

## Реферати

**ОЦІНКА ГІГІЄНИЧНОГО СТАНУ ПОРОЖНИНИ РОТА ТА ІНТЕНСИВНОСТІ КАРІЄСУ ЗУБІВ У ПАЦІЄНТІВ З В-ТАЛАСЕМІЄЮ**  
Шадлінська Р.В.

У дослідженні брали участь 321 пацієнта з гомозиготною формою  $\beta$ -таласемії і 382 соматично здорові особи. Для об'єктивної оцінки твердих тканин зубів і гігієни порожнини рота використовувалися клінічні тести: гігієнічний індекс Гріна-Вермільйона (Green J.C., Vermillion J.R., 1960), індекс Ю.А. Федорова і В.В. Володкіної (1971) і показник інтенсивності карієсу КПУ. При порівняльному аналізі в групах виявлена достовірна різниця між показниками індексу КПУ і індексу ОНІ-S. Спостерігалася тенденція до погіршення гігієнічного індексу зі збільшенням віку пацієнтів з  $\beta$ -таласемією. При цьому, найбільше значення виявлено в групі старше 18 років ( $3,60 \pm 0,11$ ). Більш високий ризик розвитку карієсу був виявлений в групі з  $\beta$ -таласемією в порівнянні з обстежуваним контингентом без соматичних захворювань. Профілактична стоматологічна допомога є першочерговою необхідністю для пацієнтів з великою  $\beta$ -таласемією.

**Ключові слова:**  $\beta$  - таласемія, карієс, гігієна порожнини рота, профілактика стоматологічних захворювань.

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**ОЦЕНКА ГИГИЕНИЧЕСКОГО СОСТОЯНИЯ ПОЛОСТИ РТА И ИНТЕНСИВНОСТИ КАРИЕСА ЗУБОВ У ПАЦИЕНТОВ С В-ТАЛАССЕМИЕЙ**  
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В исследовании принимали участие 321 пациента с гомозиготной формой  $\beta$ -талассемии и 382 соматически здоровые лица. Для объективной оценки твердых тканей зубов и гигиены полости рта использовались клинические тесты: гигиенический индекс Грина-Вермилльона (Green J.C., Vermillion J.R., 1960), индекс Ю.А. Федорова и В.В. Володкиной (1971 г.) и показатель интенсивности кариеса КПУ. При сравнительном анализе в группах выявлена достоверная разница между показателями индекса КПУ и индекса ОНІ-S. Наблюдалась тенденция к ухудшению гигиенического индекса с увеличением возраста пациентов с  $\beta$ -талассемией. При этом, наибольшее значение обнаружено в группе старше 18 лет ( $3,60 \pm 0,11$ ). Более высокий риск развития кариеса был обнаружен в группе с большой  $\beta$ -талассемией по сравнению с обследуемым контингентом без соматических заболеваний. Профилактическая стоматологическая помощь является первостепенной необходимостью для пациентов с большой  $\beta$ -талассемией.

**Ключевые слова:**  $\beta$  – талассемия, кариес, гигиена полости рта, профилактика стоматологических заболеваний.

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**FEATURES OF THE RAYNAUD'S SYNDROME COURSE IN PATIENTS WITH RHEUMATOID ARTHRITIS**

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Often, patients with rheumatoid arthritis develop secondary Raynaud's syndrome, which is a prognostically unfavorable symptom of its course. Raynaud's syndrome is more common in patients with an existing rheumatoid factor in the blood serum. In patients with rheumatoid arthritis there is an impaired endothelium dependent vasoregulation in the shoulder artery, indicating the endothelial function disorder. In patients with rheumatoid arthritis with secondary Raynaud's syndrome, there are more pronounced signs of endothelial dysfunction, indicating a high risk of atherosclerosis and cardiovascular complications. The index of open capillaries permits to objectively assess the Raynaud's syndrome severity in patients with rheumatoid arthritis.

