

Cardiovascular risk factors in 100 patients with retinal artery occlusion – a single-centre registry

Czynniki ryzyka sercowo-naczyniowego w grupie 100 pacjentów
z zatorem tętnic siatkówki – rejestr jednośrodkowy*

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Abstract

Introduction. The aim of the study was to evaluate cardiovascular risk factors in patients after retinal artery occlusion (RAO). Additionally, our findings were compared with the results of epidemiological studies on the prevalence of cardiovascular risk factors in the Polish population.

Material and methods. We conducted a retrospective study which involved a group of 100 patients admitted to the ophthalmology service due to RAO in 2004–2014.

Results. In our study group, hypertension was found in 78% of patients, hypercholesterolemia in 67% of patients, ischemic heart disease in 53% of patients, previous myocardial infarction in 20% of patients, heart failure in 17% of patients, diabetes type 2 in 16% of patients, atrial fibrillation in 14% of patients, and kidney dysfunction in 11% of patients. Twelve percent of patients had a history of stroke, and 31% were smokers. Doppler ultrasonography (USG) showed carotid atherosclerotic plaques in 78% of patients and $\geq 70\%$ carotid artery stenosis in 33% of patients. Transthoracic echocardiography revealed aortic valve calcifications in 63% of patients.

Conclusions. Cardiovascular risk factors are present in a large majority of patients with RAO. Compared to the general population, patients with RAO often suffer from hypertension, hypercholesterolemia, type 2 diabetes and renal dysfunction. Due to an association between RAO and cardiovascular risk factors, appropriate diagnostic work-up is of major importance in these patients. Basic investigations in patients after a RAO event should include carotid artery Doppler ultrasound, echocardiography, electrocardiography, blood pressure measurement, and laboratory tests

Key words: cardiovascular risk factors, retinal artery occlusion, hypercholesterolemia, hypertension, stroke

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Introduction

Retinal artery occlusion (RAO) is an ophthalmologic emergency that requires urgent diagnosis and treatment. The major cause of RAO is carotid artery and aortic arch atherosclerosis, and less frequent causes include mitral and aortic valve disease, infective endocarditis, coagulopathies, atrial fibrillation, and autoimmune diseases including giant cell arteritis. Population studies indicate that RAO is associated with increased acute coronary syndrome (ACS) and stroke rates [1, 2]. Incident RAO in patients with atrial fibrillation is associated with an increased thromboembolic risk [3]. The aim of this study was to evaluate cardiovascular risk factors in patients with a RAO event and compare these findings with epidemiological data on the prevalence of cardiovascular risk factors in the Polish population.

Material and methods

The study included patients admitted to the ophthalmology service due to RAO over 11 years (in 2004–2014). The study was a retrospective analysis which was approved by the Bioethics Committee at the regional Świętokrzyskie branch of the Polish Chamber of Physicians and Dentists. The inclusion criterion was the finding of RAO on physical examination. The exclusion criterion was the diagnosis or suspicion of giant cell arteritis.

Patients with the diagnosis of RAO (60% men) were divided into 2 groups: those below 65 years of age (21%) and those 65 years of age and above (79%). The evaluation included concomitant conditions, cardiovascular risk factors, carotid ultrasound, echocardiography, electrocardiography, and laboratory tests. The history regarding tobacco smoking was obtained from 71% of study participants. The following parameters were included in the statistical analysis: gender, presence of cardiovascular disease (CVD), diabetes type 2, tobacco smoking, carotid artery lesions, echocardiographic parameters, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides (TG), creatinine, estimated glomerular filtration rate (eGFR) (using the Modification of Diet in Renal Disease [MDRD] formula), and fasting blood glucose. LDL cholesterol level was estimated using the Friedewald formula. Echocardiography was performed in 89% of patients and included evaluation of left atrial anteroposterior (LA-AP) dimension in the long axis parasternal view, left ventricular ejection fraction (LVEF), aortic valve calcifications, and the presence of aortic stenosis (AS), defined as the mean aortic valve pressure gradient above 10 mm Hg.

Hypercholesterolemia was defined according to the current European Society of Cardiology guidelines on CVD prevention as total cholesterol level ≥ 190 mg/dL or LDL cholesterol level ≥ 115 mg/dL [4]. This group also includ-

ed patients who were treated with statins due to elevated cholesterol levels or for secondary CVD prevention at the time of the diagnosis of RAO.

