Sympatho-adrenal dysregulation and clinical manifestations of angiogenic activity in patients with secondary neovascular glaucoma

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Симпато-адреналова дисрегуляція та клінічні прояви ангіогенної активності при вторинній неоваскулярній глаукомі

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Abstract

Purpose. *To examine the relationship of beta-adrenoreceptor (β-AR) activity as a marker of sympatho-adrenal dysregulation with clinical manifestations of angiogenic activity in patients with secondary neovascular glaucoma.*

Material and Methods. *This prospective observational study included 188 patients with secondary neovascular glaucoma (NVG). Of these, 112 had NVG associated with proliferative diabetic retinopathy (PDR), and 76, NVG secondary to retinal vein occlusion (RVO). The control group comprised 34 individuals. All study subjects underwent routine ophthalmological examination, and the grade of rubeosis was determined according to the Weiss grading system. β-AR activity was determined by assessing specific lymphocyte sensitivity to adrenaline. Non-parametric statistical methods, Spearman correlation analysis and receiver operating curve (ROC) analysis were employed for analysis.*

Results. *β-AR level was 1.7–2.0 times higher in patients with NVG than in controls, and this difference was significant ($p < 0.05$). β-AR level was strongly positively correlated with the Weiss grade of rubeosis ($rs = 0,69$; $p < 0.001$). ROC analysis demonstrated a moderate discriminative ability for detecting clinically significant iris rubeosis (Weiss ≥ 2) (AUC = 0.70). At a threshold level of β-AR ≥ 14, there was a five-fold increase in the risk of developing clinically significant iris rubeosis (odds ratio = 5.02; 95% confidence interval, 2.64–9.56; $p < 0.001$).*

Conclusion. *Secondary NVG is associated with an increased β-AR activity, which may reflect the involvement of sympatho-adrenal dysregulation in the course of the disease. The finding of the correlation of β-AR with the grade of rubeosis indicates an association of systemic neuroautonomic mechanisms with clinical manifestations of angiogenic activity. β-AR level can be considered a promising marker for determining a phenotype of clinically active NVG.*

Keywords: *neovascular glaucoma, beta-adrenoreceptor activity, sympatho-adrenal dysregulation, iris rubeosis, angiogenesis, proliferative diabetic retinopathy, retinal vein occlusion.*

Резюме

Мета. *Дослідити взаємозв'язок між β - адренорецепторною активністю як маркером симпато-адреналової дисрегуляції та клінічними проявами ангіогенної активності у пацієнтів із вторинною неоваскулярною глаукомою.*

Матеріал та методи. *У проспективне обсерваційне дослідження включено 188 пацієнтів із вторинною*

DOI: https://doi.org/10.31288/Ukr.j.ophthalmol.202632230

UDC: 617.7:616.13-008.331.1:612.82

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Received 2025-12-17

Accepted 2026-05-23

Cite this article as: Guzun OV, Velychko LM, Bogdanova OV, Sementsova MM. Sympatho-adrenal dysregulation and clinical manifestations of angiogenic activity in patients with secondary neovascular glaucoma. Ukr J Ophthalmol. 2026;3:22-30.

неоваскулярною глаукомою (112 – на тлі проліферативної діабетичної ретинопатії та 76 – внаслідок оклюзії вен сітківки) та 34 особи контрольної групи. Усім учасникам виконували стандартне офтальмологічне обстеження з оцінкою ступеня рубеозу райдужки за класифікацією Weiss. β-адренорецепторну активність (β-AR) визначали за методикою оцінки специфічної чутливості лімфоцитів до адреналіну. Для статистичного аналізу використовували непараметричні методи, кореляційний аналіз Спірмена, ROC-аналіз та логістичну регресію.