**Key words:** rheumatoid arthritis, Raynaud's syndrome, endothelial dysfunction.

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Rheumatoid arthritis (RA) is an autoimmune disease of unknown etiology with the development of symmetrical erosive arthritis (synovitis) and a wide range of extra-articular (systemic) manifestations [9]. This is the most common and disabling connective tissue disease (affects about 1% of the world and 0.4% of Ukrainian population) [10]. In 58.7-72% of patients with RA, comorbid conditions such as Raynaud's syndrome (RS) and arterial hypertension, which can significantly modify the course of the disease, impair the treatment efficacy and reduce the life expectancy of patients [10].

An important pathogenetic link of RA is the microcirculation system impairment, and the microvasculature serves as the target organ in which the immune, inflammatory and metabolic mechanisms of the pathological process are implemented. Disorders in the microcirculation system are associated with the systemacity of lesions, duration of the disease, antioxidant protection disorders, endothelial dysfunction indices and reliably play a leading role in the pathogenesis of RA systemic manifestations. As of today, the endothelium is known to be the target of oxidative stress, which reduces endothelium dependent vasodilatation of blood vessels, promotes the increase of cellular processes course rate and accelerates their apoptosis.

In recent years, the results of numerous studies show that endothelial dysfunction (ED), as well as the increasing intima-media thickness, is a predictor of future cardiovascular morbidity in the general population and one of the diagnostic criteria for early detection of atherosclerotic vascular lesions. This also applies to RA, since the presence of ED is even observed at its early stages and is also interpreted as a sign of accelerated development of atherosclerosis. Thus, the presence of ED is considered to be the first manifestations of atherogenesis in patients with RA [4, 5, 8].

Patients with RA frequently have secondary Raynaud's syndrome (RS), which serves as a prognostically unfavourable sign of its course. Mechanisms of RS development are still insufficiently studied. The nature of the disease is multifactorial, vascular and immune mechanisms playing an important role. Local ischemia of tissues with the possible development of dystrophy, which is observed in RS, may arise either due to the vascular functions regulation impairment caused by the sympathetic nervous system, or due to the increased formation of vasoconstrictor substances in the process of autoimmune inflammation.

Vascular changes in the inflammatory process are proliferation or destruction of the endothelium, hyperplasia and thickening of the intima, which leads to the tissues ischemia [2, 3]. Further study of the clinical-pathogenetic and immunological features of the secondary RS course in patients with RA is relevant and will permit to improve the schemes of its correction in the complex therapy of RA.

**The purpose** of the work was to study the features of the RS course in patients with RA using laboratory and instrumental research methods.

**Materials and methods.** The total of 85 patients with RA (12 men and 73 women) were examined, being under inpatient treatment at the rheumatologic department of Ivano-Frankivsk Regional Clinical Hospital. RS was diagnosed in 43 patients (6 men and 37 women). Mean duration of RA was  $9.3 \pm 2.4$  years. The diagnosis of RA was established based on the criteria of the American College of Rheumatology (2010). The criteria by E.Allen and G.Brown were used to diagnose RS [7].

All patients with RA were divided into two groups: group 1 consisted of patients with RA - 38 patients, and group 2 included RA patients with secondary RS - 47 patients. The control group was represented by 25 healthy volunteers whose age and sex corresponded to those in groups 1 and 2.

Endothelin-1 (ET-1) content was determined by immunoassay (ELISA) using a reagent set produced by Peninsula Laboratories Inc. (USA). It is a sandwich ELISA method, which measures "free" forms of human endothelin-1. Concentration of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) was determined by standardized ELISA using a set of CYTELISA-TNF- $\alpha$  reagents. (USA).

The level of C-reactive protein (CRP) and rheumatoid factor (RF) were determined by the method of latex agglutination. To determine the amount of CRP in mg / l in the sample, the maximum dilution of the blood serum giving visible agglutination should be multiplied by 6 mg / l. The norm is considered to be indices of up to 6 mg / l, sensitivity of the test to be 6 mg / l. To determine the amount of RF in IU / ml in the sample, the maximum dilution of blood serum, which gave visible agglutination, must be multiplied by 12 IU / ml. Normal values are up to 12 IU / ml, test sensitivity is 12 IU / ml.