Hypertension was defined as systolic blood pressure > 140 mm Hg and/or diastolic blood pressure > 90 mm Hg or antihypertensive drug treatment on admission. Renal dysfunction was defined as eGFR below 60 mL/min.

Carotid Doppler ultrasonography was performed in 80% of patients. Ultrasound studies were performed according to the Polish Ultrasound Society recommendations [5]. Significant lesions were defined as vessel lumen stenosis of $\geq 70\%$. The intima-media thickness was measured approx. 10 mm proximal to the carotid bifurcation and values > 0.9 mm were considered abnormal. Atherosclerotic plaque was defined as the intima-media thickness > 1.5 mm or a focal thickening to $> 50\%$ of the vessel wall thickness.

Statistical analysis was performed using the Statistica software. Population characteristics were reported as mean values \pm standard deviation or numbers and percentages. Parametric data were evaluated using the Student t test, and differences in patient group sizes within the study population were evaluated using the chi-square test. $P < 0.05$ was considered statistically significant.

Results

In 2004–2014, overall 19,117 patients were admitted to the ophthalmology department. The diagnosis of RAO was made in 100 patients (60% males), amounting to 0.52% of all hospitalization. The patient age ranged from 43 to 93 years, mean 71.8 years (± 10.4). Diagnoses in the evaluated population of patients with RAO included hypertension (78%), hypercholesterolemia (67%), ischemic heart disease (53%), previous myocardial infarction (20%), diabetes type 2 (16%), previous stroke (12%), atrial fibrillation (14%), heart failure (17%), chronic kidney disease (11%), and tobacco smoking (31%) (Table 1). Imaging studies showed carotid artery atherosclerotic plaques in 78% of patients, $\geq 70\%$ carotid artery stenosis (CAS) in 33% of patients, aortic valve calcifications in 63% of patients, and at least mild aortic stenosis in 15.7% of patients. The mean interventricular septum thickness was 11.4 mm, mean LA-AP dimension was 39.9 mm, and mean LVEF was 55.3%. The mean values of laboratory parameters in patients with RAO included total cholesterol of 205 mg/dL, LDL cholesterol 126 mg/dL, HDL cholesterol 47.6 mg/dL, TG 147.9 mg/dL, creatinine 1.1 mg/dL, eGFR (MDRD) 69.5 mL/min, and fasting blood glucose level of 102 mg/dL (Table 2).

The study population was divided into patients < 65 and ≥ 65 years of age. The older patients were found to have significantly higher rates of hypertension (57 vs. 83%, $p = 0.009$), ischemic heart disease (33 vs. 58%, $p = 0.04$), atrial fibrillation (0 vs. 17.7%, $p = 0.037$), and heart failure (0 vs. 21.5%, $p = 0.019$). Patients below

Table 1. Cardiovascular risk factors in patients with retinal artery occlusion in the overall study group and in patients < 65 and ≥ 65 years of age

| Parameter | Overall (N = 100) | < 65 years (N = 21) | ≥ 65 years (N = 79) | p* |
|---|----------------------|------------------------|------------------------|-------|
| Number of patients | 100 | 21 | 79 | |
| Age, years (SD) | 71.8 (10.4) | 56.4 (6.2) | 75.9 (6.2) | |
| Males, n [%] | 60 (60) | 15 (71) | 45 (56) | 0.2 |
| Hypertension, n [%] | 78 (78) | 12 (57) | 66 (83) | 0.009 |
| Hypercholesterolemia, n [%] | 67 (67) | 13 (61.9) | 54 (68.3) | 0.57 |
| Cardiovascular disease, n [%] | 53 (53) | 7 (33) | 46 (58) | 0.04 |
| History of myocardial infarction, n [%] | 20 (20) | 2 (9) | 18 (22.7) | 0.17 |
| Diabetes type 2, n [%] | 16 (16) | 1 (4.7) | 15 (19) | 0.11 |
| Previous stroke, n [%] | 12 (12) | 2 (9) | 10 (12.6) | 0.69 |
| Atrial fibrillation, n [%] | 14 (14) | 0 (0) | 14 (17.7) | 0.037 |
| Heart failure, n [%] | 17 (17) | 0 (0) | 17 (21.5) | 0.019 |
| Kidney dysfunction, n [%] | 11 (11) | 0 (0) | 11 (13.9) | 0.06 |
| Tobacco smoking, n [%] | 22(31) | 10 (62) | 12 (22) | 0.001 |

