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S A D R Ž A J / C O N T E N T S

Prof. dr Đorđe P. Nešić (Šabac, 15. jun 1873 – Beograd, 24. oktobar 1959), jedan od prvih srpskih oftalmologa, redovni član Srpske akademije nauka i umetnosti od 1947. godine, dao je značajan doprinos naučnom i stručnom razvoju oftalmologije, ne samo u Srbiji. Nosilac je brojnih odlikovanja koje je kao vojni lekar dobio za učešće u balkanskim ratovima i Prvom svetskom ratu. Od 1970. godine Klinika za očne bolesti Kliničkog centra Srbije u Beogradu nosi njegovo ime (vidi str. 339–344).

Prof. Dr. Đorđe P. Nešić (Šabac June 15, 1873 – Belgrade October 24, 1959), one of the first Serbian ophthalmologists, a member of the Serbian Academy of Sciences and Art from 1947, made a significant contribution to scientific and professional development of ophthalmology not only in Serbia. He was awarded by numerous decorations for taking part in the Balkan Wars and World War I as a military physician. The Clinic for Ophthalmology, Clinical Center of Serbia, Belgrade has been bearing the name of Prof. Dr. Đorđe P. Nešić since 1970 (see p. 339–344)

P R E L I M I N A R Y R E P O R T UDC 005.32::614.2

Influence of healthcare institution managers' proactive approach to communication activities on patient satisfaction

Uticaj proaktivnog pristupa menadžera zdravstvenih institucija komunikacijskim aktivnostima na zadovoljstvo bolesnika

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Abstract

Background/Aim. Over the recent years customer satisfaction program as a tool for patient satisfaction has been recognized as an important issue in healthcare services. The aim of this preliminary study was to explore an influence of healthcare institution managers' approach and attitudes to marketing and public relations activities (communication activities), in the context of implementation of customer satisfaction programs, on patient satisfaction. **Methods.** The study was conducted among managers from different state-owned healthcare institutions (healthcare centres, clinics, hospitals) in Serbia. The structured questionnaire form, comprising both open and closed questions, was used as a main research tool. The total number of sent questionnaires was 120; 56 questionnaires were sent back, while 49 of them were valid. **Results.** It was shown that 42.9% of healthcare institutions apply proactive media approach, and that 35.7% of the organizations have a person who, besides his/her basic engagements, performs activities connected with marketing and public relations. Using Chi-square likelihood ratio test it is confirmed that these activities have a significant role in supporting customer satisfaction program implementation ($p < 0.05$). The results showed that in 69.4% cases, positive attitude of healthcare institutions managers toward marketing and public relations activities had positive influence on patient satisfaction ($p < 0.05$). **Conclusion.** Managers in healthcare sector in Serbia who used proactive approach toward media and who had already institutionalized communication activities with external stakeholders have a positive attitude to implementation of customer satisfaction program. Furthermore, managers' attitude toward communication activities has influence on patient satisfaction.

Key words:
patient satisfaction; quality assurance, health care; programs; marketing; public relations.

Apstrakt

Uvod/Cilj. Programi zadovoljstva korisnika usluga proučavaju se i primenjuju u sektoru zdravstvenih usluga kao instrumenti za postizanje zadovoljstva bolesnika. Cilj ovog preliminarnog istraživanja među menadžerima zdravstvenih institucija bio je ispitivanje uticaja njihovog pristupa i stavova prema aktivnostima marketinga i odnosa s javnošću (aktivnostima komunikacije) u kontekstu primene programa zadovoljstva korisnika usluga na zadovoljstvo bolesnika. **Metode.** Istraživanje je sprovedeno među menadžerima državnih zdravstvenih institucija (domova zdravlja, klinika, bolnica). Struktuirani upitnik, sa otvorenim i zatvorenim pitanjima, korišćen je kao osnovni instrument istraživanja. Poslato je ukupno 120 upitnika, a vraćeno 56, od kojih je 49 bilo validno. **Rezultati.** Pokazano je da 42,9% zdravstvenih institucija primenjuje proaktivan pristup medijima i da 35,7% ustanova ima zaposlenog koji, pored redovnih zaduženja, obavlja i aktivnosti marketinga i odnosa s javnošću. Upotrebom hi-kvadrat LR testa potvrđena je pretpostavka da ove aktivnosti imaju značajnu ulogu u primeni programa zadovoljstava korisnika ($p < 0,05$). Kod 69,4% slučajeva, pozitivan stav menadžera zdravstvenih institucija prema aktivnostima marketinga i odnosa s javnošću ima pozitivan uticaj na zadovoljstvo bolesnika ($p < 0,05$). **Zaključak.** Menadžeri zdravstvenih institucija u Srbiji koji primenjuju proaktivan pristup medijima i koji su već institucionalizovali komunikacijske aktivnosti unutar ustanove imaju i pozitivan stav prema primeni programa zadovoljstva korisnika usluga. Nadalje, stav menadžera prema komunikacijskim aktivnostima ima uticaja na zadovoljstvo bolesnika.

Ključne reči:
bolesnik, zadovoljenje; zdravstvena zaštita, ocena kvaliteta; programi; marketing; odnosi sa javnošću.

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Introduction

Over the recent years customer satisfaction program as a tool for patient satisfaction has been recognized as an important issue in health services by many academics and practitioners.

Healthcare institutions are faced with new environmental changes and various challenges. Perception of environmental changes influences strategic response (efficiency-oriented or market-focused) of healthcare organization, which is related to appropriate measures of performance [1]. According to Avali and Yasin [2] factors that determine success in healthcare sector include: environmental change factors (customer and external environmental factors, innovation and competitive factors), healthcare industry, competitive responses (customer focus, service quality, strategic focus, efficiency and cost structure), implementation of quality improvement initiatives (Total Quality Management - TQM and other), and organizational benefits.

The healthcare market in Serbia is characterized by the rise of competition. The intensive growth of private sector, changing needs of customers, increase of health costs, development of knowledge and technologies are just some of the challenges that have brought a new perception of health care institution functioning. The relevance of market orientation, customer focus, service quality, quality improvements and other factors are recognized in the Serbian healthcare system. As the incumbent Minister of Health in the Serbian Government reported at the Fourth National Conference on Permanent Quality Improvement in Health Care (2008), important steps have already been made in this field: legislation for permanent quality improvement of healthcare has been developed; several projects related to healthcare quality have been implemented with international partners in recent years, national conferences on healthcare permanent quality improvement have been organized since 2005. Some outputs of these initiatives and activities are as follows: better understanding of healthcare quality and introduction of permanent quality improvements culture, training of employees on TQM, defining the indicators for quality and periodical examination of patients' satisfaction that started five years ago.

In the context of the presented initiatives and realized activities in healthcare sector in Serbia regarding quality improvements, the authors of the paper started to explore the correlation between management approach to external stakeholders and institutionalization of communication activities toward external stakeholders with attitudes toward introducing the quality improvement program. On the other side, the authors explored the correlation between managers' attitude to marketing and public relations activities (communication activities) and patient satisfaction.

Customer satisfaction is one of the fundamental concepts in marketing. Customer satisfaction could be defined as an overall assessment of the performance of various attributes that constitute a product or a service [3–4]. Concept of customer satisfaction is very important in the field of health care, because patients are not a usual category of customers. Patient satisfaction could be used as an instrument for measuring the success of quality improvement effort [5]. More comprehensive patient satisfaction is a tool for overall performance improvement [6], and way to business excellence [7].

Antecedents to satisfaction have been investigated by different authors. In main antecedents to customer satisfaction identified by consumers are expectations, perceived quality (product and service) and disconfirmation [8]. Other antecedents besides mentioned are image, perceived quality of hardware and human ware and perceived value [9]. Outcomes could be connected with consumers, employees, efficiency and overall performances [10–14]. A more detailed classification was presented in the study of Luo and Homburg [15].

In the healthcare literature authors show a positive correlation between nursing care and overall patient satisfaction [16–19]. Main characteristics that have impact on patient satisfaction are: how seriously institution viewed a patient's problem, how courteously staff treated a patient and how well institutions paid attention to a patient's needs [20].

In order to achieve a higher customer satisfaction, organizations must develop appropriate customer satisfaction programs. Success of a customer satisfaction program is not secured by a simple procedure for obtaining a customer feedback. A customer satisfaction program requires turning the obtained information into action plans and then effective implementation for the purpose of business results improvement.

Customer satisfaction program [21–23] is a process that consists of several stages and begins with an understanding of customer satisfaction drivers. Successful implementation of any customer satisfaction program requires paying attention to influential factors. The factors associated with all successful programs are: top management support and guidance, satisfaction that is incorporated into the strategic focus, function integration and multifunctional team formation, first line employees are responsible for satisfaction program execution and questionnaires, satisfaction measurements must involve combination of qualitative and quantitative research methods, evaluation must include companies and competitors' satisfaction performance, good communication and implementation plan, feasible and achievable action planning and implementation that should be in line with short and long-term objectives [23, 24].

The aim of this preliminary research of the was to explore approach and attitudes of healthcare institutions managers toward marketing and public relations activities (communication activities) in the context of implementation of customer satisfaction programs and their influence on patient satisfaction.

Methods

The research was designed to define and investigate the relevance of marketing and public relations activities of healthcare institutions and their influence on implementing customer satisfaction program and customer satisfaction. The respondents were managers from different state-owned healthcare institutions (health centers, clinics, hospitals) in Serbia. The structured questionnaire form, comprising both

open and closed questions, has been used as a main research tool. The total number of sent questionnaires was 120. During the research, we received 56 filled-in questionnaires, but 49 out of them were valid.

The problems of research of managerial implementation of customer satisfaction program and patient satisfaction are based on internal analysis of health institutions, through managers' attitude on marketing and public relations activity, institutionalization of these activities within healthcare institutions and relations with media, one of the important external groups from business environment. The media approach was researched in our study through a 3–stage scale, where a response 2 describes proactive approach (health care institution communicates with media on a regular basis), while responses 1 and 3 represent other possible approaches to media (1- reactive approach, 3 – occasionally).

The starting hypotheses were the following: H1: healthcare institutions managers who apply proactive media approach have positive attitude toward implementation of customer satisfaction program; H2: healthcare institutions which have institutionalized marketing or public relations activities have positive attitude toward implementation of customer satisfaction program; H3 positive attitude of healthcare institutions managers to marketing and public relations activities has positive influence on customer satisfaction.

In data analysis, the SPSS statistical computer analysis package was used to analyze research findings.

Results

The results showed that 42.9% healthcare institutions apply proactive media approach, meaning that they communicate with media on a regular basis, 22.4% apply reactive approach, and 34.7% of them communicate with media occasionally. Moreover, 35.7% organizations have a person who, besides his/her basic engagements, performs activities connected with marketing and public relations, 26.5% have a person whose only activity is communication, while 28.6% of institutions do not have anyone engaged in such activities although there is a need for that. Only 4.6% of institutions do not have a need for communication activities and the same number of institutions hire consultants and marketing and public relations agencies.

Based on cross tab analysis using Chi-square likelihood ratio test we found support for hypothesis 1 ($p < 0.05$). Hypothesis 2 can also be accepted. The existence of a person or department responsible for marketing and public relations activities in the healthcare institutions has a significant role in supporting the change related to customer satisfaction program implementation ($p < 0.05$). The results about relationship between managers' positive attitude toward implementation of customer satisfaction program and patient satisfaction, are presented in Table 1. As a multiply response in hypothesis 3, we can accept that positive attitude of healthcare institutions managers to marketing and public relations activities has positive influence on patient satisfaction (69.4%). Furthermore, negative attitude of healthcare institutions managers on marketing and public relations activities has negative influence on patient satisfaction almost in the same percent (69.2%). The odds ratio was OR = 3.833 (95%CI = 1.093–13.450) and relative risk for negative attitude to generate negative influence on patient satisfaction is RR = 2.063 (95%CI = 1.086–3.918). Mantel-Haenszel Common Odds Ratio Estimate statistics revealed a statistically significant relationship ($p = 0.036$).

Table 1

Relationship between positive attitude of healthcare institution managers toward implementation of custumer satisfaction program and patient's satisfaction

Hypotheses	Variables	χ^2 LR test	df	*p*	Contingency Coefficient	*p*
H1	Proactive approach to media	11.224	2	0.004	0.454	0.002
	Opinion of manager about media importance for customer	6.288	2	0.043	0.398	0.026
H2	Existence of person or department responsible for marketing and public relations activities	12.959	5	0.024	0.467	0.018
H3	Positive managers attitude on marketing and public relations activities	4.611	1	0.032	0.294	0.032

H1 – Healthcare institutions managers who apply proactive media approach have positive attitude toward implementation of customer satisfaction program,
H2 – Healthcare institutions which have institutionalized marketing or public relations activities have positive attitude toward implementation of customer satisfaction program,
H3 – Positive attitude of healthcare institutions managers to marketing and public relations activities has positive influence on customer satisfaction,
LR – likelihood ratio

Discussion

A successful implementation of various programs and business changes implicates various management skills and recognition of various tasks [25]. The role of managers, especially their leadership style is proven as very important in implementation of decisions within any organization [26], which also refers to healthcare organization [27, 28].

In the TQM literature, top management support is crucial for successful implementation of quality programs [29, 30]. As customer satisfaction program roots are in TQM, management support is crucial for its implementation [23, 24].

The role of managers in implementation of programs within healthcare organizations is usually explored in the domain of quality programs, which leads to service excellence. Management support, commitment and leadership have significant relevance for implementation of TQM program in the service sector [31], in quality improvement program [32], in the success or failure of any customer satisfaction program [23], and belong to external factors that affect quality assurance program success [33].

As we determined the significance of managers in quality program implementation, the key considerations are to determine the domain of their influence, their main tasks, attitudes and behaviour toward stakeholders and correlation with the successful program implementation, etc. Homes [25] reported tasks of managers for successful implementation of any business change, such as establishing change program terms of reference, setting up steering committee, establishing finances, establishing change control procedures, defining change program standards, conducting risk management study, determination of methodology and determination of resource requirements. Den Hartog and Verburg [34] identified main tasks of higher level managers in order to contribute attainment of high service quality, as first communicating norms and values of high quality service, and then creating rules and procedures that should be applied.

As marketing is a process of creating, communicating and delivering values to customers [35] and public relations activities imply managing communication between organization and its stakeholders [36] the authors of this study explored greater influence of marketing and public relations activities (communication activities) on customer satisfaction in health care sector.

As previously mentioned, one of the antecedents to customer satisfaction is organization image [9]. On the other hand, it is known that organization image depends on relations with external stakeholders. In this study, the authors explored the relevance of external target stakeholders of healthcare organization, especially media, and managers' behavior toward them, in order to find if there is the correlation with managers' attitude regarding implementation of quality programs, especially customer satisfaction program.

Media, as mediators in communication between any organization and its target groups, are considered as very important in healthcare sector. At general level, they have influence on healthcare system and public trust in health care [37]. The main goal of activities directed to media is to generate publicity, as specific way of communication with all other stakeholders, and the advantages of good relations with media are numerous [38]. For healthcare organizations media have significant role in creating a positive image as an important part of attaining service quality [39]. In planning and organizing activities towards media, healthcare institution could apply one of the following approaches: defensive (reactive) – after the expressed interest of media; strategic (proactive) – active effort to create and maintain professional relationship with media; and only in an event of crisis [40]. The extreme situation is the case that activities towards media do not exist at all, but even in this case, media will find the information on healthcare issue and/or organization from other sources, if they need it. That is the reason why healthcare organization should use the media in the best way, as a tool in providing service quality [39].