The endothelium function was assessed using the so-called endothelium dependent vasodilatation of the brachial artery (EDVBA). The reactive test was carried out using the technique developed by D.S. Celermajer and co-authors (1992). The normal reaction of the brachial artery was considered to be its dilation against the background of reactive hyperemia by 10% or more of the initial diameter, and lower indices were regarded as a pathology [6].

We used capillaroscopy of the nail bed to objectivize the RS assessment in patients with RA. The index of open capillaries (IOC) was calculated reflecting the ratio of functioning and desolate anse capillaires. The IOC normally makes 50-70%.

To study the subjective picture of the peripheral circulation status, we used the assessment scale by A.B. Scherbakov (1987). The scale of the RS attacks severity is a visual 10-point scale, in which 0 is a complete absence of attacks, and 10 points - the presence of gangrene changes in the fingers. The frequency and duration of SR attacks were also assessed.

Statistical processing of the data obtained was performed with the definition of the arithmetic mean, its mean square deviation and the error of the arithmetic mean. The reliability of the differences (p) between the compared groups of patients was established using the t-criterion. To determine the variables interaction, the correlation index (r) was determined.

**Results of the study and their discussion.** Signs of ED were detected in 76 patients examined, which amounted 89.4% (table 1). All patients with RA in combination with secondary RS have been diagnosed for ED. We found that patients with RA and RA in combination with RS have insufficient EDVBA. In patients of group 2, the EDVBA score was significantly ( $p < 0.05$ ) lower ( $6.5 \pm 0.2\%$ ) compared

to patients in group 1 ( $8.8 \pm 0.3\%$ ). This is most likely due to constant vasospastic attacks in these patients, which leads to disruption of the endothelium integrity.

In RA patients with secondary RS, the level of endothelin-1 by 1.7 times higher compared to RA patients without RS ( $p < 0.05$ ). It all suggests a greater probability of endothelial damage in patients of group 2. Concentration of ET-1 in RA patients with RS correlated with RA activity ( $r = 0.68$ ,  $p < 0.05$ ).

Table 1

Indices of EDVBA, ET-1, TNF- $\alpha$  and CRP in examined patients

Index	Control group, n=25	All patients, n=85	RA, n=38	RA +RS n=47	Degrees of RA activity		
					Degree I, n=8	Degree II n=25	Degree III n=52
ED	-	76 (89.4%)	29 (34.1%)	47 (55.3%)	1 (1.2%)	24 (28.2%)	51 (60.0%)
EDVBA, %	12.9 $\pm$ 0.4	7.5 $\pm$ 0.3*	8.8 $\pm$ 0.3*	6.5 $\pm$ 0.2*•	9.3 $\pm$ 0.3*•	7.8 $\pm$ 0.2*•°	6.3 $\pm$ 0.2*•°'
Endothelin-1, пкг/мл	1.5 $\pm$ 0.1	7.0 $\pm$ 0.3 *	5.1 $\pm$ 0.3*	8.6 $\pm$ 0.3*•	4.4 $\pm$ 0.2*•	6.4 $\pm$ 0.2*•°	9.1 $\pm$ 0.3*•°'
TNF- $\alpha$ , pg/ml	24.4 $\pm$ 3.1	72.6 $\pm$ 7.6*	64.1 $\pm$ 5.2*	79.3 $\pm$ 6.2*•	50.7 $\pm$ 5.1*•	66.1 $\pm$ 5.2*•°	82.3 $\pm$ 7.2*•°'
CRP, mg/l	6.3 $\pm$ 0.3	68.4 $\pm$ 7.6*	52.4 $\pm$ 7.6*	88.4 $\pm$ 7.6*•	24.3 $\pm$ 4.5*•	53.2 $\pm$ 5.7*•°	86.5 $\pm$ 8.5*•°'

Notes: n – number of patients; \* - reliable difference from the control group,  $p < 0.05$ ; • - reliable difference between RA and RA+RS patients,  $p < 0.05$ ; ° - reliable difference between patients with I and II RA activity degrees,  $p < 0.05$ ; ' - reliable difference between patients with II and III RA activity degrees,  $p < 0.05$ .

