respectively. At rest, the oxyhemoglobinic desaturation (SO_2) secondary to hypoxia was statistically significantly different (p=0.03) in Group I (–13.8) compared with Group II (–9.3). At exercise, the SO_2 desaturation secondary to hypoxia was similar in the two groups: Group I = –17.6 and Group II = –17.5. However, there was a statistically significant increase in both systolic (189 versus 155 mmHg; p=0.01) and diastolic (94 versus 77 mmHg; p=0.03) blood pressure in Group I when compared with Group II. Ventilation parameters and increase of heart rate during hypoxia were higher in Group I but were not statistically significant. One patient (Patient 4) in Group I could not complete exercise in hypoxia because of extreme fatigue with malaise.

A comparative analysis (Tab. III) of the clinical forms of RVO and corresponding changes in SO_2 and blood pressure, induced by hypoxia at rest and at exercise, indicated that all three patients with the ischemic form had significant SO_2 desaturation at rest during hypoxia. Only one patient (Patient 5) with a recurrent edematous form had significant SO_2 desaturation at rest during hypoxia. All the other patients with the edematous form had an abnormal cardiovascular response with increase of systolic blood pressure at rest and/or exercise during hypoxia, with one of them (Patient 8) also having an increase of diastolic blood pressure at exercise during hypoxia. Patient 1, with one eye ischemic and the other edematous, had both significant SO_2 desaturation as well as an abnormal cardiovascular response (increased systolic blood pressure at rest during hypoxia).

DISCUSSION

RVO are frequent with the potential for recurrence and bilaterality (9). It is a potentially blinding disease of probably multifactorial etiologies (7). The risk factors associated with this condition are usually represented by cardiovascular diseases including hypertension, diabetes, hyperlipidemia, abnormal blood viscosity, platelet and other systemic diseases such as lupus or neoplasms. This disease can also be associated with glaucoma (10). Six out of our

TABLE II - CHANGES IN SO_2 AND BLOOD PRESSURE INDUCED BY HYPOXIA AT REST AND DURING EXERCISE IN GROUP II (healthy subjects)

Group II (healthy subjects)	Age, yr	Δ SO_2 at rest (%)	Δ SO_2 at exercise (%)	Systolic BP at rest, mmHg	Diastolic BP at rest, mmHg	Systolic BP at exercise, mmHg	Diastolic BP at exercise, mmHg
T1	68	8	20	108	85	164	88
T2	50	11	22	111	83	151	73
T3	15	7	16	115	68	139	68
T4	65	8	11	123	72	134	76
T5	62	6	14	114	76	153	83
T6	43	9	19	146	91	176	77
T7	66	13	22	112	68	147	65
T8	57	12	16	141	88	173	82
Mean ± SE	53±6.3	9.3*±0.9	17.5±1.4	121±5.1	79±3.2	155†±5.4	77*±2.7

*0.05>p>0.01.
†0.01>p>0.001.
Δ SO_2 = changes in hemoglobin oxygen desaturation; SE = standard error of the mean.

eight patients had at least one of these risk factors. The more important fact was that all our study patients had been exposed to transient hypoxia a few weeks before their RVO during ascent in the mountains or during long distance air travel. The effect of high altitude on the retina was first described in 1969 as an engorgement of retinal veins with occasional papilledema and vitreous hemorrhage (11).

Normal retinal function is sensitive to oxygen tension. Any change in the perfusion pressure of the eye affects the retina although the eye is able to autoregulate its hemodynamics. Systemic hypoxia or a vascular disease in the retina can cause retinal hypoxia. All the hypoxia-dependent events in cells appear to share a common denominator: the hypoxia-inducible factor (HIF). Oxygen plays a key role in stabilizing HIF-1alpha and its function. When cells become hypoxic, HIF-1alpha triggers the activation of a large number of genes such as the vascular endothelial growth factor (VEGF) (12). VEGF is a vasodilator that also increases microvascular permeability and was originally referred to as the vascular permeability factor. The dramatic effect of anti-VEGF on capillary diffusion and retinal venous dilation observed in RVO implicates hypoxia-induced VEGF in this pathology (13, 14). Thus, there is indirect evidence for a contributing role of HIF-1alpha in high-altitude retinopathy.