Результати. *Рівень β-AR був достовірно вищим у пацієнтів із неоваскулярною глаукомою порівняно з контрольною групою та перевищував контрольні значення у 1,7–2,0 рази (p < 0,05). Встановлено сильний позитивний кореляційний зв'язок між β-AR та ступенем рубеозу райдужки за Weiss (rs=0,69; p<0,001). ROC-аналіз продемонстрував помірну дискримінаційну здатність β-AR щодо виявлення клінічно значущого рубеозу райдужки (Weiss ≥ 2) (AUC = 0,70). При пороговому значенні β-AR ≥ 14 ризик клінічно значущої неоваскуляризації райдужки зростав у 5,0 разів (OR = 5,02; 95% ДІ 2,64–9,56; p < 0,001).*

Висновки. *Вторинна неоваскулярна глаукома асоціюється з підвищенням β-адренорецепторної активності, що може відображати залучення симпато-адреналової дисрегуляції до перебігу захворювання. Виявлений зв'язок між β-AR та вираженістю рубеозу райдужки свідчить про асоціацію системних нейровегетативних механізмів із клінічними проявами ангіогенної активності. β-AR може розглядатися як перспективний фенотип-визначальний маркер клінічної активності неоваскулярної глаукоми.*

Ключові слова: *неоваскулярна глаукома; β - адренорецепторна активність; симпато-адреналова дисрегуляція; рубеоз райдужки; ангіогенез; проліферативна діабетична ретинопатія; оклюзія вен сітківки.*

Introduction

Neovascular glaucoma (NVG) is one of the most severe forms of secondary glaucoma, is associated with a high risk of rapid progression of visual loss and is resistant to medical treatment. It can develop due to chronic retinal ischemia, which results in hyperexpression of proangiogenic growth factors (first and foremost, vascular endothelial growth factor (VEGF)), leading to neovascularization of the iris and the anterior chamber angle with a progressive increase in intraocular pressure (IOP) [1, 2]. Although proliferative diabetic retinopathy (DBR) and retinal vein occlusion (RVO) are the major etiological factors of NVG, the clinical course and response to treatment may vary depending on the primary disease [3, 4]. Our current understanding of the pathogenesis of NVG extends beyond the concept of pure ocular hypertension. NVG is increasingly considered as a multifactorial ischemic angiogenic process with marked microvascular, inflammatory and neurohymoral components [2, 3]. The concept of vascular dysregulation underscores the importance of the systemic mechanisms of perfusion control and vasomotor reactivity in the formation of ocular ischemic lesions [5]. Therefore, the sympatho-adrenal system may act as a systemic modifier of endothelial function, microcirculation and anti-angiogenic response.

According to current understanding, endothelial dysfunction and impaired cellular response to hypoxia are key components in the development of retinal ischemic disease. Hypoxia induces the expression of VEGF and other proangiogenic mediators that promote endothelial cell proliferation and pathologic neovascularization [6, 7]. Additionally, β-adrenergic receptor (β-AR) signaling is viewed as an important mechanism of the control of vascular tone, endothelial reactivity and angiogenesis. β-AR is known to be involved in the regulation of vascular function and tissue remodeling under conditions of chronic ischemia [8]. Experimental studies demonstrated that β-AR activation may increase angiogenic response, whereas pharmacological blockade of beta-adrenergic activation is accompanied by a reduction in pathological neovascularization [9].

The role of β3-AR in the regulation of angiogenesis has drawn special attention recently. It has been established that, under hypoxic conditions, β3-AR signaling is involved in VEGF-mediated activation of endothelial and Müller cells, contributing to the formation of a proangiogenic microenvironment [10, 11]. These findings indicate a possible relationship between the systemic sympatho-adrenal activation and neovascularization processes in ischemic eye disease. In PDR, systemic abnormalities associated with autonomic neuropathy, chronic low-grade inflammation and endothelial dysfunction may increase anterior segment ischemia and contribute to active iris neovascularization [6, 12]. Similarly, in ischemic RVO, persistent retinal hypoperfusion, venous stasis and capillary non-perfusion create conditions for activation of VEGF-dependent angiogenesis and development of NVG [13, 14].

Cell target sensitivity to mediators of the sympathoadrenal system is an important aspect of systemic control of vascular tone and cell regulation. Experimental and clinical studies have demonstrated that functional activity of adrenal receptors can be quantitatively assessed through the receptor-modifying effects of pharmacologic agents and cell response to adrenergic stimulation [15]. Similar approaches have been used in ophthalmology, where a changed sensitivity of peripheral immune competent cells to adrenaline and acetylcholine in chronic eye disorders has been demonstrated, reflecting systemic mechanisms of neuroautonomic dysregulation [16].