TNF- $\alpha$  belongs to proinflammatory cytokines. Therefore, the inflammatory process activity degree has the most important meaning for assessing the level of TNF- $\alpha$ . In particular, in patients with minimal activity of the pathological process, this index reliably grows by 2.1 times in comparison with healthy donors. With the moderate activity of the inflammatory syndrome, the TNF- $\alpha$  level grows even more (by 23.3% higher than the TNF- $\alpha$  titre with degree I of RA activity). Whereas with maximal activation of the pathological process, the TNF- $\alpha$  value increases to  $82.3 \pm 7.2$  pg / ml. It should be noted that the level of this cytokine is significantly higher in group 2 of patients compared to group 1 (20.0%). A strong correlation between the degree of RA activity and the level of TNF- $\alpha$  ( $r = 0.73$ ;  $p < 0.01$ ) in RA patients with secondary RS was established. Summarizing the above, it can be argued that TNF- $\alpha$  is an important pro-inflammatory agent, which increased production with RA complicates the course of the disease. The revealed correlation between the TNF- $\alpha$  level and the degree of the inflammatory syndrome activity permits to use determined value of this cytokine as a marker of inflammation in RA. Stably high TNF- $\alpha$  concentration in blood serum of patients with secondary RS is a prognostically unfavorable symptom and a predictor of RA progression.

Both CRP and TNF- $\alpha$  serve as a nonspecific markers of inflammation, which were determined at significantly higher concentrations ( $88.4 \pm 7.6$  mg / l,  $p < 0.01$ ) in patients with RS, than in patients with pure RA ( $52.4 \pm 7.6$  mg / l). This testifies to the high RA activity in patients of group 2.

An important factor in predicting the course of RA and secondary RS is the presence of the RF (RF +) in the blood. In patients of group 2, the concentration of RF was  $89.3 \pm 7.2$  IU / ml and was significantly higher than in group 1 ( $49.4 \pm 5.2$  IU / ml,  $p < 0.01$ ). Among the patients of group 2, 43 patients had a seropositive variant of RA (table 2).

Table 2

## RF frequency and concentration levels in examined patients

Index	Control group, n=25	All patients, n=85	RA, n=38	RA +RS n=47	Degrees of RA activity		
					Degree I, n=8	Degree II n=25	Degree III n=52
RF+	-	63 (74.1%)	20(23.5%)	43 (50.3%)	2 (2.35%)	18 (21.2%)	43 (50.6%)
RF-	30(100%)	22(25.9%)	18(21.2%)	4 (4.7%)	6 (7.1%)	7 (8.2%)	9 (10.6%)
RF, IU/ml	8.3 $\pm$ 1.8	65.3 $\pm$ 5.8*	49.4 $\pm$ 5.2*	89.3 $\pm$ 7.2*•	43.4 $\pm$ 3.8*•	55.3 $\pm$ 4.6*•°	108.3 $\pm$ 8.8*'

Notes: n – number of patients; \* - reliable difference from the control group,  $p < 0.05$ ; • - reliable difference between RA and RA+RS patients,  $p < 0.05$ ; ° - reliable difference between patients with I and II RA activity degrees,  $p < 0.05$ ; ' - reliable difference between patients with II and III RA activity degrees,  $p < 0.05$ .

After monitoring the data obtained, it was found that in patients of group 2 with high activity degree, frequency ( $7.8 \pm 0.5$ ), duration ( $24.7 \pm 3.6$ ) and severity ( $6.6 \pm 0.6$ ) of RS attacks was significantly higher ( $p < 0.05$ ) than in patients with activity degree I ( $3.7 \pm 0.5$ ,  $12.8 \pm 2.1$  and  $3.1 \pm 0.2$ , respectively).