Therefore, we believe that it is important to evaluate hypoxia tolerance in patients with RVO to determine if hypoxia intolerance, and not hypoxia alone, could be a risk factor or a trigger factor for this disease. It is well documented that intolerance to hypoxia in individuals susceptible to HAPE or AMS induces an abnormal increase in blood pressure, reduced hypoxic ventilatory response, and abnormal hemoglobin oxygen desaturation.

We also thought to examine if it is possible to predict an increased predisposition to RVO by performing the tests used to predict the risk of HAPE or AMS. The analyses of our two study groups showed a significant difference between their respective responses to hypoxia with the presence of hypoxia intolerance in our RVO patients. Moreover, it appears that the two types of abnormal responses to hypoxia correlate with the two clinical forms of RVO: when the patients had significantly abnormal SO_2 desaturation, they usually present the ischemic form of RVO, and when the patients had abnormal cardiovascular response to hypoxia during rest or exercise, they usually

TABLE III - CLINICAL AND TEST DETAILS OF RVO (Group I) PATIENTS

No.	Eye; type of RVO	Clinical form of RVO	ΔSO$_2$ at rest	ΔSBP at rest	ΔDBP at rest	ΔSBP at exercise	ΔDBP at exercise	SBP	DBP
P1	2 eyes; CRVO then BRVO	ISCH + ED	+ *	25	6	18	8	131	93
P2	1 eye; BRVO	ED		00	11	26	16	152	77
P3	1 eye; CRVO	ED		15	03	31	01	122	78
P4	1 eye; CRVO	ISCH	+ *	03	01			118	70
P5	1 eye; CRVO, then recurrence	ED	+ *	08	02	17	06	128	84
P6	2 eyes; CRVO	ISCH	+ *	-08	00	09	00	106	86
P7	1 eye; CRVO	ED		29	00	28	02	134	87
P8	1 eye; CRVO	ED		00	00	47	25	103	87

RVO = retinal vein occlusion; Δ = change; SO_2 = hemoglobin oxygen desaturation; SBP = systolic blood pressure; DBP = diastolic blood pressure; CRVO = central retinal vein occlusion; BRVO = branch retinal vein occlusion; ISCH = ischemic; ED = edematous.
*Statistically significant desaturation.

present the edematous form of RVO. Unfortunately, our sample is too small to statistically confirm this correlation.

All our RVO patients demonstrated one or both kinds of hypoxia intolerance and these abnormalities could be detected with tests used in evaluating the risks of HAPE and AMS. On the other hand, none of our healthy subjects demonstrated any kind of intolerance to hypoxia. We accept that the number of patients included in this study is small. However, this does not detract from the conclusions of this study since we used appropriate statistical tests and our results were statistically significant. Even so, we believe that it would be worthwhile to perform a larger study to explore this possible new pathologic path and other types of hypoxic situations such as the sleep apnea syndrome.

Our pilot study suggests that it is important to consider hypoxia intolerance as a plausible additional risk factor for the occurrence or recurrence of RVO. The frequency of hypoxic situations in our modern life such as mountain trips and long distance air travel, combined with 6% to 10% of the general population with hypoxia intolerance, could significantly increase the predisposition to acute occlusive vascular disorders such as RVO, especially in the presence of any other presumed risk factor for RVO. A secondary prevention measure, for example acetazolamide, could be advocated in such patients since acetazolamide has the potential to increase ventilation and cerebral blood flow without any worsening effects on AMS (15, 16).

In conclusion, our pilot study suggests that patients with RVO may have intolerance to hypoxia when this vascular disorder has occurred subsequent to exposure to transient hypoxia such as mountain ascent or air travel. A larger study is currently ongoing to confirm these preliminary results.

None of the authors has any proprietary interest in any of the instruments used in this study.

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