*For comparison of patients < 65 and ≥ 65 years of age

Table 2. Laboratory parameters in patients with retinal artery occlusion in the overall study group and in patients < 65 and ≥ 65 years of age

| Parameter | Overall (N = 100) | < 65 years (N = 21) | ≥ 65 years (N = 79) | p* |
|--|----------------------|------------------------|------------------------|--------|
| Carotid atherosclerotic plaques, n [%] | 63 (78) | 12 (63) | 51 (85) | 0.03 |
| Carotid artery stenosis, n [%] | 27 (33) | 5 (26) | 22 (36) | 0.6 |
| Interventricular septal thickness [mm] | 11.4 ± 2.5 | 10.5 ± 1.4 | 11.4 ± 1.6 | 0.47 |
| LA-AP dimension [mm] | 39.9 ± 7.3 | 35 ± 16.2 | 41.3 ± 6.9 | 0.0003 |
| LVEF [%] | 55.3 ± 7.8 | 59.1 ± 11.5 | 54.1 ± 2.5 | 0.0075 |
| Aortic valve calcifications, n [%] | 56 (63) | 7 (33) | 49 (62) | 0.018 |
| Aortic stenosis, n [%] | 14 (15.7) | 1 (4.7) | 13 (16.4) | 0.169 |
| Total cholesterol [mg/dL] | 205.3 ± 67.2 | 227 ± 38.4 | 199 ± 31 | 0.07 |
| LDL cholesterol [mg/dL] | 126.2 ± 51.6 | 145 ± 35.8 | 120.6 ± 26.7 | 0.048 |
| HDL cholesterol [mg/dL] | 47.6 ± 12.3 | 54 ± 11.7 | 45.7 ± 17.9 | 0.01 |
| TG [mg/dL] | 147.9 ± 71.8 | 157 ± 71.8 | 145 ± 63.1 | 0.27 |
| Creatinine [mg/dL] | 1.1 ± 0.4 | 0.97 ± 0.2 | 1.14 ± 0.4 | 0.11 |
| eGFR by MDRD [mL/min] | 69.5 ± 25 | 82.2 ± 16 | 66.1 ± 18.5 | 0.008 |
| Fasting blood glucose [mg/dL] | 102 ± 17.6 | 100.9 ± 11.3 | 102 ± 11.3 | 0.41 |

*For comparison of patients < 65 and ≥ 65 years of age

65 years of age were more frequently smokers (62 vs. 22%, $p = 0.001$). No differences were found in regard to the rates of hypercholesterolemia (61.9 vs. 68.3%, $p = 0.57$), previous myocardial infarction (9 vs. 22.7%, $p = 0.17$), diabetes type 2 (4.7 vs. 19%, $p = 0.11$), previous stroke (9 vs. 12.6%, $p = 0.69$), and kidney dysfunction (0 vs. 13.9%, $p = 0.06$).

Imaging studies showed higher rates of carotid atherosclerotic plaques (63 vs. 85%, $p = 0.03$), aortic valve calcifications (33 vs. 62%, $p = 0.018$), and higher LA-AP dimension (35 vs. 41 mm, $p = 0.0003$) in older patients, while LVEF was significantly higher in younger patients (59 vs. 54%, $p = 0.0075$). No differences were found in the rates of CAS (26 vs. 36%, $p = 0.6$), at least mild aortic

stenosis (4.7 vs. 16.4%, $p = 0.169$), and interventricular septal thickness (11.4 vs. 10.5 mm, $p = 0.47$).

Laboratory tests showed significantly higher mean LDL cholesterol level (145 vs. 120 mg/dL, $p = 0.048$), HDL cholesterol (54 vs. 45 mg/dL, $p = 0.01$), and eGFR by MDRD (82.2 vs. 66.1 mL/min, $p = 0.008$) in younger patients. No differences were found in the mean total cholesterol (227 vs. 199 mg/dL, $p = 0.07$), TG (157 vs. 145 mg/dL, $p = 0.27$), creatinine (0.97 vs. 1.14 mg/dL, $p = 0.11$), and fasting blood glucose (100 vs. 102 mg/dL, $p = 0.41$).