IOC had a correlation interaction with the frequency ( $r = 0.59$ ;  $p < 0.05$ ), duration ( $r = 0.58$ ;  $p < 0.05$ ) and severity ( $r = 0.53$ ,  $p < 0.05$ ) of RS attacks. The highest values were observed in patients with high RA activity ( $95.2 \pm 5.2$ ) and significantly differed from those in patients with RA activity degree II ( $76.2 \pm 4.2$ ;  $p < 0.05$ ) and the activity degree I ( $66.3 \pm 3.5$ ;  $p < 0.05$ ) (table 3).

IOC, frequency, duration and severity of RS attacks in patients with RA

Index	Control group, n=25	RA +RS n=47	Degrees of RA activity		
			Degree I, n=8	Degree II n=25	Degree III n=52
Frequency of attacks	-	6.7±0.5	3.7±0.5	4.7±0.5*°	7.8±0.5*°'
Duration of attacks, min	-	23.7±3.6	12.8±2.1	16.4±3.3*°	24.7±3.6*°'
Severity of attacks, points	-	5.3±0.5	3.1±0.2	4.1±0.5*°	6.6±0.6*°'
IOC, %	54.3±3.5	84.5±4.6*	66.3±3.5*	76.2±4.2*°	95.2±5.2*°'

Notes: n – number of patients; \* - reliable difference from the control group, p<0.05; ° - reliable difference between patients with I and II RA activity degrees, p<0.05; ' - reliable difference between patients with II and III RA activity degrees, p<0.05.

Clinical manifestations, features of the inflammatory process and changes in the parameters of the endothelium functional status in RA patients in combination with secondary RS are still understudied and require a targeted study. In general, the results of our study coincide with the literature data. High levels of CRP, TNF- $\alpha$ , and ET-1 in RA patients in combination with RS were presented in domestic and foreign studies [3, 5, 10]. Early development of ED and the presence of high RF titres in RA patients were shown in the studies of I.I. Blahinina [5].

However, in our study for the objective assessment of peripheral blood circulation, a capillaroscopic examination of the patient was used. Capillaroscopy of the nail bed is a highly informative, fast and convenient method for diagnosing and monitoring the RS progression in patients with RA. We first used IOC to objectively assess the peripheral circulation changes and showed its high informational value in the instrumental assessment of RS course in RA patients.

### Conclusions

1. In patients with secondary RS, the activity of RA inflammatory syndrome is higher than in patients with RA without RS, as evidenced by higher CRP, RF and TNF- $\alpha$  in the study group 2.
2. The RF presence in the blood serum of patients with RA serves as an unfavourable sign of its course, and more frequently occurs in patients with secondary RS.
3. The ED severity and frequency in patients with secondary RS is higher than in RA patients without RS.
4. In patients with RA in combination with secondary RS, high values of ET-1 and IOC levels, low rates of EDVBA appear to be a prognostically unfavorable sign in the course of this disease.
5. A detailed study of the pathophysiological and immunological features of the secondary RS will improve the treatment regimens in RA patients, reduce clinical and laboratory manifestations of RA, and improve the life quality of these patients.

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### Реферати

#### ОСОБЛИВОСТІ ПЕРЕБИГУ СИНДРОМУ РЕЙНО У ХВОРИХ НА РЕВМАТОЇДНИЙ АРТРИТ

Штефюк О.В., Яцишин Р.І., Герич П.Р., Карпюк Ю.Я., Бойчук В.Б.

Нерідко у хворих на ревматоїдний артрит розвивається вторинний синдром Рейно, який є

#### ОСОБЕННОСТИ ТЕЧЕНИЯ СИНДРОМА РЕЙНО У БОЛЬНЫХ РЕВМАТОИДНЫМ АРТРИТОМ

Штефюк А.В., Яцишин Р.И., Герич П.Р., Карпюк Ю.Я., Бойчук В.Б.