Communication between a patient and healthcare organizations can be improved by institutionalization of marketing or public relations activities, meaning planning and applying of communication strategy. Following our research, we can state that regarding media (one of the most important external stakeholders) it is preferable to use proactive communication strategy.

The study also showed media as important stakeholders in implementation of customer satisfaction program. This implies that both national healthcare institutions and media should cooperate, promote and actively participate in the process of quality improvement in healthcare institutions.

For the healthcare service marketer, proactive approach toward media influences to effective implementation of customer satisfaction program.

This preliminary study was based upon the results obtained in healthcare institutions in Serbia and was just a part of a longitudinal research project. It is necessary to perform further research in other countries in the region in order to compare various outcomes. We also need to investigate other important external stakeholders that have relevant influence on customer satisfaction program. The broader framework should also include patient perception in healthcare sector in the context of customer satisfaction.

Conclusion

Positive attitude of healthcare institutions managers towards marketing and public relations activities generates patient satisfaction in 70% of cases, and negative attitude generates negative patient satisfaction also in about 70% of cases. Negative attitude is two times higher in risk to generate negative patient satisfaction.

Healthcare institutions should apply a proactive approach to communication activities because it will positively influence better implementing and managing customer satisfaction program and patient satisfaction. By managing customer experience, healthcare institutions will be able to drive positive image, secure patient loyalty and ultimately increase profit.

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Позив на рекламирање у 2010. години

У прилици смо да вам понудимо могућност оглашавања и рекламирања производа и услуга у часопису „**Војносанитетски преглед**“ (ВСП). То је сигурно најбољи вид и најзаступљенији начин упознавања евентуалних корисника са вашим услугама и производима.

Часопис „**Војносанитетски преглед**“, званични орган лекара и фармацеута Војске Србије, научно-стручног је карактера и објављује радове из свих области медицине, стоматологије и фармације. Радове равноправно објављују стручњаци из војних и цивилних установа и из иностранства. Штампа се на српском и енглеском језику. Часопис излази непрекидно од 1944. године до сада. Једини је часопис у земљи који излази месечно (12 бројева), на око 100 страна А4 формата, а повремено се објављују и тематски додаци (суплементи). Путем размене или претплате ВСП се шаље у 23 земље света. Радове објављене у ВСП-у индексирају: *Science Citation Index Expended (SCIE)*, *Journal Citation Reports/Science Edition*, *Index Medicus (Medline)*, *Excerpta Medica (EMBASE), EBSCO* (преко ове базе ВСП је *on line* доступан од 2002. године у *pdf* формату) и *Biomedicina Serbica*.

Цене реклама и огласа у часопису „Војносанитетски преглед“ у 2009. години су:

1.	Оглас у црно-белој техници А4 формата за један број	20 000,00 динара
2.	Оглас у ц/б техници А4 формата за целу годину (11-12 бројева)	200 000,00 динара
3.	Оглас у боји А4 формата за један број	35 000,00 динара
4.	Оглас у боји А4 формата за целу годину (11-12 бројева)	330 000,00 динара
5.	Оглас у боји на корицама К3 за један број	50 000,00 динара
6.	Оглас у боји на корицама К3 за целу годину (11-12 бројева)	455 000,00 динара
7.	Оглас у боји на корицама К2 и К4 за један број	55 000,00 динара
8.	Оглас у боји на корицама К2 и К4 за целу годину (11-12 бројева)	530 000,00 динара

За сва објашњења, упутства и понуде заинтересовани контактирају редакцију часописа „Војносанитетски преглед“. Средства се уплаћују на жиро рачун код Управе јавних плаћања у Београду број: 840-941621-02 **ВМА (за Војносанитетски преглед или за ВСП)**, **ПИБ 102116082**. Уплатницу (доказ о уплати) доставити лично или поштом (писмом, факсом, *e-mail*-ом) на адресу: Војносанитетски преглед, Црнотравска 17, 11000 Београд; тел/факс: 011 2669 689, e-mail: vmaini1@eunet.rs или vmavsp@hotmail.com

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Angiotensin II type 1 receptor gene polymorphism could influence renoprotective response to losartan treatment in type 1 diabetic patients with high urinary albumin excretion rate

Uticaj polimorfizma gena za AT1 receptor na renoprotektivnu efikasnost losartana kod bolesnika sa dijabetesom tip I i povišenom urinarnom ekskrecijom albumina

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Abstract

Background/Aim. Diabetic nephropathy (DN) is a clinical syndrome characterized by persistent albuminuria, increasing arterial blood pressure and progressive decline in glomerular filtration rate (GFR). When persistent albuminuria is established, antihypertensive treatment becomes most important factor in slowing the progression of diabetic glomerulopathy. The aim of this study was to examine if renoprotective response to a short-term losartan therapy depends on 1166 A/C gene polymorphism for its target receptor. **Method.** The study included 35 patients with diabetes mellitus type 1 and persistently high urinary albumin excretion rate (UAE: > 30 mg/24 h), genotyped for the 1166 A/C gene polymorphism for the angiotensin II type 1 receptor (AT1R). The participants were segregated into 3 genotype groups according to combinations of A or C allele: AA(16%), AC(15%) and CC(11%). The patients received losartan 50 mg daily for 4 weeks, following 100 mg daily for another 8 weeks. At baseline and after 12 weeks of the treatment period UAE, blood pressure, GFR and filtration fraction (FF) were determined. **Results.** After 12 weeks of the treatment with losartan, albuminuria was reduced from baseline by 9% [95% confidence interval (CI): 1–17, $p = 0.039$] in the AA genotype, and by 11% (95% CI: 6–17, $p = 0.0001$) in the AC genotype. Losartan treatment reduced albuminuria in the CC group by 5% (95%CI: -13–22, $p = 0.47$). Glomerular filtration rate remained unchanged in all genotype groups. Filtration fraction was significantly reduced from baseline by 0.018 ± 0.024 ($p = 0.012$) only in the AC genotype. In the AA genotype, FF was reduced from baseline by 0.017 ± 0.03 ($p = 0.052$), and in the CC genotype by 0.01 ± 0.008 ($p = 0.092$). In the AA group, systolic blood pressure declined from 136 ± 24 mmHg at baseline, to an average of 121 ± 18 mmHg at the end of the study ($p = 0.001$). The AC group achived reduction from 131 ± 10 mmHg at baseline to 115 ± 7 mmHg ($p = 0.001$) during the investigation period. In the AA genotype group losartan reduced diastolic blood pressure from 86 ± 13 mmHg at baseline to 78 ± 8 mmHg ($p = 0.004$), and in the AC genotype from 88 ± 5 mmHg at baseline to 11.7 ± 5.6 mmHg during the investigation period ($p = 0.001$). In the CC genotype diastolic blood pressure reduction remained nonsignificant ($p = 0.066$). **Conclusion.** The results of our small sample size study provide the evidence that 1166 A/C AT1R polymorphism could be associated with the renoprotective response to losartan therapy.

Key words:
diabetes mellitus, type 1; diabetic nephropathies; polymorphism, genetic; angiotensin II; losartan.

Apstrakt

Uvod/Cilj. Dijabetesna nefropatija (DN) je klinički sindrom koji karakterišu trajna albuminurija, povišeni krvni pritisak i progresivno sniženje jačine glomerulske filtracije. Kada se pojavi trajna albuminurija, uvođenje antihipertenzivne terapije predstavlja najvažniji faktor za usporavanje progresije dijabetesne glomerulopatije. Naša studija imala je za cilj da ispita u kolikoj meri je renoprotektivni odgovor na lečenje losartanom, blokatorom receptora za angiotenzin II, uslovljen polimorfizmom gena za njegov ciljni receptor. **Metode.** Ispitivanjem je bilo obuhvaćeno 35 bolesnika sa dijabetesom tip 1 i trajno povišenom urinarnom ekskrecijom albumina od preko 30 mg/24 h. Ispitanici su lečeni lo-

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sartanom u dozi od 50 mg dnevno tokom četiri sedmice, nakon čega je doza povećana na 100 mg dnevno, narednih osam sedmica. Na početku ispitivanja i nakon 12 sedmica lečenja izmerene su vrednosti dnevne urinarne ekskrecije albumina (UEA), jačine glomerulske filtracije (JGF), glomerulske filtracione frakcije (FF) i sistemskog krvnog pritiska. U zavisnosti od postojanja A i C alela u okviru 1166A/C polimorfizma gena za receptor tip 1 angiotenzina II (AT1R), ispitanici su bili podeljeni u tri grupe (AA, AC i CC) radi utvrđivanja razlike ispitivanih parametra na početku i na kraju lečenja. **Rezultati.** Posle 12 sedmica lečenja, losartan je snizio albuminuriju za 9% [interval poverenja (IP) 95%: 1–17, $p = 0,039$] u AA homozigotnoj grupi i za 11% (IP 95%: 6–17, $p = 0,0001$) u AC heterozigotnoj grupi. Redukcija albuminurije kod CC homozigota nije bila značajna. Jačina glomerulske filtracije ostala je nepromenjena u sve tri genotipske grupe. Terapija losartanom dovela je do značajnog smanjenja FF za 0,018 ± 0,024 ($p = 0,012$) jedino u AC grupi, dok se redukcija FF u AA grupi za 0,017 ± 0,03 ($p = 0,052$) približila statističkoj značajnosti. Kod CC homozigota smanjenje FF nije bilo značajno. U grupama AA i AC, postignuto je visoko statistički značajno sniženje i sistolnog i dijastolnog krvnog pritiska ($p < 0,01$), dok sniženje arterijskog pritiska u CC grupi nije bilo značajno ($p > 0,05$). **Zaključak.** Individualni renoprotektivni odgovor na terapiju losartanom, bar jednim delom mogao bi biti uslovljen 1166 A/C polimorfizmom gena za AT1R.

Ključne reči:
dijabetes melitus, insulin-zavisni; dijabetesne nefropatije; polimorfizam, genetički; angiotenzin II; losartan.

Introduction

Diabetic nephropathy (DN) is a clinical syndrome characterized by persistent albuminuria, increasing arterial blood pressure and progressive decline in glomerular filtration rate (GFR) [1]. When persistent albuminuria is established (over 30 mg/24 h), antihypertensive treatment becomes most important factor in slowing the progression of diabetic glomerulopathy. It is recommended that this therapy should be started as early as possible, at the microalbuminuric stage, even if the hypertension is absent [2].

Extensive investigations have documented the key role of the renin-angiotensin-aldosterone system (RAAS) in the pathogenesis and pathophysiology of diabetic renal disease. Angiotensin II (Ang II), the major effector of this system, acts as the circulating vasoconstrictory hormone, as well as paracrine peptide that modulates renal function. Most of its effects are mediated via Ang II type 1 receptors, localisated in glomerular vascular smooth muscle cells, mesangial cells and on the luminal surface of tubular cells. This hormone also has the fundamental role in starting and progression of DN by its hemodynamic and non-hemodynamic effects [3].

Angiotensin II type receptor 1 (AT1R) antagonists are a group of antihypertensive drugs that act on the terminal cascade of RAAS by selective binding to AT1R. This provides more complete blockade of Ang II actions in systemic and local manner, which is especially important in diabetic state where the intrarenal RAAS activity is enhanced [4].

Despite good glycemic control, lipid lowering agents and antihypertensive treatment, these patients have 3-6 times faster decline in renal function comparing to non-diabetic patients [5]. One of the possible reasons for currently nonadequate renoprotective treatment and bad prognostic values, are individual variations in response to the first-line therapy of these patients. This variations could be genetically influenced, due to the existence of polymorphisms within the genes that encode for enzymes related with drug metabolism, or genes for proteins of the physiological pathway on which the drug acts [6, 7]. Because of the central role of RAAS in pathogenesis of DN, it would be important to evaluate the type of genetic polymorphisms binding to this system, that could influence individual renoprotective efficacy of drug treatment.

As we mentioned before, most of the actions of Ang II are mediated by stimulation of AT1R, including vasoconstriction, regulation of the vascular tone and proliferative processes in glomerule. Moreover, genetic variations of this specific receptor can alter AT1R-mediated reactions by altering its expression or structure [7, 8].

This human receptor gene is composed of 5 exons and 4 introns with a length of more than 50 kb. So far, various genetic polymorphisms of this receptor gene have been reported, but the best evaluated of all is the 1166 A/C single nucleotide polymorphism (SNP). This SNP is an A/C transversion in the 3' untranslated region of the gene [9]. There is a growing evidence to suggest that the 1166 A/C AT1R polymorphism is implicated in higher risk for cardiovascular events, and the C allele became serious candidate for genetic variations that lead to enhanced activity of systemic and/or paracrine RAAS [10–13]. Considering previous studies, treatment with AT1R antagonists could overcome some other forms of polymorphisms [14, 15]. We, therefore, wanted to evaluate if the renoprotective effect of losartan could be influenced by polymorphism of its target receptor gene.

Methods

Thirty-five patients, men (n = 20) and women (n = 15), with diabetes mellitus type 1 and persistently high urinary albumin excretion rate (UAE > 30 mg/24h) [16] were included in this study . Each patient underwent a detailed history, physical and laboratory examination, in order to evaluate inclusion and exclusion criteria. Before enrollment, each patient was examined for urinary albumin excretion rate. All patients fulfilled the following inclusion criteria: diabetes mellitus type 1 more than 5 years; of over 18 years age and persistently high albuminuria. The patients were excluded if they had a history of congestive heart failure, malignant hypertension, valvular heart and aortic disease, renal artery stenosis, creatinin clearance less than 60 mL/min and earlier

established persistent erythrocyturia and/or urinary infection. Dietary intake of protein or salt was not restricted.

After evaluation for the inclusion criteria, the patients underwent the measurement of renal hemodynamic parameters and blood pressure. Then, the participants received two daily oral doses of losartan: 50 mg daily in the first 4 weeks, followed by 100 mg for another 8 weeks. After 12 weeks of treatment, renal hemodynamics and measurement of blood pressure and albuminuria were repeted. The subjects were genotyped for 1166 A/C AT1R polymorphism, and subdivided into three groups (AA, AC and CC) in order to establish statistically significant differences in the examined parameters, before and after the treatment period.

Urinary albumin excretion was determined as the mean values obtained in the two separate 24 h urine collections using an immunonephelometric assay (BN 100 Dade Behring analyzer) [16]. It was measured at baseline and again after 12 weeks of the treatment.

Blood pressure was measured using mercury sphygmomanometar in the seated positon after resting for at least 10 minutes and was determinated as the average of three measurements taken 5 minutes apart [17]. During the treatment, blood pressure was measured 24 h after the last dose.

Genomic DNAs were extracted with Applied Biosystems 6 100 Nucleic Acid prep Station instrument. Concentration of DNA was determinated by measuring the optical density at 260 nm. The A1166C gene polymorphism was analyzed by polymerase chain reaction (PCR) and subsequent restriction-endonuclease digestion according to description of Dzida et al [18]. Polymerase chain reaction product was visualized by electrophoresis on 2% agarose gel stained with 2 μL of 10 mg/mL ethidium bromide solution.