The role of β-AR activity as a systemic marker of sympathoadrenal dysregulation and its relationship with clinical manifestations of antiangiogenic activity in patients with NVG, however, has been insufficiently studied. To the best of our knowledge, no clinical study has integrated a quantitative assessment of β-AR activity with NVG phenotyping, compared major etiological forms of the disease with regard to this activity, and analyzed its association with the grade of iris rubeosis within a single analytical approach, which makes the present study important.

The purpose of this study was to examine the relationship of β-AR activity with clinical manifestations of angiogenic activity in patients with NVG.

Material and Methods

Study design and sample characteristics

This prospective, open-label comparative observational study included 188 patients with clinically verified secondary NVG. Patients were divided into two groups based on the etiology of retinal ischemia. Group 1 included 112 patients with NVG associated with PDR (NVG/PDR), and group 2, 76 patients with NVG secondary to RVO (NVG/RVO).

Our age- and gender-matched control group comprised 34 patients with no signs of glaucoma, retinal ischemia or systemic disorders that could have effect on autonomic regulation parameters.

This study followed ethical standards as outlined in the Declaration of Helsinki of the World Medical Association (1964–2013) and the European Convention on Human Rights and Biomedicine (1997). This study was approved by the Bioethics Committee of SI "The Filatov Institute of Eye Diseases and Tissue Therapy of the National Academy of Medical Sciences of Ukraine", Odesa, Ukraine (Meeting Minutes No. 23 of May 1, 2025). Written informed consent was obtained from all study subjects.

Inclusion criteria were patients with NVG either associated with PDR or secondary to RVO; IOP ≥ 22 mm Hg despite maximum medical therapy; and presence of grade 1-3 rubeosis of the iris and/or anterior chamber angle according to the Weiss grading system [17].

Exclusion criteria were NVG secondary to other etiology; presence of a severe general disease precluding participation; closed anterior chamber angle in the presence of Weiss grade 4 rubeosis; active infection or malignancy; ocular trauma or history of intraocular surgery; or a systemic condition that could have an effect on autonomic regulation parameters.

It is noteworthy that diabetes mellitus (DM) and arterial hypertension (AH) were considered not as independent factors but as the components of the clinical phenotype of NVG of respective etiology. Because the study aimed to examine the β-AR activity under conditions of real-world clinical practice, it included patients with compensated or subcompensated DM or AH, whereas acute or decompensated DM or AH were excluded.

Clinical ophthalmological examination

Ophthalmological examination included visual acuity, tonometry, anterior segment biomicroscopy, ophthalmoscopy, and gonioscopy with evaluation of the presence and grade of neovascularization of the iris and the anterior chamber angle. The grade of rubeosis was determined according to the Weiss grading system which has been widely used for evaluating the activity of neovascular process [17].

Assessing β-AR activity

Laboratory tests were performed during patient inclusion (prior to laser intervention). Fasting peripheral venous blood samples were drawn for complete blood counts.

A method for assessing the functional sensitivity of peripheral blood lymphocytes to adrenaline has been developed at Immunology laboratory, SI "The Filatov Institute of Eye Diseases and Tissue Therapy of the National Academy of Medical Sciences of Ukraine", and protected by a patent of Ukraine [15, 16] and was used for assessing β-AR activity.

The method is based on a parallel sampling principle and enables quantitative evaluation of individual cell reactivity to adrenergic stimulation. Peripheral blood mononuclear cells from whole blood were separated through density gradient centrifugation using Ficoll separating solution with density of 1.077 g/mL (Simesta, Ukraine) and washed twice to obtain lymphocyte suspension for further analysis.

Mixture samples of cell suspension (lymphocyte cell suspension mixed with NaCl 0.9% and that mixed with adrenaline 0.18% (manufactured by JSC Darnytsia, Kyiv, Ukraine) were incubated in parallel at 37oC for one hour to assess adrenergic sensitivity to adrenaline. Subsequent calculation of β-AR activity was performed based on the proprietary methodology [15, 18].

In this study, β-AR activity was considered an integral characteristic of the function of β-adrenergic autonomic control which was determined by the reactivity of peripheral blood lymphocytes to adrenaline. It is noteworthy that β-AR activity reflects the function of β-AR signaling but not the β-AR expression or number.