Discussion

The association of cardiovascular risk factors and CVD with RAO has been well documented [6–9]. Risk factors for RAO include hypercholesterolemia, hypertension, carotid artery and aortic arch atherosclerosis, ischemic heart disease, kidney dysfunction, diabetes, stroke, smoking, mitral and aortic valve disease, and thrombi or vegetations which might be a source of embolic material [8, 10]. Multiple studies show that RAO is a predictor of ACS, stroke, and mortality [1, 2, 7]. Chang et al. showed a 70% increase in the risk of ACS in patients with RAO, and even higher in patients with central retinal artery occlusion (CRAO) [1]. In 2012, the same authors reported that RAO increased the risk of stroke by a factor of 2.07, and the risk was increased more than threefold in patients below 60 years of age [2]. Based on an analysis of 8580 patients including 111 with the diagnosis of RAO, Wang et al. showed an increased risk of all-cause mortality (HR 1.3) and mortality due to stroke (HR 2.0) in patients after a RAO event [7].

Considering the current European Society of Cardiology (ESC) guidelines on the management of peripheral arterial disease, RAO in a patient with CAS should be considered symptomatic carotid artery disease equivalent to a transient ischemic attack (TIA) or stroke, with significant implications in regard to the management of patients with CAS. In patients with 70–99% CAS and RAO, carotid endarterectomy (CEA) should be performed, optimally within 2 weeks after RAO. In patients with 50–69% CAS, indications for CEA are not so clear. All patients with a RAO event should be offered lifelong treatment with antiplatelet drugs and a statin [11].

Our findings were compared with the epidemiological NATPOL 2011 study that evaluated cardiovascular risk factor rates in the Polish population [12]. The prevalence of hypertension in our patients with RAO was much higher compared to the general Polish population evaluated in the NATPOL 2011 study (78 vs. 31.9%) [13]. Regarding lipid parameters, our patients with RAO had more hypercholesterolemia (67% vs. 61.1%) and higher total cholesterol, LDL cholesterol, and TG levels compared to the NATPOL 2011 study population (205 vs. 198 mg/dL, 126 vs. 123 mg/dL, and 147 vs. 122 mg/dL, respectively) while

the mean HDL cholesterol in patients with RAO was lower (47 vs. 50 mg/dL) [14]. In a similar WOBASZ II study in the Polish population, the rate of hypercholesterolemia was 67%, close to our findings [15].

Patients with RAO in our study had more diabetes compared to the NATPOL 2011 study population (16 vs. 6.7%) [16].

In our study population, kidney dysfunction was also more common (11 vs. 5.8%) but in contrast to the NATPOL 2011 study, albuminuria was not measured in our study. We believe that evaluation for albuminuria in patients with RAO would increase the proportion of patients with the diagnosis of chronic kidney disease [13].

The proportion of smokers was 27% in the NATPOL 2011 study population compared to 31% in our patients with RAO [13].

Table 3 summarized studies that evaluated the rates of cardiovascular disease and risk factors in patients with RAO. Studies that evaluated only patients with CRAO or branch retinal artery occlusion (BRAO) were excluded from the analysis. One of the most important observations was made in regard to carotid artery disease. Study findings indicate that $\geq 70\%$ CAS is present in 21–33% of patients with RAO. In these studies, the most common cardiovascular condition in patients with RAO was hypertension, except for the study by Hayreh et al. in which the most common cardiovascular conditions were carotid atherosclerotic plaques followed by hypercholesterolemia and hypertension [8]. The prevalence of carotid atherosclerotic plaques in our patients with RAO was 69–78%, and similar rates were reported by Hayreh et al. [8]. The proportion of smokers among patients with RAO was reported at 31–40%. Thus, the most common modifiable cardiovascular risk

Table 3. Comparison of studies evaluating cardiovascular disease and risk factors in patients with retinal artery occlusion

| Parameter | Hayreh et al. [8] | Hankey et al. [17] | Schmidt et al. [18] |
|---|-------------------|--------------------|---------------------|
| Number of patients [n] | 375 | 98 | 416 |
| Mean age [years] | 62,5 | 64 | 66 |
| Males [%] | 59 | 55 | 65.9 |
| Hypertension [%] | 52 | 56 | 75.9 |
| Hypercholesterolemia [%] | 60 | 53 | 34.7 |
| Ischemic heart disease [%] | 25 | 18 | 23.8 |
| Diabetes type 2 [%] | 17 | 5 | 18.2 |
| Smoking [%] | 33 | 40 | 32.7 |
| Previous stroke [%] | 18 | – | 14.2 |
| Carotid artery stenosis $\geq 70\%$ [%] | – | 24 | 21 |
| Carotid atherosclerotic plaques [%] | 69 | – | 31 |

factors in patients with RAO are hypertension, hypercholesterolemia, and smoking [8, 17–18]. In our study group, the most common risk factors for RAO were hypertension, hypercholesterolemia, and ischemic heart disease.