Glomerular filtration rate was measured as the renal uptake of 99mTc-diethylenetriaminepentaacetic acid (DTPA), 2 to 3 minutes after traces arrival in the kidney by the method of Goates et al [19]. A total GFR was calculated using a formula derived from regression analysis comparing 24 h creatinine clearance to percent renal uptake:

GFR (mL/min) = % renal uptake × 9.8127 − 6.82519; where 9.8127 is the regression coefficient and 6.8219 the y-intercept. The results were standardized for 1.73 m^2 body surface area, using the patients surface area at the start of the study.

Effective renal plasma flow (ERPF) was measured as the uptake of 131-iodine-lebeled hippuran in the kidney, 1 to 2 minutes after the *i.v.* injection, with a correction for renal depth and with background substraction [20]. Filtration fraction (FF) was determined by dividing GFR by ERPF [12].

All data were presented as mean ± SD except for albuminuria, which was given as median (interquartile range). The one–way ANOVA test was used to analyse between-group and within-group differences. The paired Student's *t*-test was used to test the differences between the baseline values and those after the treatment with losartan. The values of albuminuria were logarithmically transformed, owing to its skewed distribution, and then tested by the Student's *t*-test. A *p*-value less than 0.05 was considered statistically singificant.

Results

The average age of the 35 patients with diabetes mellitus type 1 and high values of albumin excretion rate was 33 ± 9 years, and the average diabetes duration was 16 ± 7 years. All patients were genotyped for 1166 A/C AT1R polymorphism. Sixteen subjects had the AA genotype, 15 subjects had the AC genotype, while the rest four subjects had the CC genotype in 1166 A/C AT1R polymorphism.

There were no significant differences in the clinical parameters before the treatment with losartan among three genotype groups ($p > 0.05$) (Table 1).

Table 1
Baseline clinical characteristics of 35 type 1 diabetic patients with high values of daily urinary albumin excretion segregated by genotype

Patients' characteristics	AA (n = 15)	AC (n = 16)	CC (n = 4)
	$\bar{x}$ ± SD	$\bar{x}$ ± SD	$\bar{x}$ ± SD
Sex (men/women)	12/3	12/4	1/3
Age (years)	32 ± 11	34 ± 8	23 ± 3
DM duration (years)	18 ± 8	14 ± 7	13 ± 2
BMI (kg/m^2)	22.8 ± 11.28	22.8 ± 2.33	22.4 ± 1.95
HbA1c (%)	9.34 ± 1.82	8.83 ± 1.22	9.88 ± 1.62
Albuminuria (mg/24h)§	99 (43-5838)	87 (45-830)	190 (45-854)
GFR (mL/min/1.73m^2)	97 ± 19	96 ± 20	104 ± 20
FF	0.18 ± 0.04	0.17 ± 0.03	0.19 ± 0.05
Systolic BP (mmHg)	136 ± 24	131 ± 10	133 ± 19
Diastolic BP (mmHg)	86 ± 13	88 ± 5	95 ± 6

All data are expresed as means ± SD except albuminuria. DM – diabetes mellitus; BMI – body mass index; HbA1c – hemoglobin A1c; GFR – glomerular filtration rate; FF – filtration fraction; BP – blood pressure; § median (minimum – maximum)

After 12 weeks of the treatment with losartan, the mean values of daily urinary albumin excretion was significantly reduced in the AA genotype and in the AC genotype group, while the changes of albuminuria in the CC genotype group remained nonsignificant (Table 2). Albuminuria was reduced from the baseline by 9% [95% confidence interval (CI):1–17, $p = 0.039$] in the AA group, and by 11% (95%CI: 6–17, $p = 0.0001$) in the AC group. The losartan treatment reduced albuminuria in the CC group by 5% (95%CI: -13–22, $p = 0.47$). There were no significant differences between the

Table 2

Comparison of clinical findings among the three different genotypes after 12 weeks treatment with losartan

Clinical findings	AA	AC	CC
	$\bar{x} \pm SD$	$\bar{x} \pm SD$	$\bar{x} \pm SD$
Albuminuria (mg/24h) §	96 (18 – 7335) †	55 (16 – 783) ‡	154 (17 – 1130)
GFR(mL/min/1.73m^2)	93 ± 18	92 ± 23	99 ± 20
FF	0.16 ± 0.02	0.15 ± 0.03 †	0.18 ± 0.04
Systolic BP (mmHg)	121 ± 18‡	115 ± 7‡	120 ± 12
Diastolic BP (mmHg)	78 ± 8‡	75 ± 8 ‡	85 ± 11
Reduction rate			
albuminuria (%) (95% CI)	9 (1–17) †	11(6–17) ‡	4 (-13–22)
SGF (mL/min)	3.4 ± 10.8	4.0 ± 15.4	4.7 ± 5.7
FF	0.017 ± 0.03	0.018 ± 0.024†	0.01 ± 0.008
systolic BP (mmHg)	15.5 ± 9.4 ‡	10.3 ± 21.5 ‡	12.5 ± 13.2
diastolic BP (mmHg)	8.2 ± 9.2 ‡	11.7 ± 5.6 ‡	10.3 ± 6.2

All data are expresed as means ± SD except albuminuria. BMI – body mass index; HbA1c – hemoglobin A1c; GFR – glomerular filtration rate; FF – filtration fraction; BP – blood pressure; CI – confidence interval; § median (minimum-maximum); † $p < 0.05$ vs baseline; ‡ $p < 0.01$ *vs* baseline

albuminuria reduction among three different genotype groups during the study.

Glomerular filtration rate remained unchanged in all examined groups ($p > 0.05$).

After 12 weeks of the losartan treatment, FF was significantly reduced from the baseline by 0.018 ± 0.024 ($p = 0.012$) only in AC genotype. In the AA genotype, FF was reduced from baseline by 0.017 ± 0,03 ($p = 0.052$), and in the CC genotype by 0.01 ± 0.008 ($p = 0.092$) (Table 2). There were no significant differences between GFR anf FF reduction in the three examined groups during the study.

The mean values of systolic blood presssure was significantly lowered in the AA and in the AC genotype groups, while the CC genotype group achieved nonsignificant reduction. In the AA group, systolic blood pressure declined from 136 ± 24 mmHg (mean ± SD) at baseline to an average of 121 ± 18 mmHg at the end of the study ($p = 0.001$). The AC group achieved reduction from 131 ± 10 mmHg at baseline to 115 ± 7 mmHg ($p = 0.001$) during the investigation period. Similar results were obtained in the diastolic blood pressure reduction. In the AA genotype losartan reduced diastolic blood pressure from 86 ± 13mmHg at baseline to 78 ± 8 mmHg ($p = 0.004$) during the investigation period, and in the AC genotype from 88 ± 5mmHg at baseline to 11.7 ± 5.6 mmHg during the study ($p = 0.001$). In the CC genotype, diastolic blood pressure reduction remained nonsignificant ($p = 0.066$) (Table 2).

There were no significant differences between systolic or diastolic blood pressure reduction among three different genotype groups during the study.

Discussion

The intrarenal RAAS may be activated early in the course of diabetes mellitus, despite normal or suppressed levels in plasma [21]. Increased intraglomerular capillary hydraulic pressure, as a result of Ang II mediated efferent arteriolar vasoconstriction has been identified as a potential therapeutic target for the prevention of progressive diabetic renal damage. So, the beneficial effect of AT1R antagonism is a result of predominant efferent arteriolar vasodilatation, tending to lower filtration fraction and intraglomerular hypertension. The result of this change is the reduction of albumin urinary loss [22]. The reduction in arterial blood pressure is also important, because the transmission of blood pressure on glomerules becomes smaller. Losartan is an antihypertensive drug which acts by directly blocking AT1 receptors [23].

Genetic variations of AT1R genes can alter AT1R–mediated reactions by altering its expression or structure. To date, 1166 A/C SNP has been the best evaluated of all AT1R polymorphisms with an A to C transversion in the 3' untranslated region of the gene. Within this SNP, the C allele remains a candidate for genetic variations that leads to an enhanced activity of systemic and/or paracrine RAAS [7–9].

In patients with diabetes type 1, during hyperglycemic clamp conditions, Miller et al [12], demonstrated that only the C allele carriers exibited a significantly augmented systemic pressor response to high glucose. This observation may indicate that the C allele predicts enhanced Ang II responsiveness. In another study with healthy subjects, the same author demonstrated that the C allele is associated with enhanced intrarenal and peripheral Ang II activity, resulting in an augmented efferent arteriolar resistance [13]. The baseline values of vascular tone in AC/CC subjects were augmented with the associated higher values of FF and intrarenal vascular resistance compared to AA carriers.

Measurement of FF provides a good estimate of intraglomerular pressure; higher values of this parameter are associated with higher values of urinary albumin loss. Twelve weeks of the losartan therapy in our study group decreased FF in all participants, but the most pronaunced reduction was observed in AC carriers. In AA homozygous subjects, a change of FF reached bordered values of statistical significance, while CC homozygous subjects responded by modest dilatation of efferent arteriolas. Nevertheless, GFR remained unchanged in all participants. Stabilization of GFR despite the reduction of intraglomerular and systemic arterial pressure is another approval of beneficial renoprotective effect of chronic AT1R blockade.

Similar results have been demonstrated in the study with hypertensive patients, measuring the acute renovascular

response to on active metabolite of losartan - EXP3174 [24]. This study confirmed the association of the C allele with higher sensitivity to Ang II. When EXP3174 was infused, CC homozygous subjects revealed enhanced rigidity of efferent arteriolas, compared to AA carriers, expressed by smaller reduction in FF with unchanged SGF. It is therefore somewhat unexpected to find the strongest hemodynamic response in the AC group in our study population. Neverthless, Miller et al. [12] observed the AC group associated with CC carriers (as AC/CC group), while Spiering at al. [24] pointed their examination only on homozygous subjects (AA or CC). So, the AC genotype results in these studies remained unavailable.

In our study, losartan therapy significantly reduced daily albuminuria in the AA genotype and AC genotype groups. Reduction of albuminuria after a short-term treatment is a hemodynamic fenomenon reflecting the highest reduction in FF and intraglomerular pressure at the same genotype [25]. Redon et al. [26] did not reveal any association of 1166 A/C AT1R polymorphism with reduction of albuminuria in telmisartan treated hypertensive patients. Among patients with non-diabetic renal disease Coto et al. [6] also did not confirm any influence of 1166 A/C polymorphism on losartan-induced reduction of proteinuria. Considering previous results, a more pronounced difference in antiproteinuric response could be expected in AA and CC genotype. However, we found the best losartan-induced antiproteinuric response in AC group, by the mechanisms that still could not be easily undersood.

In our study, AA and AC carriers experienced the greater values of systolic and diastolic blood pressure reduction, while homozygous for the C allele, expressed weaker antihypertensive response during the study.

Good antihypertensive response in the AA carriers group is consistent with observations of Spiering et al. [24]. In that study of hypertensive patients it was demonstrated that homozygous for the C allele experienced modest decrease in blood pressure during intravenous administration of the active metabolite of losartan. In another study, de Nus et al. [27] also observed more pronounced mean arterial blood pressure reduction in AA carriers comparing to the AC group after a short-term treatment with telmisartan. In hypertensive patients with non-diabetic renal disease, treated with losartan, singificantly decreased diastolic blood pressure in AA carriers comparing to the AC group was observed [6].

Some other studies did not confirm any association of this gene polymorphism with antihypertensive effect of AT1R antagonists. Kurland et al. [17] and Redon et al. [26] did not find any connection between 1166 A/C AT1R polymorphism and individual response to irbesartan and telmisartan therapy. Unlike the previous studies, in Russian population of hypertensive patients, C allele carriers were more sensitive to candesartan antihypertensive effect [28]. Miller et al. [13] also found that healthy normotensive C allele carriers expressed a more pronounced reduction in blood pressure following the administration of single oral dose of losartan.

The reasons for these discrepancies are still not well understood, as well as the clinical meaning of A/C AT1R polymorphism. The 1166 AT1R allele is located in the 3' uncoding region, so the polymorphism of this gene does not affect the binding of Ang II to AT1R or signal transduction directly. So, the A/C1166 AT1R polymorphism may be linked to another coding region of AT1R by linkage disequilibrium, or the stability of DNA transcript of AT1R may be altered by this polymorphism [29]. Furthermore, diabetes mellitus is associated with local increase in the intrarenal Ang II formation, which appears to be more dependent on paracrine factors rather than on circulating concentrations of other RAAS components. Because of the compensatory suppression of systemic RAAS in diabetics, this could have completely different effects on blood pressure regulation, comparing to healthy or hypertensive individuals. On the other hand, it is not well defined if the increased sensitivity of vascular structures to Ang II stimulation in C allele carriers arises from differences in the number of AT1R binding sites, or from the functional activity of this receptor [30, 31].

Conclusion

We can conclude that examination of 1166 A/C polymorphism-dependent individual, systemic or paracrine responsiveness to losartan therapy must be considered as an interreaction between systemic and intrarenal RAAS activity. In addition, our small sample size of homozygous C allele carriers, limits the conclusions that could be drawn from the obtained issues of CC genotype. Neverthless, the results from CC genotype group are almost equalized in suggestion that these patients may be less sensitive to the AT1R antagonistic effects of losartan. Finally, our study provides the evidence that 116A/C AT1R polymorphism could influence the renoprotective response to treatment with losartan, making the rational basis for future longitudinal examination of individualized therapy with AT1R blockers.

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Određivanje efekata hiperbarične oksigenacije u terapiji hronične okluzivne bolesti arterija donjih ekstremiteta metodom perfuzione scintigrafije

Hyperbaric oxygenation effects determination in the therapy of chronic occlusive lower extremities arteries disease by the use of perfusion scintigraphy

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Apstrakt

Uvod/Cilj. Hiperbarična oksigenacija (HBO) je medicinski tretman tokom koga bolesnik udiše 100% kiseonik na pritisku višem od atmosferskog, a obavlja se u specijalno dizajniranim uređajima u kojima je celo telo bolesnika u komori. Cilj rada bio je da se kod bolesnika sa hroničnom, okluzivnom, neoperabilnom bolešću arterija donjih ekstremiteta utvrde efekti primene HBO merenjem parametara perfuzione scintigrafije (perfuziona rezerva, relativna perfuzija). **Metode.** Ispitivano je 22 bolesnika (19 muškaraca i 3 žene). Uz kliničku procenu stanja donjih ekstremiteta na osnovu izgleda kože i njenih adneksa vršeno je merenje klaudikacione distance. Kliničko stanje ocenjivano je petostepenom nominalnom skalom. Kod svih ispitanika perfuziona scintigrafija ^{99m}Tc-tetrafosminom izvršena je 10 dana pre početka i 10 dana nakon tretmana HBO. Snimane su potkolenice iz posteriorne projekcije. Pred snimanje, u mirovanju bolesnik je obavezno ležao oko pola sata. **Rezultati.** Kod 18 (86%) bolesnika došlo je do poboljšanja koje se manifestovalo boljim subjektivnim osećajem i popravkom izgleda kože i njenih adneksa. Posle tretmana HBO postojala je statistički značajna promena nakupljanja radiofarmaka u fazi mirovanja, posle davanja druge doze. Nalaz ukazuje na povećanje vijabilnosti mišića i povećanu perfuzionu rezervu. Srednje vrednosti perfuzione rezerve za desnu potkolenicu bile su povećane sa 39,99% na 50,86%, a za levu potkolenicu sa 38,46% na 49,33%. Ovaj parametar jasno ukazuje na pozitivne efekte HBO tretmana u vidu neoangiogeneze, a samim tim i povećanu vijabilnost mišića potkolenice, što je jasno uočljivo i u vizuelnoj analizi dobijenih slika. **Zaključak.** Dobijeni rezultati potvrđuju da je perfuzija tkiva, merena parametrima perfuzione scintigrafije ^{99m}Tc-tetrafosminom (perfuziona rezerva, relativna perfuzija) kod neoperabilne okluzivne bolesti donjih ekstremiteta znatno povećana nakon sprovedenog HBO tretmana.