Statistics

JASP software (JASP Team, Amsterdam, Netherlands; Version 0.19.2) was used for analysis. Quantitative data were tested for normality using the Shapiro–Wilk's test. Non-normally distributed qualitative data were presented as median (interquartile range (IQR)). The Mann-Whitney U test was used to test for significant differences between two unpaired groups, and the Kruskal–Wallis test, among the three groups, with subsequent post hoc testing as appropriate. Categorical variables were compared by Fisher's exact test or the χ^2 test as appropriate. The area under the receiver operating characteristic (ROC) curve (AUC) and relevant 95% confidence intervals (CI) were used for assessing the discriminative ability of β-AR ac-

tivity for clinically significant iris rubeosis (Weiss grade ≥ 2). The Youden's index was used to determine the optimal cut-off point for β-AR. The association between β-AR activity and the Weiss grade of rubeosis was evaluated using Spearman's rank correlation. The association between β-AR activity and the risk of clinically significant rubeosis was evaluated using univariate logistic regression, and odds ratios (OR) and 95% confidence intervals were calculated. Significance was established at $p < 0.05$.

Results

Our analysis of rubeosis iridis grade found differences between the diabetic phenotype and post-occlusive phenotype of NVG. The distribution based on the Weiss classification is shown in Table 1.

Although the NVG/PDR and NVG/RVO groups were similar with regard to the percentage of patients with clinically significant rubeosis (Weiss grade ≥ 2; 46.4% and 47.3%, respectively), severe rubeosis (Weiss grade 3) was more common in the former group (17.9% versus 10.5%). This may indicate not so much a higher incidence of angiogenesis but rather its higher intensity and aggressiveness associated with diabetic microangiopathy and systemic neuroautonomic dysregulation.

Comparing the NVG/PDR and NVG/RVO groups and controls for differences with regard to β-AR activity

There was a significant difference between all patients with NVG and controls, and between the NVG/PDR and NVG/RVO groups with regard to β-AR activity. The NVG/PDR group had the highest β-AR activity, followed by the NVG/RVO group and the control group (Table 2).

There was a gradient increase in the distribution of β-AR with a shift from controls to the NVG/RVO group and the NVG/PDR group (Fig. 1). The distribution of β-AR among patients with diabetic NVG was characterized by a greater shift towards larger values than among patients with NVG secondary to RVO.

Discriminative ability of β-AR activity for clinically significant rubeosis

Table 1. Distributions of patients with neovascular glaucoma (NVG) secondary to proliferative diabetic retinopathy (PDR) and those with NVG secondary to retinal vein occlusion (RVO) by grade of rubeosis of the iris according to the system devised by Weiss

Weiss grade of rubeosis	NVG/PDR, n (%)	NVG/RVO, n (%)	Total, n (%)
Weiss grade 1	60 (53.6 %)	40 (52.6 %)	100 (53.2 %)
	$\chi^2 = 0.02$, $p = 0.90$		
Weiss grade 2	32 (28.6 %)	28 (36.8 %)	60 (31.9 %)
	$\chi^2 = 1.43$, $p = 0.23$		
Weiss grade 3	20 (17.9 %)	8 (10.5 %)	28 (14.9 %)
	$\chi^2 = 1.90$, $p = 0.17$		
Total	112 (100 %)	76 (100 %)	188 (100 %)

Note: Data are presented as number and percentage for each etiological subgroup of NVG. p, significance of difference between the NVG/PDR and NVG/RVO groups for Weiss grades 1–3 as determined by χ^2 test. Abbreviations: NVG, neovascular glaucoma; PDR, proliferative diabetic retinopathy; RVO, retinal vein occlusion

Table 2. β adrenergic receptor (β-AR) activity in patients with neovascular glaucoma (NVG) secondary to proliferative diabetic retinopathy (PDR), those with NVG secondary to retinal vein occlusion (RVO) and controls

Characteristic	NVG / PDR (n = 112)	NVG / RVO (n = 76)	Controls (n = 34)
β-AR activity, median (IQR)	14.0 (12–19)*‡	12.0 (12–17)*	7.0 (6–8)

Note: Data are presented as median and IQR. p, significance of difference; *, significant difference compared to controls ($p < 0.05$); ‡, significant between-group difference ($p < 0.05$). Abbreviations: β-AR activity, β-adrenergic receptor activity; IQR, interquartile range; NVG, neovascular glaucoma; PDR, proliferative diabetic retinopathy; RVO, retinal vein occlusion