A history of stroke is reported in 14–18% of patients with RAO [8, 18], compared to 12% in our patients.

Of note, only two patients in our study group, both below 65 years of age, had no established cardiovascular risk factors.

Rudkin et al. and Calizzo et al. focused on newly diagnosed conditions in patients with CRAO. In their group of patients with CRAO, Rudkin et al. found hypercholesterolemia in 73% of patients, and this diagnosis was made only after the occurrence of CRAO in 36% of patients. Carotid artery stenosis of more than 50% was diagnosed in 9 (27%) patients, 6 of which were treated with endarterectomy or carotid artery stenting [19]. Calizzo et al. showed that CAS and hypercholesterolemia were the most common undiagnosed conditions in patients with CRAO. On admission, CAS was diagnosed in 3% of patients compared to 38% at discharge, and hypercholesterolemia was diagnosed in 8% of patients on admission and in 44% of patients at discharge [20].

Conclusions

Cardiovascular risk factors are present in a large majority of patients with RAO. Compared to the general population, patients with RAO have more hypertension, hypercholesterolemia, type 2 diabetes and renal dysfunction. They are also characterised by higher total cholesterol, LDL cholesterol, and TG levels, and lower HDL cholesterol levels.

The most common risk factors for RAO in the study population were hypertension, hypercholesterolemia, male gender, and ischemic heart disease. The most common cardiovascular risk factors in patients < 65 years of age were male gender, hypercholesterolemia, hypertension, and smoking, while hypertension, hypercholesterolemia, ischemic heart disease, and male gender were the most common risk factors in older patients.

When age-related differences were analysed, patients < 65 years of age with RAO were found to have less structural heart disease but significantly higher LDL and HDL cholesterol levels and were significantly more frequently smokers.

Investigations in patients with RAO should include carotid artery Doppler ultrasound, blood pressure measurement, lipid levels, echocardiography, and electrocardiography.

Streszczenie

Wstęp. Celem pracy była ocena obecności czynników ryzyka sercowo-naczyniowego w grupie pacjentów po epizodzie zamknięcia naczynia tętniczego siatkówki (RAO). Cel dodatkowy stanowiło porównanie wyników badań epidemiologicznych dotyczących rozpowszechnienia czynników ryzyka sercowo-naczyniowego wśród ludności Polski z wynikami przeprowadzonego badania.

Materiał i metody. Przeprowadzono badanie retrospektywne, które objęło grupę 100 pacjentów hospitalizowanych na oddziale okulistyki w latach 2004–2014 z powodu RAO.

Wyniki. W badanej grupie nadciśnienie tętnicze stwierdzono u 78% pacjentów, hipercholesterolemię u 67% pacjentów, chorobę niedokrwienną serca u 53% pacjentów, zawał serca u 20% pacjentów, niewydolność krążenia u 17% pacjentów, cukrzycę typu 2 u 16% pacjentów, migotanie przedsionków u 14% pacjentów, upośledzoną funkcję nerek u 11% pacjentów. Dwanaście procent pacjentów było po udarze mózgu. Nikotyzm stwierdzono u 31% pacjentów. Błazkę miażdżycową w wykonanych badaniach ultrasonografii (USG) metodą Dopplera uwidoczniono u 78% pacjentów, zwężenie tętnicy szyjnej równe lub większe 70% dotyczyło 33% pacjentów. W wykonanych badaniach echokardiograficznych stwierdzono obecność zwapnień na płatkach zastawki aortalnej u 63% pacjentów.

Wnioski. Znamienna większość pacjentów z rozpoznaniem RAO jest obciążona czynnikami ryzyka sercowo-naczyniowego. Pacjenci ci, w porównaniu z populacją ogólną, częściej chorują na nadciśnienie tętnicze, hipercholesterolemię, cukrzycę typu 2, częściej też stwierdza się u nich dysfunkcję nerek. Ze względu na związek między RAO a czynnikami ryzyka sercowo-naczyniowego niezwykle istotna jest odpowiednia diagnostyka. Wśród podstawowych badań u pacjentów po epizodzie RAO powinny się znaleźć badanie USG tętnic szyjnych z oceną dopplerowską, badanie echokardiograficzne i elektrokardiograficzne, pomiar ciśnienia tętniczego a także badania laboratoryjne.

Słowa kluczowe: czynniki ryzyka sercowo-naczyniowego, zator tętnicy siatkówki, hipercholesterolemia, nadciśnienie tętnicze, udar mózgu

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