Ključne reči:
hiperbarička oksigenacija; arterije, okluzione bolesti; perfuziono snimanje, donji ekstremiteti.

Abstract

Background/Aim. Hyperbaric oxygenation (HBO) is a medical treatment of a patient with 100% oxygen inspiration under the pressure higher than atmospheric in a special unit designed to let the whole patient′s body rest in a chamber. The aim of the study was to determine the effect of the application of HBO treatment on the patient′s lower extremities with chonic inoperabile occlusive disease by measning the parameters of perfusion scintigraphy (perfusion reserve, relative perfusion). **Methods.** This investigation included 22 patients (19 males and 3 famales). Following clinical assessment of lower extremities condition according to the skin appearance and its adnexa, claudication distance was performed. Clinical condition was graded by the use of 5-point nominal scale. In all of the patients ^{99m}Tc-tetraphosmine lower extremities scintigraphy was done ten days prior to the treatment start and ten days after the treatment with HBO. Lower legs were imaged from the posterior view. Prior to imaging the patients were obligatory lying approximately half an hour. **Results.** In 18 (86%) of the patients there was an improvement manifested as better subjective condition and better skin and its adnexa appearance. Following HBO treatment there was a statistically significant change in collecting the radiopharmac at rest. This finding indicates an increased viability of muscles as well as an increased perfusion reserve. Perfusion reserve mean values increased from 39.99 to 50.86%, and from 38.46 to 49.33% for the right and the left lower leg, respectively. This parameter clearly indicates favorable effects of HBO treatment pertaining neoangiogenesis and, consequently, increased viability of the lower leg muscles. It was also obvious in visual analysis of the obtained images. **Conclusion.** The obtained results confirm that muscle perfusion measured by the parameters of perfusion scintigraphy using ^{99m}Tc-tetrophosmine (perfusion reserve, relative perfusion) in patients with inoperabile occlusive disease of the lower leg arteries significantly increases after the application of HBO treatment.

Key words:
hyperbaric oxygenation; arterial occlusive diseases; perfusion imiging, lower ekstremity.

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Uvod

Hronična okluzivna bolest arterija donjih ekstremiteta (HOBADE) glavni je uzrok ishemijske bolesti donjih ekstremiteta. Ona u svojoj osnovi ima proces arterioskleroze koji dominira nad ostalim etiološkim faktorima. Terapija podrazumeva primenu konzervativnih i hirurških mera. Hiperbarična oksigenacija (HBO) je medicinski tretman kada bolesnik udiše 100% kiseonik na pritisku višem od atmosferskog, a obavlja se u specijalno dizajniranim uređajima pri čemu je celo telo bolesnika u komori [1]. Ovako primenjena terapija dovodi do poboljšanja perfuzije ishemičnog tkiva, a samim tim i do adekvatnog snabdevanja tkiva energetskim i gradivnim materijama, kao i kiseonikom [2, 3].

Hiperbarična oksigenacija generalno poboljšava cirkulaciju krvi (snižava viskoznost plazme i agregaciju trombocita, ubrzava neokapilarizaciju i povećava elastičnost opne eritrocita). Minimum od 20 mmHg pO_2 neophodan je za proliferaciju fibroblasta i produkciju kolagena. Pritisak od 20 mmHg pO_2 prisutan je u normalnom tkivu na daljini od 30 mikrona od kapilarnog zida. Primenom HBO, adekvatan pO_2 može se održavati do 280 mikrona od kapilarnog zida. Sa razvojem bogate kolagene mreže, kapilarni pupoljci brzo napreduju, prorastaju tkivo i formiraju nove kapilarne lukove. Ova proliferacija tkiva ispunjava prazan prostor pa zarastanje rane napreduje [4]. Hronična okluzivna bolest arterija donjih ekstremiteta u toku svoje evolucije neminovno dovodi do ishemijske bolesti donjih ekstremiteta čiji je najvažniji simptom intermitentna klaudikacija koja se razvija kada protok krvi pri naporu nije dovoljan da zadovolji povećane zahteve mišića i njihovu povećanu metaboličku aktivnost, te tkivo lišeno kiseonika trpi posledice neodgovarajućeg metabolizma.

Cilj rada bio je da se na našem uzorku bolesnika sa hroničnom neoperabilnom okluzivnom bolešću donjih ekstremiteta utvrde efekti primene HBO merenjem parametara perfuzione scintigrafije (perfuziona rezerva, relativna perfuzija).

Metode

Ispitivano je 22 bolesnika, pretežno muškaraca (19) i samo tri žene, što je delom uslovljeno profilom ustanove u kojoj je ispitivanje vršeno, a delom procene procentualno manje zastupljenosti žena kod ovog oboljenja. Prosečna starost ispitanika bila je $70,8 \pm 8,6$ godina. Ispitanici su imali pretežno normalnu telesnu masu. Indeks telesne mase za celu grupu bio je 25,5 kg/m^2, dok je opseg telesne mase bio u rasponu 62–105 kg. Od ukupnog broja bolesnika najviše su bili zastupljeni pušači (60%). Uz kliničku procenu stanja donjih ekstremiteta na osnovu izgleda kože i njenih adneksa vršeno je merenje klaudikacione distance (razdaljina koju bolesnik može da prepešači pre nego što se javi bol u potkolenici). Kliničko stanje ocenjivano je petostepenom nominalnom skalom (0-loše, 1-malo bolje, 2-bolje, 3-dobro, 4-veoma dobro). Svi bolesnici lečeni su zbog generalizovane ateroskleroze, a u ispitivanoj grupi nije bilo bolesnika koji se leče od šećerne bolesti. Prema klasifikaciji Lariche-Fontaine pripadali su II i III stadijumu bolesti. Bolesnici su kompletno dijagnostički obrađeni (dopler, angiografija, laboratorijska obrada) i na osnovu kliničke slike i dijagnostičke obrade svrstani u kategoriju neoperabilnih, te je postavljena indikacija za primenu hiperbarične oksigenoterapije. Bolesnici su svrstani u neoperabilne zbog stanja na magistralnim krvnim sudovima nogu koji su poprimili formu oskudnog kolateralnog krvotoka, a on ne obezbeđuje ni minimum mogućnosti za izvođenje bilo koje operativne revaskularizacione metode.

Kod svih bolesnika perfuziona scintigrafija donjih ekstremiteta sa ^{99m}Tc-tetrofosminom izvršena je do 10 dana pre početka primene HBO, kao i 10 dana posle ovog tretmana. Pre započinjanja procedure bolesnik se odmarao 15 min, a potom je u toku 3 min vršio ritmične pokrete plantarne i dorzalne fleksije, zatim je *iv* dat ^{99m}Tc-tetrofosmin i posle 15 min vršeno je snimanje nakupljenog radiofarmaka u potkolenicama. Ovo registrovanje označeno je kao kontrolna dinamika (dinamika I K), a doza korišćenog radiofarmaka kretala se u rasponu 5–10 mCi (185–370 MBq).

Posle 180 min odmora, kod bolesnika ponovo je registrovano stanje nakupljenog radiofarmaka. Ova faza označena je kao stacionarna (statika K). Iza registrovanja stacionarnog nivoa dodata je nova doza ^{99m}Tc-tetrofosmina i posle 15 min registrovana je količina nakupljenog radiofarmaka. To merenje označeno je kao kontrolna dinamika 2 (dinamika II K) sa dozom korišćenog radiofarmaka u rasponu 10–15 mCi (370–555 Mbq). Identična procedura ponovljena je kod svakog bolesnika posle tretmana sa HBO. Snimanje nakupljanja ^{99m}Tc-tetrofosmina u potkolenicama vršeno je kamerom Gamma Orbiter – Simens sa paralelnim kolimatorom opšte upotrebe za srednje energije uz podršku računara MikroDelta. Dinamski deo studije rađen je 15 min sa po jednom slikom u svakom minutu, a statička studija pre druge dinamike u mirovanju trajala je jedan minut. Prva doza radiofarmaka aplikovana je nakon opterećenja, a druga doza nakon urađene statike u miru, takođe u trajanju od 15 min, sa po jednom slikom u svakom minutu.

Snimane su potkolenice iz posteriorne projekcije. Pred snimanje u mirovanju bolesnik je obavezno ležao oko pola sata.

Kvantifikacija scintigrafskih podataka vršena je iz regiona od interesa (ROI) na osnovu prosečnog broja impulsa po pikselu. Na taj način dobijeni su parametri koji daju informaciju o perfuziji donjih ekstremiteta datog ispitanika – perfuziona rezerva i relativna perfuzija donjih ekstremiteta. Perfuzionu rezervu izračunavali smo kao odnos perfuzije pre i nakon HBO u sve tri faze dinamske studije, a relativnu perfuziju kao odnos perfuzije leve i desne noge u istom stanju: npr. (perf. leve noge) / [(perf. leve noge) + (perf. desne noge)] = rel. perf. leve noge.

Ovi parametri računati su pre i nakon tretmana HBO. Statistička analiza primenjena na parametre za datu grupu ispitanika dala je vrednosti na osnovu čijih su se promena razmatrali efekti HBO.

Rezultati su tumačeni vizuelno i uz pomoć kvantitativne metode za koju je korišćen program u kome se u regiji od interesa (mišići obe potkolenice iz posteriorne projekcije) izračunava broj impulsa po pikselu u 15. min. dinamske studije, a čime su dobijeni numerički podaci za procenu perfuzije. Vizuelno je procenjen odnos vezivanja između obe noge pre

i nakon HBO i ocenjen kao: 1) mala razlika u vezivanju nad obe noge pre i nakon HBO; 2) srednja razlika i 3) značajna razlika.

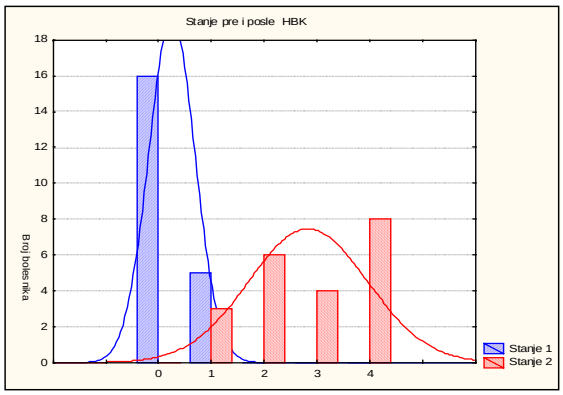
Terapija se odvijala u hiperbaričnoj komori za jednu osobu tipa BLK 301 ruske proizvodnje. Predviđeni tretman sproveden je u dvadeset seansi u trajanju od 60 min na pritisku od 2,2 ATA, radnim danima. Terapija je ukupno trajala četiri nedelje.

Statistička obrada rezultata vršena je pomoću programa Statistica 7.0 na PC računaru. Rezultati su prikazivani pomoću parametara deskriptivnog statističkog metoda ($\bar{x}$, SD, SE mod). Poređenja su vršena pomoću *t*-testa za mali zavisni uzorak. Korelaciona analiza vršena je upotrebom regresione linearne analize. Statistički značajna razlika je prihvaćena za $p < 0,05$.

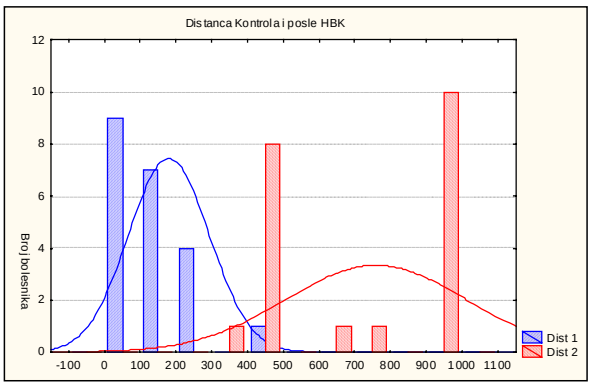
Rezultati

Klinička procena stanja efekata HBO

Pre i posle tretmana HBO izvršena je klinička procena stanja u odnosu na izgled nogu i merenja rastojanja koje su ispitanici mogli da pređu pre pojave bolova (slike 1 i 2).



Sl. 1 – Procena kliničkog stanja na osnovu subjektivne procene ispitanika i izgleda kože nogu pre (stanje 1) i posle (stanje 2) tretamana u hiperbaričnoj komori – HBK (0-loše, 1-malo bolje, 2-bolje, 3-dobro, 4-veoma dobro)



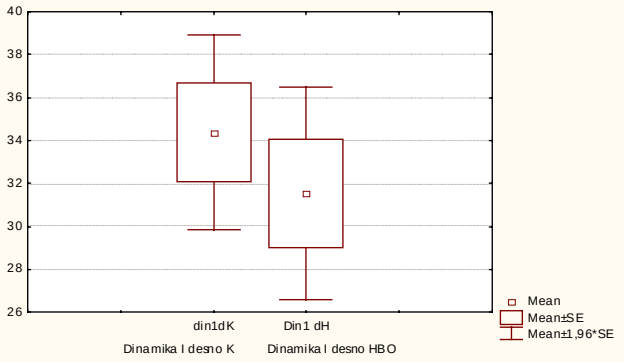
Sl. 2 – Veličina klaudikacione distance pre (plavo) i posle tretmana u hiperbaričnoj komori – HBK (crveno)

Podaci pokazuju da je pre primene HBO stanje ispitanika ocenjeno kao loše kod 16 (76%) bolesnika. Posle tretmana histogram frekvencije ocene stanja pokazuje veoma uočljivo pomeranje u desnu stranu (slika 1). Kod 18 (86%) bolesnika došlo je do poboljšanja koje se manifestovalo boljim subjektivnim osećajem i popravkom izgleda kože i njenih adneksa. Uticaj tretmana u hiperbaričnoj komori (HBK) procenjivan je u odnosu na klaudikacionu distancu tj. rastojanje koje je bolesnik mogao prepešačiti pre pojave bola. Očigledno poboljšanje dužine klaudikacione distance posle tretmana u HBK prikazano je na slici 2.

Dužina klaudikacione distance pre tretmana u HBK bila je prosečno 179,6 ± 109,8 m, a posle tretmana 765,9 ± 250,4 m.