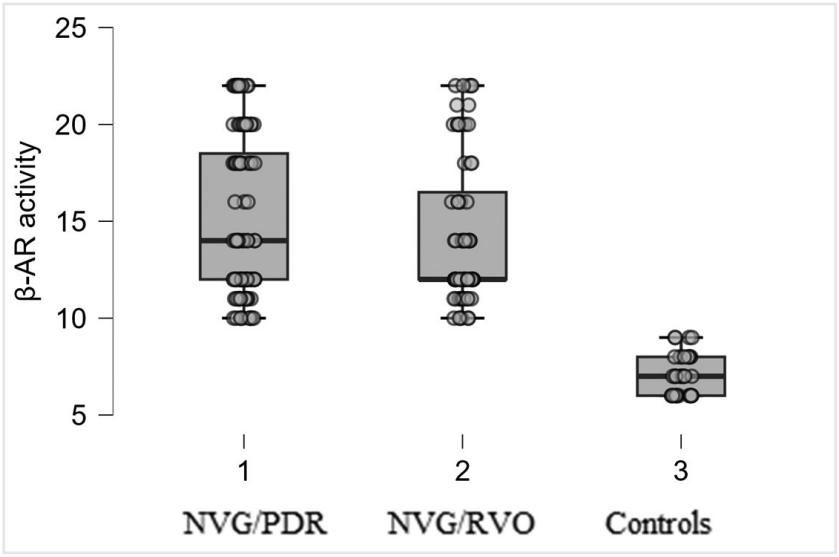

Fig. 1. Box plots showing distributions of β-adrenergic receptor (β-AR) activity levels in neovascular glaucoma secondary to proliferative diabetic retinopathy (NVG/PDR), neovascular glaucoma secondary to retinal vein occlusion (NVG/RVO) and controls. The horizontal line inside each box indicates the median, the top and bottom of the box indicate the interquartile range, and the whiskers extending from the box indicate the minimum and maximum after excluding outliers.

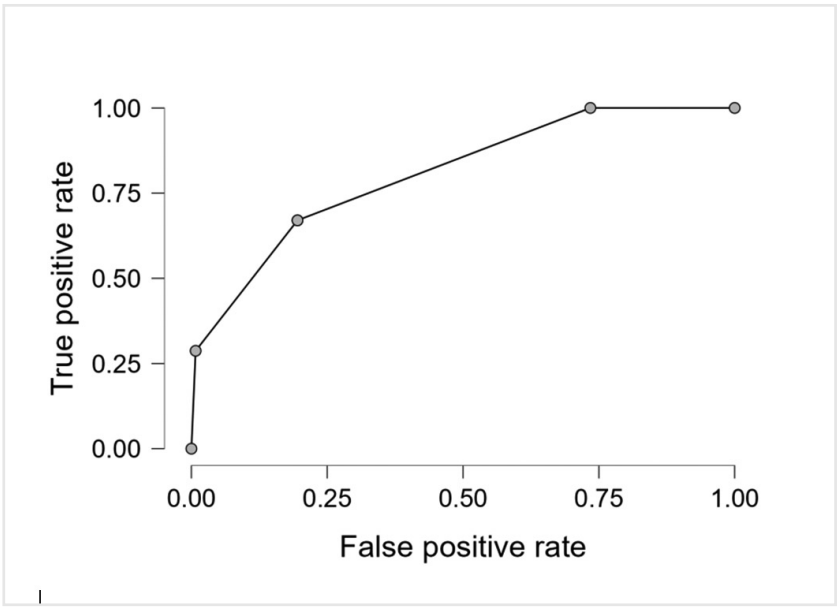

Fig. 2. Receiver operating characteristic (ROC) curve for β-adrenergic receptor activity (β-AR) for detecting clinically significant iris rubeosis (Weiss grade ≥ 2) in patients with neovascular glaucoma

ROC analysis for all patients with NVG showed a moderate but significant discriminative ability of β-AR activity for clinically significant rubeosis (Weiss grade ≥ 2). An AUC of 0.70 indicated that β-AR activity has the ability to reflect the systemic proangiogenic status in NVG (Fig. 2).