Нередко у больных ревматоидным артритом развивается вторичный синдром Рейно, который служит

прогностично несприятливою ознакою його перебігу. Синдром Рейно частіше виникає у пацієнтів з наявним ревматоїдним фактором у сироватці крові. У хворих на ревматоїдний артрит має місце недостатня ендотеліальна залежна вазорегуляція у плечовій артерії, що вказує на порушення ендотеліальної функції. У хворих на ревматоїдний артрит з вторинним синдромом Рейно спостерігаються більш виражені ознаки ендотеліальної дисфункції, що є свідченням високого ризику розвитку атеросклерозу та серцево-судинних ускладнень. Індекс відкритих капілярів дає можливість об'єктивно оцінити вираженість синдрому Рейно у хворих на ревматоїдний артрит.

**Ключові слова:** ревматоїдний артрит, синдром Рейно, ендотеліальна дисфункція.

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прогностически неблагоприятним признаком его течения. Синдром Рейно чаще возникает у пациентов с имеющимся ревматоидным фактором в сыворотке крови. У больных ревматоидным артритом имеет место недостаточная эндотелий зависящая вазорегуляция в плечевой артерии, что указывает на нарушение эндотелиальной функции. У больных ревматоидным артритом с вторичным синдромом Рейно наблюдаются более выраженные признаки эндотелиальной дисфункции, что свидетельствует о высоком риске развития атеросклероза и сердечно-сосудистых осложнений. Индекс открытых капилляров дает возможность объективно оценить выраженность синдрома Рейно у больных ревматоидным артритом.

**Ключевые слова:** ревматоидный артрит, синдром Рейно, эндотелиальная дисфункция.

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## CARDIOVASCULAR SYSTEM INDICATORS IN THE PRIMARY SCHOOL-AGED CHILDREN DURING THE ADAPTATION TO EDUCATIONAL LOADS IN THE REGION WITH IODINE EFFICIENCY

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The purpose of the study was to study the adaptive capacity of the cardiovascular system and to identify changes in the performance of heart rate variability in the primary school-aged children with iodine deficiency during the school year. It was found that among the 1st grade schoolchildren with iodine deficiency, 30% of children had the adaptive strategy tension at the beginning of the school year. The largest share of schoolchildren with low adaption level at the beginning of the school year was revealed. According to the indicators of heart rate variability, in 1-4 grades students with iodine deficiency the sympathetic nervous system influence is prevalent during the school year, while the parasympathetic nervous system is predominant in schoolchildren, properly provided with iodine.

**Keywords:** adaptation, heart rate variability, autonomic nervous system regulation, children, iodine deficiency.

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The course of adaptation processes best reflects the functional state of the cardiovascular system (CVS), and the heart rate variability (HRV) allows to speak directly about the involvement of certain levels of the central nervous system (CNS) in the physiological functions regulation, in other words about the level of their centralization. According to the theory of R.M. Baevsky, the heart rate structure allows us to evaluate the state of the autonomic nervous system, the degree of organism adaptive resistance, the possibility of adaptive reserves [1, 5]. It is known that the higher the CNS level involved in the regulation of functional systems, the higher the adaptation tension [4, 9]. At the same time, it has been proved that thyroid hormones are essential for the maturation and functioning of the nervous system. Therefore, iodine deficiency (ID) may indirectly impair the adaptation course because of the negative effect on the nerve cell differentiation. One of the most scientifically based and informative methods of quantitative evaluation of the Autonomic Activity Indices, whose parameters are considered as integral indicators of regulation processes of the organism, is a method of computer cardiointervalography [3].

In this regard, to assess the iodine deficiency effect on the CVS activity, all children underwent cardiointervalography to determine the impact of individual autonomic nervous system sections.

**The purpose** of the study was to study the adaptive capacity of the child's organism to the school loads and to identify changes in the performance of cardiovascular system using heart rate variability in the primary school-aged children with iodine deficiency during the school year.

**Materials and methods.** The total of 243 schoolchildren from 1st to 4th grade were surveyed at the beginning, the middle and the end of the school year. In the first grade, 64 schoolchildren were healthy, 29 were with iodine deficiency, in the 2nd grade 34 children were healthy, and 18 were with iodine