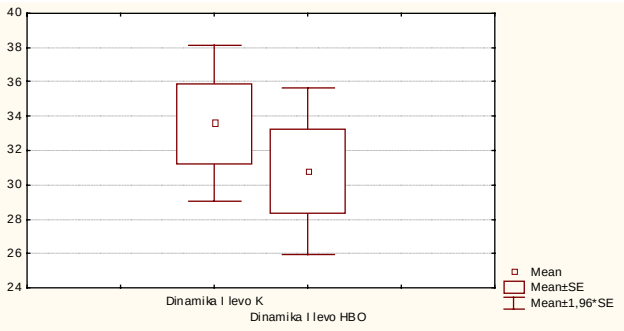
Dinamika nakupljanja radiofarmaka nakon testa opterećenja

Pad vrednosti perfuzije koji se registruje posle tretmana u HBK nije značajan, ali je obostran (slike 3 i 4). Ovaj nalaz ukazuje na slabije nakupljanje radiofarmaka posle testa opterećenja.



	$\bar{x}$	Std. Dev.
K	34,4	10,9
HBO	31,5	11,8

Sl. 3 – Promene vrednosti perfuzije na osnovu promene intenziteta nakupljanja radiofarmaka posle testa opterećenja (dinamika I na desnoj potkolenici); uočava se pad vrednosti nakon tretmana hiperbaričnom oksigenacijom – HBO (razlika nije statistički značajna)
K – pre HBO; HBO – posle HBO

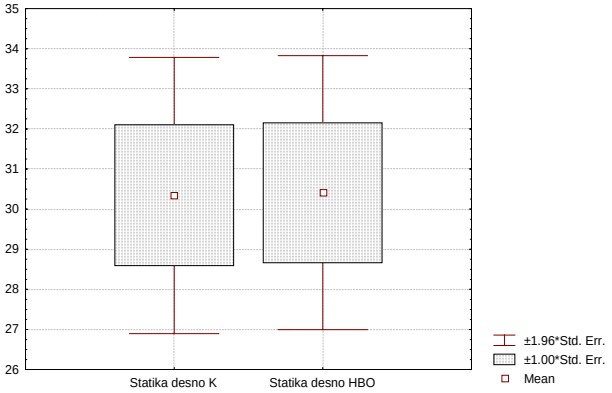


	$\bar{x}$	Std. Dev.
K	33,6	10,9
HBO	30,8	11,6

Sl. 4 – Promene vrednosti perfuzije na osnovu promene intenziteta nakupljanja radiofarmaka posle testa opterećenja (dinamika I na levoj potkolenici); uočava se pad vrednosti nakon tretmana hiperbaričnom oksigenacijom – HBO (razlika nije statistički značajna)
K – pre HBO
HBO – posle HBO

Dinamika nakupljanja radiofarmaka posle mirovanja

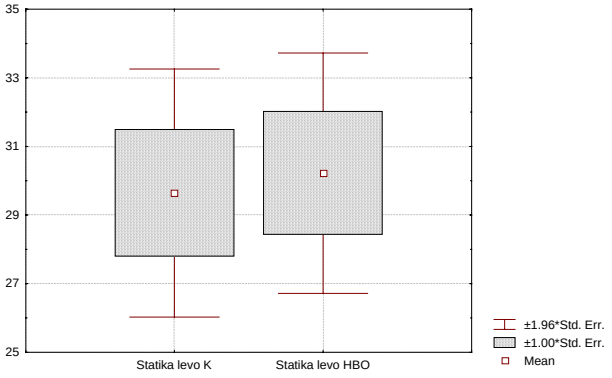
Na slici 5 predstavljena je statička studija (scintigrafija) desne potkolenice pre i posle HBO koja je izvođena posle tri sata odmaranja od testa opterećenja, a trajala je 1 minut. Uočava se neznatna promena prosečnog broja impulsa po pikselu.



	x̄	Std. Dev.
K	30,3	8,2
HBO	30,4	8,2

Sl. 5 – Intenzitet nakupljanja radiofarmaka 180 min posle testa opterećenja u desnoj potkolenici (K – pre hiperbarične oksigenacije; HBO – posle hiperbarične oksigenacije)

Na slici 6 uočavaju se iste promene perfuzije kao na slici 5 koja predstavlja studiju urađenu za desnu potkolenicu. Neznatno variranje vrednosti perfuzije u miru ukazuje da bolest i dalje postoji, a da se prisutne promene nalaze u domenu dinamske sfere.



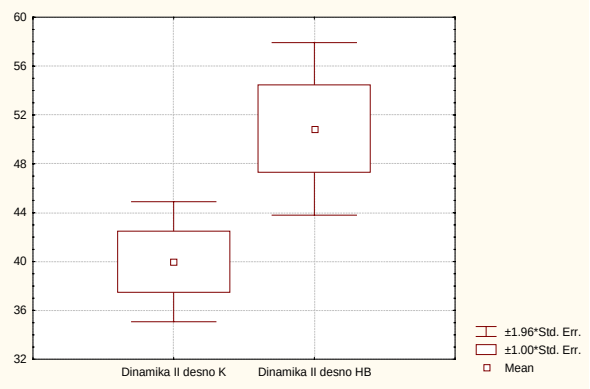
	x̄	Std. Dev.
K	29,6	8,6
HBO	30,2	8,3

Sl. 6 – Statička studija (scintigrafija) leve potkolenice urađena pre (K) i nakon hiperbarične oksigenacije (HBO)

Dinamika nakupljanja radiofarmaka nakon mirovanje i date druge doze

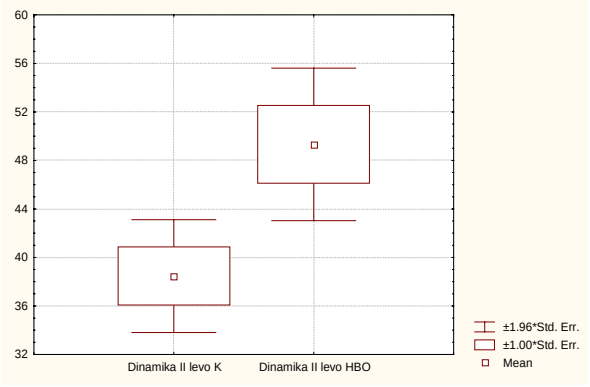
Posle tretmana HBO postoji statistički značajna promena nakupljanja radiofarmaka u fazi mirovanja, posle davanja druge doze. Nalaz ukazuje na povećanu vijabilnost mišića i povećanu perfuzionu rezervu.

Na slikama 7 i 8 prikazana je dinamska studija urađena nakon tri sata mirovanja, kada se prvo uradi statička scintigrafija potkolenica i odmah zatim, u toku 15 min, još jedna dinamska scintigrafija potkolenica sa dodatnom dozom Tc-tetrofosmina koja predstavlja vrednosti druge dinamike. Dinamski deo studije rađen je 15 min sa po jednom slikom u svakom minutu (15 slika), a uočava se znatan porast vrednosti perfuzije u potkolenicama nakon provedene HBO. Srednje vrednosti perfuzione rezerve za desnu potkolenicu su povećane sa 39,99% na 50,86%, a za levu potkolenicu sa 38,46% na 49,33%. Ovaj parametar jasno ukazuje na pozitivne efekte HBO u vidu neoangiogeneze a, samim tim, i povećanu vijabilnost mišića potkolenica, što je jasno uočljivo i u vizuelnoj analizi dobijenih slika.



	x̄	Std. Dev.	
K	40,0	11,8	
HBO	50,9	16,9	$p < 0,02$

Sl. 7 – Vrednosti perfuzije u drugoj dinamici dobijene pre (K) i nakon hiperbarične oksigenacije (HBO) za desnu potkolenicu (postoji statistički značajna razlika pre i posle tretmana u hiperbaričnoj komori)



	x̄	Std. Dev.	
K	38,5	11,0	
HBO	49,3	15,1	$p < 0,01$

Sl. 8 – Vrednosti perfuzije u drugoj dinamici pre (K) i nakon hiperbarične oksigenacije (HBO) za levu potkolenicu (postoji statistički značajna razlika u odnosu na stanje pre primene HBO)

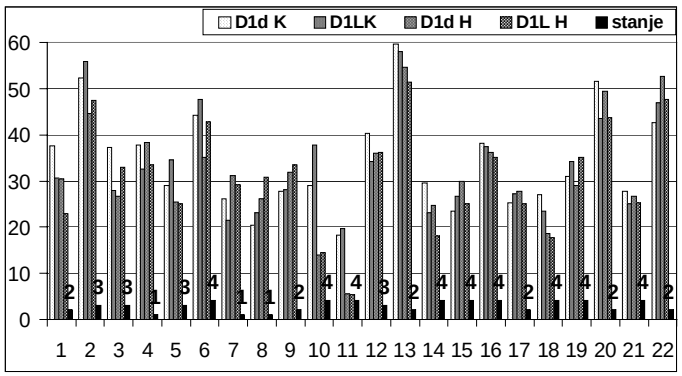
Dinamika nakupljanja radiofarmaka i procena kliničkog stanja

Uz razmatranje srednjih vrednosti parametara dinamske scintigrafije vršili smo i procenu stanja za svaki slučaj posebno. Rezultati su nam ukazali na prilično veliku varijabilnost

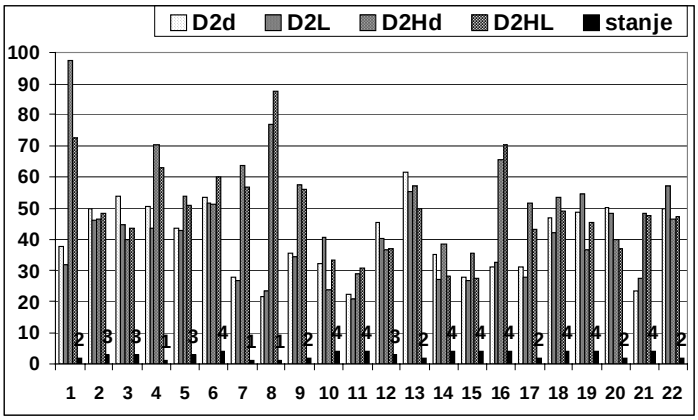
posmatranih parametara dinamske scintigrafije (slike 9–11), uz negativnu korelaciju između dinamike I i dinamike II. Poređenje dinamike I, II i statike sa ocenom kliničkog stanja pokazuje da su najbolji rezultati tretmana HBO postignuti kod onih bolesnika kod kojih dolazi do pada vrednosti dinamike I, a porasta dinamike II.

U delu studije koji je nazvan statika, a koja je rađena nakon tri sata mirovanja bolesnika i neposredno pred drugu dozu radiofarmaka, nije došlo do bitnijeg pomaka vrednosti perfuzije.

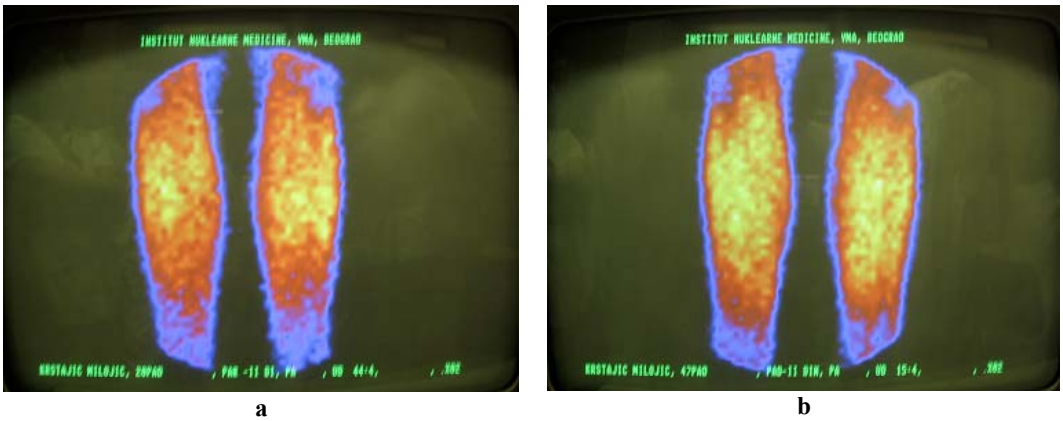
Za svakog ispitanika uz procenu kliničkog stanja vršena je kvalitativna vizuelna analiza vezivanja radiofarmaka. Analizirajući razliku u intenzitetu vezivanja tetrofosmina jasno je uočljivo da postoji značajna razlika u intenzitetu nakupljanja pre i posle HBO (slika 11).



Sl. 9 – Grafički prikaz dinamike I (D1) za obe potkolenice pre (K) i nakon hiperbarične oksigenacije (H) kod svih ispitanika sa ocenjenim stanjem ispitanika d – desna potkolenica; L – leva potkolenica; stanje: 0-loše; 1-malo bolje; 2-bolje; 3-dobro i 4-veoma dobro



Sl. 10 –Grafički prikaz dinamike II (D2) za obe potkolenice pre i nakon hiperbarične oksigenacije (H) kod svih ispitanika sa ocenjenim stanjem ispitanika d – desna potkolenica; L – leva potkolenica; stanje: 0-loše; 1-malo bolje; 2-bolje; 3-dobro i 4-veoma dobro



a **b**

Sl. 11 – Intenzitet vezivanja radiofarmaka u toku druge dinamike (a) i posle hiperbarične oksigenacija (b)

Diskusija

Životni vek osoba sa HOBADE kraći je za približno deset godina u poređenju sa zdravim osobama. Rezultati bazelske studije i skorašnjih istraživanja ukazuju na to da su ove promene u značajnom porastu i u vezi su sa prisustvom okluzivnih promena na drugim arterijama, arterijama srca i karotidnim arterijama. Približno 50% osoba sa HOBADE imaju značajnu stenozu karotidnih arterija [5]. Petogodišnja incidencija novih bolesnika sa HOBADE je 3,2–13,9% u asimptomatskom stadijumu i 1–4,6% u simptomatskom stadijumu, zavisno od životnog doba [5]. Faktori rizika od razvoja HOBADE su pušenje, gojaznost, insulin-nezavisni dijabetes, arterijska hipertenzija, hiperlipoproteinemija. Pošto s godinama života broj faktora rizika raste, raste i incidencija HOBADE. Perfuzija tkiva, posebno mišića donjih ekstremiteta, podrazumeva onaj protok krvi koji obezbeđuje adekvatnu količinu kiseonika, energije i gradivnih materija [6].

U oboljenjima venskog sistema posebno „dubinskih" vena donjih ekstremiteta i karlice poseban klinički značaj ima radionuklidna flebografija kao „dinamska" metoda procene protoka putem dubinskih vena i specifična detekcija tromboza vena karlice i donjih ekstremiteta kao potencijalnih fokusa plućne tromboembolije [7, 8].

Poslednjih godina koriste se izonitrili obeleženi tehnecijumom (^{99m}Tc-MIBI) za ispitivanje periferne perfuzije, kao i najnoviji radiofarmaceutik ^{99m}Tc-tetrofosmin.