Therefore, β-AR activity (Fig. 2) demonstrated a moderate discriminative ability (AUC = 0.70) which is typical for systemic neuroautonomic markers. The results obtained indicate that β-AR activity (1) can be used for clinical phenotyping of patients with NVG but (2) should not be considered an independent prognostic marker for the course of the disease or the outcome of treatment. Additionally, with a β-AR activity cut-off ≥ 14.0, the sensitivity and specificity of the method were 60% and 65%, respectively, which confirmed that the parameter can be used for clinical phenotyping of patients with NVG.

Table 3 shows percentage patient distribution by Weiss grade for β-AR ≥ 14.0 and β-AR < 14.0.

There was a significant difference between the NVG/PDR group and the NVG/RVO group ($\chi 2 = 30.85$; $p < 0.001$) with regard to clinically significant rubeosis (Weiss grade ≥ 2), which may reflect a difference in the intensity of angiogenic response between NVG phenotypes. Moreover, patients with an increased β-AR activity had 5.02 (95 % CI, 2.64–9.56; $p < 0.001$) times the odds of the presence of active rubeosis irrespective of etiology. The area under ROC curve (AUC = 0.70) indicates a moderate discriminative ability of β-AR activity for patients with clinically significant iris neovascularization, which allows to consider this parameter not so much an independent prognostic marker but rather a phenotype-determinative characteristic that can reflect the systemic mechanisms involved in the course of secondary glaucoma (Fig. 2).

Table 3. Distributions of neovascular glaucoma (NVG) patients at a β-AR ≥ 14.0 versus a β-AR < 14.0 by grade of rubeosis of the iris according to the system devised by Weiss

Weiss grade of rubeosis	β-AR activity ≥ 14.0, n (%)	β-AR activity < 14.0, n (%)	Total, n (%)
Weiss grade 1	31 (33.0%)	69 (73.4%)	100 (53.2%)
	χ^2=30.85, p<0.001		
Weiss grade 2	36 (38.3%)	24 (25.5%)	60 (31.9%)
	χ^2=3.53, p=0.06		
Weiss grade 3	27 (28.7%)	1 (1.1%)	28 (14.9%)
	χ^2=28.37, p<0.001		
Total	94 (100%)	94 (100%)	188 (100%)

Note: Data are presented as number and percentage for a sample of patients with NVG; p, significance of difference between NVG patients with a β-AR activity ≥ 14.0 and those with a β-AR activity < 14.0 (χ^2 test). Abbreviations: β-AR activity, β-adrenergic receptor activity; NVG, neovascular glaucoma; PDR, proliferative diabetic retinopathy; RVO, retinal vein occlusion

In a multivariate regression model, β-AR activity remained independently associated with the diabetic phenotype of NVG after adjustment for the etiology of the disease. A one-unit increase in β-AR activity was associated with a 1.07 increase in the odds of developing NVG/PDR (OR = 1.07; 95% CI, 1.00–1.15; p = 0.04). The etiology of PDR remained a strong predictor of the phenotype of NVG (OR = 2.40; 95% CI, 1.30–4.60; p < 0.01).

Additional correlation analysis revealed a statistically significant direct correlation between the β-AR activity and the Weiss grade of rubeosis (rs = 0.69; p < 0.001). This is in agreement with the results of ROC analysis and confirms a potential association of sympatho-adrenal dysregulation with angiogenic activity in NVG.

Discussion

The results of the current study demonstrate that NVG is associated with increased β-AR activity levels compared to controls, which can reflect the involvement of sympatho-adrenal regulation in the formation of clinical manifestations of clinical manifestations of the disease. β-AR activity level was 1.7–2.0 times higher among all patients with NVG than in controls. The finding of higher β-AR activity levels in NVG associated with PDR is in agreement with current understanding of neuroautonomic dysregulation in DM, and underscores a potential involvement of systemic regulatory mechanisms in the course of ischemic vascular disorders of the eye [12].

The adrenergic system is an important regulator of vascular activity, microcirculation and endothelial function. Recent studies have demonstrated that, under chronic ischemic conditions, β-AR can participate in the control of vascular tone, cellular response to hypoxia and tissue remodeling [8]. In this connection, abnormal β-AR signaling is viewed as a potential mechanism for modulating angiogenic response in retinal vascular disease.

In DM, sympatho-adrenal activity develops in the presence of autonomic neuropathy, chronic low-grade inflammation and endothelial dysfunction [12]. This can contribute to persistent vascular constriction, an increase in ischemic changes in the iris and ciliary body and formation of a proangiogenic microenvironment. Ischemic forms of RVO, however, are also characterized by marked retinal hypoperfusion, venous stasis and capillary non-perfusion, thus creating conditions for activation of VEGF-dependent angiogenesis [13, 14]. Therefore, despite differences in major pathogenetic mechanisms, both key phenotypes of NVG are implemented via a common ischemic-and-angiogenic cascade.

Experimental studies have confirmed a direct involvement of β-AR signaling in the control of angiogenesis. It has been demonstrated that β3-AR are activated under hypoxic conditions and are involved in the regulation of VEGF expression in retinal cells, including endothelial and Müller cells [10]. Recent studies have demonstrated that a hypoxia-induced increase in VEGF expression in retinal cells largely depends on β3-AR signaling, which confirms its role in the formation of a proangiogenic microenvironment [11]. Additionally, β-AR blockade in models of ischemic retinopathy is accompanied by reduced pathologic neovascularization with inhibition of VEGF-dependent mechanisms of angiogenesis [9]. The β-AR pathway is also involved in the control of inflammation, with the use of β1-AR antagonist metoprolol decreasing the expression of proinflammatory cytokines and adhesion molecules under hyperglycemic conditions [19]. Collectively, this data indicates that β-AR signaling may be a mechanism through which systemic neuroautonomic dysregulation impacts angiogenic response in NVG.

The clinical findings of the present study supplement experimental data and indicate that an increased β-AR activity is associated with active iris rubeosis. Particularly,

β-AR activity had a moderate discriminative ability for clinically significant rubeosis (Weiss grade ≥ 2; AUC = 0.70) and, with a β-AR cut-off ≥ 14.0, patients with an increased β-AR activity had 5.02 (95 % CI, 2.64–9.56; p < 0.001) times the odds of the presence of active rubeosis. Additionally, rubeosis grade distribution among the groups with β-AR ≥ 14.0 and β-AR < 14.0 was statistically significant ($\chi^2 = 30.85$; p < 0.001). This indicates that β-AR may reflect a systemic neuroautonomic component of angiogenic response in NVG, which is in agreement with current understanding of multifactorial nature of the course of the disease and the complexity of risk stratification [2]. Our findings are in agreement with the concept of receptor-mediated neuroautonomic cell regulation developed in a fundamental study by Velychko and colleagues [15] that demonstrated a possibility of evaluating quantitatively the receptor sensitivity as a reflection of systemic regulatory remodeling [15].

Moreover, a clinical study demonstrated a change in sensitivity of peripheral blood lymphocytes to neuromediators in recurrent posterior uveitis, which indicated the involvement of sympatho-adrenal and cholinergic control mechanisms in the pathogenesis of eye disease [16]. Within the framework of the present study, β-AR may be interpreted as an integral systemic characteristic of sympatho-adrenal dysregulation that is potentially implicated in the modulation of angiogenic processes and the clinical course of NVG.

Our multivariate analysis confirmed the clinical significance of β-AR activity as a characteristic important for determining the phenotype: a one-unit increase in β-AR activity was associated with an increase in the odds of NVG/PDR (OR = 1.07; 95% CI, 1.00–1.15; p = 0.04), whereas the presence of PDR remained a strong independent predictor of the phenotype of NVG (OR = 2.40; 95% CI, 1.30–4.60; p < 0.01). Such integration of a systemic marker of neuroautonomic regulation with the etiological factor is in agreement with the findings of our previous studies, where NVG was considered a multifactorial disease with the course determined by the interaction of local ischemic mediators and systemic modifiers of angiogenic response [20, 21]. Additionally, relatively low β-AR activity levels in NVG/RVO may reflect the predominance of local hemodynamic abnormalities with a smaller contribution from systemic sympatho-adrenal activity.