Tetrofosmin je katjonski kompleks koji se po davanju vrlo brzo preuzima iz krvi, pa nakon 10 min samo 5% date doze zaostaje u krvnom, odnosno 3,5% u plazmatskom delu cirkulacije[9]. Brzi klirens iz krvi, jetre (vezivanje u jetri do 10% date doze od koje nakon 2 sata zaostaje samo 2%) i pluća (nakon 4 sata praktično nema detekcije aktivnosti) [10–12] čine da se akvizicija sa ^{99m}Tc-tetrofosminom može početi već nakon 15 min od *iv* davanja [13, 14]. Radiofarmak se izlučuje iz organizma putem urinarnog i gastrointestinalnog trakta u približno istom procentu. Potencijal mitohondrijske membrane ima značajnu ulogu u vezivanju i/ili retenciji ^{99m}Tc-tetrofosmina, naročito u skeletnoj muskulaturi.

Kod zdravih osoba prikazuje se arterijsko stablo do nivoa poplitealne arterije u nogama, kao i do nivoa radijalne i ulnarne arterije na ruci. Protok radioobeleživa̧ča sledi krvotok i brz je, bez zastoja [15].

Kod bolesnika sa mnogobrojnim suženjima velikih aretrija u nozi zapaža se pojačano vezivanje radioobeleživa̧ča u projekciji kolenog i skočnog zgloba, dok se kod suženja jedne arterije scintigrafski vidi jasna hipoperfuzija (ishemija) mišićne mase područja irigacije bolesne arterije.

Georg i sar. [16] ispitivali su ukupno 53 ispitanika sa scintigrafijom „celog tela" ^{201}Tl u evaluaciji okluzivne arterijske bolesti kod bolesnika sa klaudikacijama. Na osnovu rezultata zaključili su da je ^{201}Tl slikanje celog tela u uslovima testa opterećenja i redistribucije jednostavna i tačna dijagnostika u evaluaciji sumnje na okluzivnu bolest arterija nogu. Farmaci obeleženi ^{99m}Tc kao što su MIBI i tetrofosmin prestavljaju indikatore periferne vaskularne perfuzije. Christian i sar. [16], te Dhenke i sar. [17] 1988. godine prvi su opisali primenu ^{99m}Tc-MIBI u dijagnostici stanja periferne cirkulacije.

Noviji radiofarmak ^{99m}Tc-tetrofosmin počeo se upotrebljavati od 1992. godine u Evropi i Japanu. Kratak poluživot ^{99m}Tc (6 sati) omogućava izvođenje dijagnostičke procedure opterećenja i mirovanja u istom danu, što ovakvu dijagnostičku metodu čini pogodnom za kliničku upotrebu [18]. Isto tako omogućava davanje *iv* većih doza, a samim tim kraće vreme akvizicije i bolju statistiku brojanja impulsa sa sledstveno boljim uočavanjem minimalnih promena na mikrovaskularnom nivou.

Talijum 201 se znatno češće upotrebljava u dijagnostici bolesti perifernih arterija, dok sadašnji ^{99m}Tc-obeleženi farmaci imju nekoliko prednosti u odnosu na talijum, te mnogi istraživači daju prednost tehnecijumom obeleženim radiofarmacima za ovu svrhu. Radiofarmaci obeleženi ^{99m}Tc daju visoko kvalitetne slike, kao i izvanredne mogućnosti kvantifikcacije nakupljanja aktivnosti u uslovima mirovanja i opterećenja. Sayman i Urgancioglu [19] dobili su slike donjih ekstremiteta u uslovima mirovanja i opterećenja i pokazali su poremećaj perfuzije u isemičnim područjima donjih ekstremiteta.

Rezultati naše studije pokazali su da je tretman HBO doveo do kliničkog poboljšanja kod 86% bolesnika, što je bilo u saglasju sa nalazima perfuzione scintigrafije. Tretman HBO doveo je do poboljšanja perfuzione rezerve za oko 10% kod obe podkolenice i do značajnog produženja klaudikacione distance (sa 179,6 ± 10,8 m na 765,9 ± 250,4 m).

S obzirom da mitohondrije troše oko 80% ćelijskog kiseonika, a da je ćelijsko vezivanje tetrafosmina proporcionalno regionalnom krvnom pritisku, možemo zaključiti da je povećao vijabilnost mišićnih ćelija proporcionalno povećanim vrednostima perfuzione rezerve, odnosno inteziteta aktivnosti nakupljenog radiofarmaka. Stoga, perfuziona scintigarfija donjih ekstremiteta pomoću ^{99m}Tc-tetrofosmina predstavlja pouzdanu i jednostavnu metodu za procenu terapijskih efekata HBO kod hronične okluzivne bolesti arterija donjih ekstremiteta.

Zaključak

Metode perfuzione scintigrafije donjih ekstremiteta ^{99m}Tc-tetrofosminom nakon testa opterećenja i mirovanja pre i nakon HBO predstavlja pouzdanu, neriziču i relativno jednostavnu metodu za određivanje efekata HBO. Kvantifikacija stepena nakupljanja radiofarmaka u regiji od interesa vrlo je korisna i reproducibilna tehnika, jer dopunjava vizuelnu analizu, uz odličnu osetljivost, specifičnosti i tačnosti u određivanju efekata HBO.

Dobijeni rezultati potvrđuju da je perfuzija tkiva, merena parametrima perfuzione scintigrafije (perfuziona rezerva, relativna perfuzija) u neoperabilnoj okluzivnojh bolesti arterija donjih ekstremiteta znatno povećana nakon sprovedene HBO.

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Histamine index and clinical expression of rheumatoid arthritis activity

Histaminski indeks i stepen aktivnosti reumatoidnog artritisa

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Abstract

Background/Aim. Many arguments prove the pathophysiologic role of histamine in the process of remodeling and joint destruction in rheumatoid arthritis. The aim of our study was to find out if there was a relation between histamine concentration in synovial fluid and blood with clinical expression of disease activity. **Methods.** Histamine concentration in synovial fluid and blood was determinated in 19 patients with rheumatoid arthritis. Histamine concentration measurement was based on the Shore's fluorometric method. Histamine index (HI) was evaluated as a ratio between histamine concentration in synovial fluid and blood. Disease activity score, DAS 28 (3), with three variables (erythrocyte sedimentation rate, the number of swelled joints and the number of tender joints) was also evaluated. **Results.** Our results showed that there was no significant difference in concentration of histamine in synovial fluid and blood related to disease activity. However, there was a significiant difference in the histamine index which was increased proportionally with disease activity. **Conclusion.** Our study indicates that histamine index could be useful in estimation of rheumatoid arthritis activity.

Key words:
arthritis, rheumatoid; histamine; blood; synovial fluid; disease progression.

Apstrakt

Uvod/Cilj. Mnogobrojni dokazi idu u prilog patofiziološkoj ulozi histamina u procesu remodelovanja i oštećenja zgloba kod reumatoidnog artritisa. Cilj načeg istraživanja bio je da utvrdimo da li postoji uzajamna povezanost nivoa koncentracije histamina u sinovijalnoj tečnosti i krvi sa klinički ispoljenom aktivnošću reumatoidnog artritisa. **Metode.** Praćena je koncentracija histamina u sinovijalnoj tečnosti i krvi 19 bolesnika koji boluju od reumatoidnog artritisa. Određivanje koncentracije histamina bilo je bazirano na Shoreovoj fluorimetrijskoj metodi. Histaminski indeks određen je kao odnos koncentracije histamina u sinovijalnoj tečnosti i krvi bolesnika. Određena je aktivnost bolesti prema skoru DAS-28 (3) sa tri varijable (sedimentaija eritrocita, broj bolno osetljivih zglobova, broj otečenih zglobova). **Rezultati.** Nije nađena statistički značajna razlika u koncentraciji histamina u krvi i sinovijalnoj tečnosti u zavisnosti od aktivnosti bolesti. Međutim, postojala je značajna razlika u histaminskom indeksu koji se povećavao proporcionalno sa povećavanjem aktivnosti reumatoidnog artritisa. **Zaključak.** Naša studija pokazuje da bi histaminski indeks mogao biti koristan parametar u proceni aktivnosti reumatoidnog artritisa.

Ključne reči:
artritis, reumatoidni; histamin; krv; sinovijalna tečnost; bolest, progresija.

Introduction

Many arguments prove the pathophysiologic role of histamine in the process of remodeling and joint destruction in rheumathoid arthritis (RA). Histamine modifies behaviour of many cells *in vitro* including chondrocytes, fibroblasts, osteoclasts, macrophages, T lymphocytes, endothelial cells. Histamine also modifies cytokine production and receptor expression [1, 2]. There are evidences of an increased production of chondrocytes matrix metalloproteinases (MMP3, MMP 13) induced by histamine, as well as chondrocytes stimulation and proliferation *via* H1 receptors [3, 4]. Histamine stimulates synovial fibroblast proliferation and that effect is mediated by H1 receptors [5]. Interaction between histamine from mast cells and macrophages and synovial fibroblasts H1 receptors has important role in the process of remodeling and joint destruction in RA [5]. Osteoclasts differentiation is induced by histamine and mediated by H2 receptors [1].

Mast cells express histidine decarboxilase, an enzyme that is essential for histamine production. Human chondrocytes also produces histidine decarboxilase. It indicates that histamine originates from chondrocytes, as well as from mast

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cells and takes place in inflammatory events in RA [6–8]. There was an evidence of decreased expression of H2 receptors on lymphocytes, bone marrow mononuclear cells and synovial fibroblasts, as well as decreased expression of H1 receptors on RA chondrocytes [9, 10]. It means that beneficial effects of histamine could be decreased due to H2 receptors hypofunction. Abnormality in the function of histamine receptors could play a significant role in maintaining the inflammation process in RA [10]. It has been suggested that histamine supress TNFα gene expression, as well as its secretion from peripheral blood mononuclear cells. This effect was mediated by H2 receptors [11]. As far as it is concerned, it could indicate that histamine released from mast cells could paradoxically limit the stage of inflammation and immune reaction by supressing cytokine secretion in the H2 bearing cells [11]. However, this effect is suppressed because of a decreased function of H2 receptors in RA patients [9, 10].

There is an increased number of mast cells in synovial tissue of RA patients, predominantly on the places with cartilage erosion. Mast cells contain potent mediators such as histamine, leukotrienes, proteinases, heparin and many cytokines. Therefore, their role in inflammation process and destruction of matrix in RA becomes evident [12]. Le et al. [13] reported that mice that lack mast cells are resistant to inflammatory and erosive arthritis induced by arthritogenic serum. It was proposed that mast cells play an important role as the cellular link among autoantibodies, the complement network, and inflammatory mediators. Therefore, the activation of mast cells makes a pivotal contribution to inflammatory arthritis [13].

It is likely that direct migration of mast cells within tissues is a very important mechanism of increasing the number of mast cells in synovial tissue in RA. There was an evidence that several factors in the synovial fluid can act as mast cell chemoattractants, such as the stem cell factor (SCF), transforming growth factor (TGF β), C5a, and platelet activation factor (PAF) [14–16]. Stem cell factor regulates growth, differentiation, adhesion and activation of the mast cells [17]. Besides that, histamine influences chemotaxis of mast cells by the H4 receptors, their activation leads to mobilisation of intracellular Ca^{++}, and includes Gαi/o protein mechanism and phospholipase C [18]. The expression of H4 receptors was reported on the two populations of cells from synovial tissue (fibroblast-like cells and macrophage-like cells) in RA patients [19–21]. It is lickely that there is a difference in H4 receptors expression in the different stages of RA activity [21].

Recent investigations indicate that the histamine releasing factor (HRF) signifficantly influences the releasing of histamine. Histamine relasing factor is an intracellular protein (as cytokine) that modulates the secretion of cytokines from human basophills, eosinophills, T and B lymphocytes [22]. The expression of HRF and its mRNA is evidented on the pannus (fibroblasts, macrophages) which destroyed cartilage in RA patients, but not in the healthy population. That confirms the role of histamine in pathogenesis of RA and other autoimmune diseases [22].

As far as histamine concentration in synovial fluid of RA patients is concerned there are many contradictory results [23–28].

The aim of our investigation was to detect histamine concentration in synovial fluid and blood in RA patients and to explore its relation with clinical expression of disease activity.

Methods

The investigated patients suffered from RA that was diagnosed in accordance with American College of Rhemumathology (ACR) criteria [29, 30]. The mean age of patients was 57.45 ± 3.56 years, (min 30 max 79, years). There were 15 female patients, and 4 male patients. All patients underwent routine clinical and laboratory investigations. Laboratory data including erythrocyte sedimentation rate, C-reactive protein, rheumatoid factors (latex test and hemaglutination test), blood count, blood urea, blood creatinine, aspartat aminotransferasis, alanin aminotransferasis, were obtained. In clinical assessment radiography of hands and clinical activity of the disease were registred. Clinical activity was determined according to the Disease Activity Score – DAS-28 (3) with three variables (erythrocyte sedimentation rate, the number of swelled joints and number of tender joins) [31, 32]. All patients were classified in three groups according to the disease activity: very active (VA) with DAS-28 (3) score more than 5.1, moderate activity (MA) with DAS-28 (3) score between 3.2 and 5.1, and inactive with DAS-28 (3) score below 3.2. The control group comprised age- and sex-matched healthy persons.

Synovial fluid was obtained from the knee under sterile procedure during therapeutic arthrocentesis, collected in heparinized tubes and centrifuged. Histamine concentration in the synovial fluid and blood of the RA patients was detected. Concentration of histamine in the blood of the 19 healthy individuals were taken as control, too. Histamine index was evaluated as a relation between synovial fluid histamine concentration and blood histamine concentration multiplied by 100.

$$\text{Histamin index} = \frac{\text{Synovial fluid histamine conc. (ng/mL)}}{\text{Blood histamine conc. (ng/mL)}} \times 100$$

Detection of histamine was based on the Shore′s fluorometric method [33].

The mean values of biological parameters were compared using the Student′s *t*-test, where p value of < 0.05 was considered as a statistically significant difference. The data in tables are presented as mean ± standard error of the mean.

Results

Our results showed histamine concentration in synovial fluid in all RA patients about 1.548 ± 0.10 ng/mL. Histamine level in blood of the same group of the patients was 48.84 ± 3.05 ng/mL, while histamine index was 3.155 ± 0.035. Histamine concentration in blood of healthy subjects in the control group was 51.35± 3.75 ng/mL. There was no significant difference in histamine concentration in blood between healthy population and RA patients.

Among the investigated patients, 73.6% (14 patients) had positive rheumatoid factors, and 26.3% (5 patients) had negative. There was no significant difference between the seropositive and seronegative patients in histamine concentration in synovial fluid and blood, as well as in histamine index (Table1).

All patients were clasiffied into three groups according to the disease activity (Table 2): very active (VA) with DAS-28 (3) score more than 5.1, moderately active (MA) disease with DAS-28 (3) score between 3.2 and 5.1, and inactive (IA) with DAS-28 (3) score below 3.2. Histamine levels in synovial fluid and blood, and histamine index, as well as a number of tender and swelled joints and erythrocyte sedimentation rate are presented in Table 2.

The mean number of tender joints in all patients suffering from RA was 6.57 ± 1.07 (median = 6, minimum = 2, maximum = 16). The mean number of swelled joints was 4.42 ± 0.54 (median = 4, minimum = 1, maximum = 9). The mean erythrocyte sedimentation rate was 25.89 ± 3.51 (median = 25, minimum = 6, maximum = 60). The mean value of DAS 28 (3) score was 4.48 ± 0.26 (median = 4.61, minimum = 2.79, maximum = 6.52).