Our clinical findings are in agreement with the experimental and clinical findings with regard to the role of β-AR signaling in the control of angiogenesis, inflammation and endothelial reactivity under chronic ischemic and hyperglycemic conditions [9, 10, 12, 22]. Collectively, these observations confirm the role of systemic neuroautonomic dysregulation as a key mechanism modulating the angiogenic response in NVG.

Additionally, the clinical significance of VEGF mechanisms has been confirmed by the results of a Cochrane systematic review that demonstrated that anti-VEGF therapy caused only a temporary regression of iris neovascularization and IOP reduction but failed to prevent disease progression and had no impact on the major pathogenetic factors [23]. This underscores the need for impact not only on the terminal component of the angiogenic cascade, but also on the systemic control mechanisms.

The generalization of clinical and statistical results made it possible to propose a clinical-and-pathogenetic concept whereby β-AR activity may reflect the systemic component of neuroautonomic dysregulation which is involved in the control of angiogenic response in NVG. The findings of (1) a strong positive correlation between β-AR activity level and the Weiss grade of rubeosis (rs = 0.69; p < 0.001) and (2) an increase in the odds of clinically significant iris rubeosis (OR = 5.02; 95% CI, 2.64–9.56; p < 0.001) at β-AR ≥ 14 indicate a possible involvement of sympatho-adrenal dysregulation in the formation of angiogenic phenotype of NVG.

Our findings make it possible to consider β-AR activity as a promising phenotype-determining marker that supplements the clinical assessment of iris rubeosis and may be used for more detailed characterization of the course of NVG. However, the concept proposed here should be verified in prospective studies with the involvement of direct markers of angiogenesis and systemic inflammation.

Limitations of this study include a single-center design and the absence of external validation. Additionally, we did not assess the effect of concomitant systemic therapy (particularly, β blockers and anti-hypertensive medications) that could impact the levels of β-AR activity. Prospective multifactorial studies with larger samples will be required to confirm the results of this study and determine whether modulating β-AR signaling would be clinically appropriate for patients with NVG.

Conclusion

β-AR activity level was 1.7–2.0 times higher in patients with secondary NVG than in controls (p < 0.05), which may reflect the involvement of sympatho-adrenal dysregulation in the systemic mechanisms of the development of the disease.

Additionally, there was a significant association between β-AR activity and clinical manifestations of angiogenic activity in NVG. β-AR level was strongly positively correlated with the Weiss grade of rubeosis (rs = 0.69; p < 0.001), indicating an association of the severity of sympatho-adrenal dysregulation with neovascularization activity.

ROC analysis for all patients with NVG showed a moderate but significant discriminative ability (AUC = 0.70) of β-AR activity for clinically significant rubeosis (Weiss grade ≥ 2). At a threshold level of β-AR ≥ 14, there was a five-fold increase in the odds of clinically significant iris rubeosis (OR = 5.02; 95% confidence interval, 2.64–9.56; p < 0.001), which makes it possible to consider β-AR activity as a promising phenotype-determining marker of the clinical activity of NVG.

Acknowledgement

The authors would like to express their deepest appreciation to Oleg Zadorozhnyy, Dr Sc (Med) and Deputy Director for Scientific Work, for his consulting on research, valuable methodological recommendations and support throughout the study. His professional experience, critical analysis of the results, and recommendations on research contributed to improvements in study design, statistics and interpretation of the results.

Author contributions

OG, LV, OB, and MS contributed to Conceptualization, Study Design, Data Collection, Analysis and Interpretation of Results and Manuscript Preparation.

Funding

This paper is a part of the 2019-2021 research program “To examine the features of changes in anterior segment structures, blood flow and heat exchange in neovascular glaucoma and trauma (registration number № 0119U101215)”.

Conflict of interest

The authors state that they have no conflict of interest that could influence their view on the subject matter or materials described and discussed in this manuscript.

Data Availability Statement

All the data relevant to this study has been included in this article. Further inquiries can be directed to the corresponding author.

Abbreviations

β-AR activity, β-adrenergic receptor activity; AUC, area under the curve; CI, confidence interval; DM, diabetes mellitus; IOP, intraocular pressure; NVG, neovascular glaucoma; PDR, proliferative diabetic retinopathy; OR, odds ratio; rs, Spearman rank correlation coefficient; RVO, retinal vein occlusion; VEGF, vascular endothelial growth factor.

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