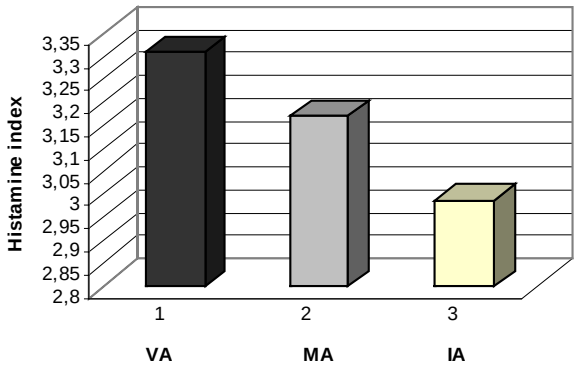

Fig. 1 – Histamine index and rheumatoid arthritis activity according to DAS 28 (3) score: very active (VA) with DAS-28 (3) score more than 5.1; moderate activity (MA) with DAS-28 (3) score between 3.2 and 5.1, and inactive (IA) with DAS-28 (3) score below 3.2. (Student's *t*-test, *$p < 0.05$)

Table 1

Histamine concentration and histamine index in dependence on rheumatoid factor presence

Rheumatoid factor	Synovial fluid (ng/ml) $\bar{x} \pm SD$	Blood (ng/ml) $\bar{x} \pm SD$	Histamine index $\bar{x} \pm SD$
Positive	1.54 ± 0.13	48.33 ± 4.05	3.170 ± 0.043
Negative	1.56 ± 0.16	49.71 ± 4.93	3.131 ± 0.064

Table 2

Dependance of DAS 28(3) score, histamine concentration in synovial fluid and blood, histamine index, number of tender and swelled joints, and erythrocyte sedimentation on rheumatoid arthritis activity

Parameters*	Disease activity		
	very active	moderately active	inactive
DAS 28 (3)score	6.056 ± 0.23	4.52± 0.12	3.07± 0.05
Histamine concentrations (ng/mL)			
sinovial fluid	1.68 ± 0.13	1.57 ± 0.14	1.4 ± 0.24
blood	50.36 ± 3.88	49.61 ± 4.35	46.56 ± 7.71
Histamine index	3.331 ± 0.041†	3.171 ± 0.023†	2.988 ± 0.038
Number of tender joints	13.4 ± 1.2	5.12 ± 0.58	2.16 ± 0.16
Number of swelle joints	7.4 ± 0.67	4.0 ± 0.37	1.66 ± 0.33
Sedimentation rate	46 ± 5.33	24.5 ± 1.42	9.0 ± 0.87

***values of all parameters are given as $\bar{x} \pm SD$; †$p < 0.05$ *vs* inactive**

Histamine concentration in synovial fluid tended to increase in relation to RA activity. Besides, there was no statisticaly significant difference in histamine levels in synovial fluid and blood related to disease activity. However, there was a significant difference in histamine index and it was increased proportionaly to the disease activity (Figure 1).

Discussion

Histamine level in synovial fluid of all the patients with RA was in accordance with the previous literature data [24, 25] that are related to determination of histamine concentration using the fluorometric assay method of Shore [33]. These authors reported increased histamine levels in synovial fluid of patients with ostheoarthritis in comparison with RA. On the other hand, there is data that shows very low (almost undetectable) amounts of histamine in synovial fluid in RA, using the radioimmunoassay method for histamine detection [26]. The authors, who used ELISA method for histamine detection reported decreased plasma histamine levels in RA patients compared to healthy population, while synovial fluid levels were even lower [27]. Other authors detected higher plasma histamine levels in RA patients compared to population without inflammatory arthritis [28]. They notified higher histamine levels in synovial fluid than in correspondent plasma samples. Radioenzyme assay for histamine detection was used in their investigations [28]. Results of various investigations indicate that histamine levels in synovial fluid and plasma depend on the method for histamine detection that is used.

Our results indicate that there are no significant differences in histamine blood concentration between the RA patients and the healthy population. Histamine levels in blood are within the previous reported values in the literature [34, 35].

Rheumatoid arthritis activity was determined in accordance with DAS 28 (3) score observing the erythrocyte sedimentation rate, the number of swelled joints and the number of tender joints [31, 32]. We registrated the lowest synovial fluid histamine levels in the patients with inactive disease (DAS-28 < 3.2). On the other hand, the patients with very active disease (DAS-28 > 5.1) had the highest levels of histamine in synovial fluid. However, these diferences in histamine concentration were not statistically significant because of the large individual variabilities. Although it could be expected that there is a relationship between histamine level in the synovial fluid and desease activity, this "hypothesis" is shown to be incorrect. The definition of the previously mentioned "hypothesis" has been confirmed by many literature data: increased histidine decarboxylase (HDC) activity influenced by cytokines IL-1 and TNF-α which are producted in larger amounts in evolutive forms of RA [36, 37]; increased number of synovial tissue mast cells in patients with active and evolutive form of RA, compared to patients with inactive form and the end stage of the disease [38]; possible different H4 receptor expression in dependance of RA activity [21]; increased histamine levels in bronchoalveolar lavat (BAL) as a useful marker for pulmonal disease activity in RA [39].

Considering the increased histamine concentration in synovial fluid of RA patients with very active disease, it can be suggested that there is a different expression of histamine releasing factor and/or different chemoattractant (SCF, TGF-β, C5a, PAF) concentration that influences mast cells migration according to the disease activity. It was also suggested that histamine could play an important role in autocrine regulation of cytokine secretion from mast cells. That indicates a possible pathway of inflamatory response modulation in certain diseases (asthma) [40].

Although histamine level in synovial fluid tends to elevate according to increased RA activity, there was no significant difference between the patients with a distinct disease activity. There was no difference in blood histamine concentration, as well. That was the reason to involve "histamine index" in our investigation as a more sensitive tool in determination of histamine role in RA.

The patients were treated in accordance with therapeutic strategies for RA, with disease modifying antirheumatic drugs (DMARD) methotrexate and/or chloroquine, nonsteroid antiinflammatory drugs (NSAID), and some of them with low doses of prednisone (≤ 10 mg per day) [41]. There has been literature data that suggests decrease of histamine release influenced by methotrexate and prednisolone [42–44]. On the other hand, a decrease of histamine catabolism by chloroquine inhibition of histamine N-methyltransferase may lead to the increase of histamine concentration [45]. Our results showed no difference in histamine index in relation to the mentioned therapeutic protocols. The reason for this may be the fact that patients were in the various phases of illness activity at the moment of our investigation. There were no difference in DAS 28 score in relation to various therapeutic protocols applied before our investigation. To investigate the effects of various therapeutic protocols on histamine index we have to measure histamine blood and synovial fluid concentrations before and after the applied therapeutic protocol. That will be the subject of our further investigations.

Our results obviously suggest that histamine index is significantly increased in patients with high disease activity. This new parameter is increased proportionally with disease activity expressed by DAS-28 score. Values of histamine index (HI) below 3.02 represent inactive disease, values of HI between 3.02 and 3.29 moderate activity of the RA and HI more than 3.29 very active disease. According to this, histamine index could be a new, additional parameter in the evaluation of disease activity.

Conclusion

It can be concluded that, although there is no difference in histamine concentration in blood and synovial fluid related to RA activity, histamine index is increased proportionally with the disease activity. According to this, histamine index can be considered as a useful parameter in the evaluation of RA activity.

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Influence of admission plasma glucose level on short- and long-term prognosis in patients with ST-segment elevation myocardial infarction

Uticaj nivoa glukoze u plazmi na prijemu na kratkoročnu i dugoročnu prognozu kod bolesnika sa infarktom miokarda i elevacijom ST segmenta

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Abstract

Background/Aim. Hyperglicemia is common in patients with ST-elevation myocardial infarction (STEMI) and is associated with high risk of mortality and morbidity. Relationship between admission plasma glucose (APG) levels and mortality in diabetic and nondiabetic patients with STEMI needs further investigation. The aim of this study was to analyse the short- and long-term prognostic significance of APG levels in patients with STEMI with and without diabetes. **Methods.** This study included 115 patients with STEMI, 86 (74,8%) nondiabetic and 29 (25,2%) dibaetic patients, in which we performed a prospective analysis of the relationship between APG levels and short- and long-term mortality. **Results.** Comparison of APG levels between nondiabetic (8.32 ± 2.4 mmol/L) and diabetic (10.09 ± 2.5 mmol/L) patients showed statistically significantly higher average APG levels in diabetic patients ($p = 0.001$). In all patients observed who died either after one month or one year after STEMI, average APG values were significantly higher in comparison with those in survived patients. There was no statistical significance in average APG levels in the diabetic patients with STEMI who died after one month and those who survived (10.09 ± 2.68 *vs* 10.0 ± 2.51 mmol/L, respectively; $p = 0.657$), as well as those who died after one year and those who survived (10.1 ± 1.92 *vs* 10.09 ± 2.8 mmol/L, respectively; $p = 0.996$). There was, however, statistical significance in average APG levels in the nondiabetic patients with STEMI who died after one month and those who survived (9.97 ± 2.97 *vs* 7.91 ± 2.08 mmol/L, respectively; $p = 0.001$), as well as those who died after one year and those who survived (9.17 ± 2.49 *vs* 7.84 ± 2.24 mmol/L, respectively; $p = 0.013$). **Conclusion.** Acute hyperglicemia in the settings of STEMI worsenes the prognosis in patients with and without diabetes. Our study showed that nondiabetic patients with high APG levels are at higher risk of mortality than patients with a known history of diabetes.

Key words:
blood glucose; myocardial infarction; diabetes melitus.

Apstrakt

Uvod/Cilj. Hiperglikemija se javlja kod bolesnika sa ST-elevacijom infarkta miokarda (STEMI) i dovodi se u vezu sa visokim rizikom od mortaliteta i morbiditeta. Veza između nivoa glukoze u plazmi na prijemu (APG) i mortaliteta kod dijabetičara i nedijabetičara sa STEMI zahteva dalje istraživanje. Cilj ove studije bio je analiza kratkoročne i dugoročne prognostičke značajnosti APG kod bolesnika STEMI sa i bez dijagnostikovanog dijabetesa. **Metode.** Ova studija obuhvatila je 115 bolesnika sa STEMI 86 (74,8%) nedijabetičara i 29 (25,2%) dijabetičara, kod kojih je izvršena prospektivna analiza veze između APG i kratko- i dugoročnog mortaliteta. **Rezultati.** Upoređivanje APG kod nedijabetičara (8,32 ± 2,4 mmol/L) i dijabetičara (10,09 ± 2,5 mmol/L) pokazalo je statistički značajno viši prosečni nivo APG kod dijabetičara ($p = 0,001$). Kod svih bolesnika sa STEMI koji su umrli posle jednog meseca ili jedne godine prosečni nivo APG bio je značajno viši nego kod onih koji su preživeli. Nije nađena statistička značajnost u prosečnom nivou APG kod dijabetičara sa STEMI koji su umrli posle mesec dana i onih koji su preživeli (10,09 ± 2,68 *vs* 10,0 ± 2,51 mmol/L; $p = 0,657$), kao ni onih koji su umrli posle godinu dana i onih koji su preživeli (10,1 ± 1,92 *vs* 10,09 ± 2,8 mmol/L; $p = 0,996$). Nađena je, međutim, statistička značajnost u prosečnom nivou APG kod nedijabetičara sa STEMI koji su umrli posle mesec dana i onih koji su preživeli (9,97±2,97 *vs* 7,91 ± 2,08 mmol/L; $p = 0,001$), kao i onih koji su umrli posle godinu dana i onih koji su preživeli (9,17 ± 2,49 *vs* 7,84 ± 2,24 mmol/L; $p = 0,013$). **Zaključak.** Akutna hiperglikemija u prisustvu STEMI pogoršava prognozu i kod bolesnika sa dijabetesom i kod onih bez dijabetesa. Pokazano je da su nedijabetičari sa visokim nvoom APG u višem riziku od mortaliteta, nego bolesnici sa istorijom dijabetesa.

Ključne reči:
glukoza u krvi; infarkt miokarda; dijabetes melitus.

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Introduction

Diabetes mellitus (DM) is a metabolic disorder characterized by chronic hyperglicemia, with disturbances of carbohydrate, fat and protein metabolism resulting from defects of insulin secretion, insulin action, or combination of both. DM has been rated as an equivalent of coronary heart disease (CHD), and conversely, many patients with established CHD suffer from diabetes or its pre-states [1]. An increased plasma glucose level during stress is a result of sympatic nervous system activation and a raised production of catecholamines and cortisol that stimulate processes of glyconeogenesis, glycogenolysis and lipolysis [2]. High admission plasma glucose (APG) levels after acute myocardial infarction (AMI) are common and associated with an increased risk of death in subjects with and without known diabetes [3–5]. Recent data indicate a high prevalence of abnormal glucose metabolism in patients with unknown diabetes at the time of AMI [6].

Although stress-induced homeostasis disbalance can partly explain the relation between APG levels and outcome, hyperglycemia itself can also be harmful. Thrombotic properties of platelets are increased in a hyperglycemic environment, and this can result in additional cardiovascular complications. Elevated glucose levels may also be associated with increased levels of free fatty acids (FFA). These FFA may increase infarct size, compromise myocardial performance during acute coronary syndrome (ACS), and reduce endothelium-derived vasodilatation in myocardial tissue, limiting myocardial reperfusion. Moreover, recent reports suggest that glucose may be an important mediator in inflammatory responses [7, 8]. One in three patients with suspected ACS had a glucose metabolism disturbance [9, 10]. Hyperglycemia might be associated with an impaired microvascular function after AMI, resulting in a larger infarct size and worse functional recovery. Hyperglycemia is associated with increased risks of heart failure, cardiogenic shock, and death after AMI, but its underlying mechanism remains unknown [11, 12]. APG level in nondiabetic patients with AMI seems to be an independent predictor of a long-term outcome. This indicates that an elevated APG level not only reflects acute stress, but also may be a marker of a disturbed glucose metabolism that worsens the prognosis and requires intervention [13]. Fasting blood glucose (FBG) might be superior to APG in predicting short-term outcomes in patients with AMI. But long-term glycemic control in diabetics may not independently predict mortality suggesting that stress hyperglicemia is of major significance [14, 15].

During an AMI, plasma FFA levels rapidly increase because of lipolytic effects of catecholamines and/or heparin. Increased FFA levels are toxic to ischemic myocardium and are associated with an increased membrane damage, arrhythmias, metabolic inefficiency, and decreased cardiac function [16].

The aim of this study was to analyse the short- and long- term prognostic significance of APG level in patients with ST-segment elevation acute myocardial infarction (STEMI) with and without diabetes.

Methods

This study included all patients registered in the Coronary Unit, Department of Cardiology in Internal Clinic, Clinical Center Kragujevac from January, 1 2007 to June 30, 2007. We prospectively studied the relationship between APG level and short- and long-term mortality in patients with STEMI. Serum glucose was determined at admission. A patient survival was measured 28 days and one year after the admission. The patients were defined as having a "previously diagnosed diabetes" (personal history of diabetes defined using ADA 1997 criteria), and as "no diabetes" (those without previously diagnosed diabetes). DM was defined as the use of insulin or glucose-lowering medication on admission, or a diet for diabetes documented in medical history.

The cardiologists used the following criteria for the diagnosis of STEMI: chest pain more than 30 minutes, elevated cardiac enzymes (CPK), and troponin, and development of electrocardiographic (ECG) changes typical for STEMI (persistent ST elevation > 0.1 mV in two or more contiguous leads). A time from the beginning of symptoms to the admission to the Intensive Care Unit had to be less than 48 h. The patients health status was followed-up by phone call interiews with the patients and their families.

Medical data from the patients medical record were collected in a dedicated database. A Statistical Package for Social Sciences Program (SPSS) for Windows XP (version 7.5) was used for all statistical analyses. The data were presented as percentages for discrete variables and as means (± SD) for continous variables. The differences in baseline characteristics were compared using the *t*-test and χ^2 test. A *p*-value < 0.05 was considered statistically significant.

Results

During period observed 393 patients were hospitalized in the Coronary Unit, including 240 patients with ACS. There were 115 patients with STEMI, 29 (25,2%) with diabetes, and 86 (74,8%) without diabetes. The majority of patients in the study were males (69.6%). The mean age of patients with STEMI was 64.25 ± 10.69 years (min 34, max 86 years). The women were older than men (69.2 ± 8.4 *vs* 62.14 ± 10.91 years, respectively; $p = 0{,}001$). Investigation of the patients' medical history showed that 29 patients (25.2%) had been previously diagnosed with diabetes mellitus, 69 patients (60%) with hypertension, 14 patients (12%) with previous myocardial infarction and 75 patients (65.2%) had a family history of ischemic heart disease. An average APG level of all patients with STEMI in this study was 8.77 ± 2.54 mmol/L. Comparison between APG levels in the nondiabetic (8.32 ± 2.4 mmol/L) and diabetic (10.09 ± 2.5 mmol/L) patients showed a statistically significantly higher average APG level in the diabetic ones ($p = 0.001$).

An average APG level was statistically significantly higher in the patients who died one month after STEMI than in those who survived (10.1 ± 2.85 *vs* 8.45 ± 2.37 mmol/L, respectively; $p = 0.006$). Similarly, an average APG level was statistically significantly higher in patients who died one

year after STEMI than in those who survived (9.4 ± 2.37 *vs* 8.42 ± 2.57 mmol/L, respectively; $p = 0.047$) (Table 1). A total one-month and one-year mortality of STEMI (one-month and one-year survival) in the patients was 19.1% and 35.6%, respectively.

Discusion

Recent studies [3, 4, 6, 7, 13, 17, 18] involving non-diabetic patients showed that even mild hyperglycemia in the setting of ACS is also a predictive factor of in-hospital mortality.

Table 1

Comparison of average admission plasma glucose (APG) level in all patients depending on one-month and one-year survival after STEMI

Time after STEMI	APG level (mmol/L)		
	survived patients	died patients	*p*
One-month	8.45 ± 2.37	10.1±2.85	0.006
One-year	8.42 ± 2.57	9.4±2.37	0.047

STEMI – ST-elevation myocardial infarction

There was no statistical significance in average APG level in the diabetic patients with STEMI who died after one month and those who survived (10.09 ± 2.68 *vs* 10.0 ± 2.51 mmol/L, respectively; $p = 0.657$), as well as those who died after one year and those who survived (10.1 ± 1.92 *vs* 10.09 ± 2.8 mmol/L, respectively; $p = 0.996$). There was, however, a statistically significant difference in average APG level in the nondiabetic patients with STEMI who died after one month and those who survived (9.97 ± 2.97 *vs* 7.91 ± 2.08 mmol/L, respectively; $p = 0.001$), as well as those who died after one year and those who survived (9.17 ± 2.49 *vs* 7.84 ± 2.24 mmol/L, respectively; $p = 0.013$) (Table 2).

Moreover, the new entity called impaired fasting glucose (IFG) (6.1–7 mmol/L) is not only an independent factor of mortality for coronary patients, but has also been associated with doubling of the risk of in-hospital mortality in the setting of ACS. Admission as well as follow-up glycemia are fundamental parameters in ACS for their prognostic value, and as a diagnostic tool in determining the presence of diabetes or IFG [19]. In 2004, the Expert Committee of the American Diabetes Association (ADA) lowered the cutoff point for IFG from 110 to 100 mg/dL on the basis of a new evidence for an increased risk for developing DM and cardiovascular disease. The relevance of this new criterion for IFG to predict

Table 2

Comparison of average admission plasma glucose (APG) level in the nondiabetc patients depending on one-month and one-year survival after STEMI

Time after STEMI	APG level (mmol/L)		*p*
	survived patients	died patients	
One month	7.91 ± 2.08	9.97 ± 2.97	0.001
One year	7.84 ± 2.24	9.17 ± 2.49	0.013

STEMI – ST-elevation myocardial infarction

The patients were classified according to the value of APG in four groups: group I with APG >10 mmol/L, group II with APG 7.8–10.0 mmol/L, group III with APG 6.1–7.8 mmol/L, group IV with APG < 6.1 mmol/L. Highest mortality was shown to be in the patient with APG value more than 10 mmol/L.

The patients were also divided into two groups: with and without DM. In the patients with a previous DM, it was shown that the highest one month mortality was in the group I. It was also shown that the highest one-year mortality was in the group II. There was a statistically significant difference in one-month and one-year mortality between these two groups ($p < 0.01$). In the patients without DM (Table 3), highest one-month and one-year mortality was in the group I (> 10 mmol/L).

the risk for DM and CAD remains controversial [20]. Hyperglycemic patients are relatively deficient in insulin. This leads to both reduced peripheral uptake of glucose and increased circulating FFA, that may impair endothelium-dependent vasodilation and, in hyperglycemic patients with AMI, have been shown to promote calcium overload and arrhythmias [21].

The most common cause of death in European adults with diabetes is CAD. Their risk is two to three times higher than that among people without diabetes. The combination of DM and previous CAD identifies patients with particularly high risk for coronary death. The relative effect of diabetes is larger in women than men [1]. Many of nondiabetic patients with raised blood glucose have undiagnosed diabetes. Dia-

Table 3

One-month and one-year mortality depending on admission plasma glucose (APG) level in nondiabetic patients with STEMI

APG (mmol/L)	No of patients	Mortality (one-month)	Mortality (one-year)
> 10	16	43,75%	56,25%
7.8–10.0	21	14,28%	33,33%
6.1–7.8	34	11,76%	23,53%
< 6.1	15	13,33%	26,66%

betic patients may have worse outcomes for many reasons, including more severe CAD, diabetic cardiomyopathy, autonomic dysfunction and decreased endogenous fibrinolytic activity [22, 23]. APG may be not only the cause of more severe myocardial damage, but also its consequence. Large infarcts are more likely to cause catecholamine release, which affects fatty acid and glucose homeostasis. The catecholamine response is proportional to the severity of infarct, as confirmed by the correlation between APG and heart rate or the Killip class on admission. In a study by Oswald et al. [17] concentrations of cortisol, epinephrine and norepinephrine were the main determinants of APG measured in nondiabetic patients with AMI. In a systematic review and meta-analysis of 15 studies in AMI populations with and without diabetes, Capes et al. [7] showed that in diabetic and nondiabetic patients stress hyperglycemia was associated with an increased risk of in-hospital death. Suleiman et al. [24] analysed the additive prognostic value of APG and FBG in a population of 735 nondiabetic patients admitted for AMI. They showed that FBG was a potent indicator of 30-day mortality and appeared more discriminant than admission blood glucose; no long-term data were reported. Foo et al. [17] in a cohort of 2 127 patients presenting with ACS, including STEMI, analysed major complications. APG was an independent and powerful predictor of in-hospital and late mortality in the presence or absence of left ventricular failure and whatever the type of infarction (STEMI or non-STEMI). Recently, Stranders et al. [17] in a retrospective study of 737 nondiabetic patients with AMI found that a 1 mmol/L increase in blood glucose was associated with a 4% increase in long-term mortality [17]. The Multinational Euro Heart Survey also pointed out that normal glucose regulation is less common than abnormal glucose regulation in patients with unstable CAD. An increased risk of short-term mortality and heart failure has been reported in patients with stress hyperglycemia, as defined by high APG. Suleiman et al. [24] reported that APG between 110 and 121 mg/dL was an independent factor for 30-day mortality.

The results of our study showed that the patients presenting with STEMI who were hyperglicemic on admission represent a high-risk population, even in the absence of an established diagnosis of diabetes. Abnormal glucose metabolism during the acute phase of STEMI is common, and admission hyperglicemia is associated with higher short- and long-term mortality in both diabetic and nondiabetic patients. Moreover, mortality is predicted even more powerfully by admission hyperglycemia in patients without known diabetes. In our study, increased APG was associated with an increase of mortality, in concordance with literature data [18, 25–29].

There are several possible causes of hyperglycemia on admission. First, hyperglycemia on admission in nondiabetic patients with STEMI might represent previously undiagnosed DM or pre-existing impaired glucose tolerance, resulting in increased endothelial damage and thus greater risk for micro- and macro-vascular morbidity. Secondly, hyperglycemia on admission might represent a response to acute and severe stress. Our findings suggest that hyperglycemia on admission is a strong risk factor for worse outcome in all patients with STEMI. Measurement of glycemia on hospital admission may be used as an early screening method to detect high-risk patients. According to diabetes guidelines, all patients with CHD and unknown diabetes status should be screened for DM by an oral glucose tolerance test (OGTT) [14, 15]. Aggressive monitoring of glucose levels may be beneficial for secondary CAD prevention. Increased APG levels are significantly and independently correlated with poor prognosis after STEMI, especially in nondiabetic patients, that was shown in our study.

In view of all these results, admission hyperglycemia during an acute phase of STEMI and its association with poor outcome represents most likely a combination of previously undiagnosed diabetes, impaired glucose tolerance and a response to acute and severe stress. The data obtained in this study showed that hyperglycemia on admission was associated with a worse outcome for all the patients with STEMI. The impact of a higher APG level on mortality was even more important for nondiabetic than for diabetic patients. Thus, nondiabetic patients with hyperglycemia on admission were at special risk, and may need particular attention. Further investigators should evaluate the effects of acute and intensive glycemic control on reducing mortality.

Conclusion

Our study demontrated that high APG level is common in patients with STEMI and associated with high risk of mortality and morbidity. Nondiabetic patients with high APG have higher risk of mortality than patients with a known history of diabetes. These findings suggest that adequate metabolic control of plasma glucose would be an important treatment target, even in nondiabetic patients.

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Vaskularizacija distalnog dela vidnog živca

Vasculature of the distal part of optic nerve

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Apstrakt

Uvod/Cilj. Klasični udžbenici anatomije ne opisuju vaskularizaciju distalnog, odnosno intrakranijalnog i intrakanalikularnog dela vidnog živca, već se opisi odnose samo na proksimalni, odnosno intraorbitalni segment nerva. Cilj ovog istraživanja bio je da se prouči šema arterijske vaskularizacije intrakranijalnog i intrakanalikularnog dela (distalni deo) vidnog živca kod čoveka. **Metode.** Proučavanje je obuhvatilo 25 preparata intrakranijalnih i intrakanalikularnih delova humanih vidnih živaca i oftalmičnih arterija (OA). Korišćene su tri metode istraživanja: makroskopska disekcija, mikroanatomsko proučavanje pod stereomikroskopom i analiza preparata histološkim tehnikama. Na preparatima vidnog živca i OA u intrakranijalni segment unutrašnje karotidne arterije i početni deo OA injicirana je 10% mešavina rastopljenog želatina i tuša. Histološki preparati su pripremljeni i bojeni histohemijskim metodama: trihromno bojenje prema Massonu, Van Giesonu, Azanu i toluidin plavim. **Rezultati.** Oftalmična arterija, po svom nastanku, iz lobanjske duplje ulazi u optički kanal, kroz koji nastavlja sadržana u duralnom omotaču vidnog živca. Oftalmična arterija bila je na 44% preparata u nivou ulaska u optički kanal na donjoj unutrašnjoj strani vidnog živca, dok je kod 72% slučajeva napuštala optički kanal na njegovoj spoljašnjoj ivici u vrhu orbite. Intrakanalikularni segment vidnog živca je vaskularizovan sa obično jednom grančicom OA kod 72% slučajeva, a ređe sa dve arterijice. Pošto se odvoje od OA, ove grančice nastavljaju naviše, probijaju duralni pokrivač OA i granaju se po pijalnom omotaču intrakanalikularnog segmenta vidnog živca. Bogato se anastomozuju sa granama gornje hipofizne arterije koje dolaze iz lobanjske duplje formirajući pijalnu arterijsku mrežu distalnog dela nerva. U našem uzorku nije bilo intraksijalnih arterija u intrakranijalnom i intrakanalikularnom delu živca. **Zaključak.** Anatomski podaci dobijeni ovim proučavanjima pružaju informacije važne za razumevanje patologije predela optičkog kanala, kao i za planiranje strategije operativnih zahvata. Dobijeni rezultati pokazuju gracilnu intrakranijalnu i intrakanalikularnu kapilarnu mrežu vidnog živca, posebno osetljivu na traumatska oštećenja.

Ključne reči:
n. opticus; krvni sudovi nerava; neuranatomija

Abstract

Background/Aim. Vascularisation of the distal, namely intracranial and intracanalicular parts of the optic nerve have not been explained in conventional textbooks of anatomy, while there have been explanations of proximal, that is intraorbital segment. The aim of this research was to study the pattern of arterial supply of the intracranial and intracanalicular part (the distal part) of human optic nerve. **Methods.** The optic nerve and the ophthalmic artery (OA), predominately in their intracranial and intracanalicular parts, were investigated in 25 human specimens by three different methods: macroscopic, stereomicroscopic, and histological observations. Mixture with 10% of India ink and gelatin was injected through the intracranial part of the internal carotid artery, and the most proximal part of the OA. Each optic canal specimen was fixed in formaldehyde and finally paraffin embedded, sectioned, and stained with Masson trichrome, Azan, Toluidin blue, and Van Gieson methods. **Results.** OA passed through the optic canal within the dural sheath of the optic nerve. In 44% of our specimens the OA was on the inferomedial side of the optic nerve at the entrance point to the optic canal. OA left the optic canal at its lateral border in the apex of the orbit in 72% of our specimens. The intracanalicular portion of the optic nerve receives arterial blood principally from the intracanalicular part of OA. OA gives one (72% of the specimens) to two branches that supply the intracanalicular part of the optic nerve. Each branch pierces the dura mater from below and then supplies the nerve through the pia mater. These arteries then terminate in a pial vascular

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network of continuous transverse centripetal arterioles and capillaries that surround each optic nerve. The rich anastomoses with branches of superior hypophyseal artery, from the cranial cavity, which take part in the optic nerve vascularization in its hole length, was observed. There were no intraaxial vessels in the intracranial and intracanalicular parts of the nerve in our specimens. **Conclusion.** These anatomical data offer important informations for understanding the variety of the pathology in the region of optic canal and orbitocranial junction, and is also useful for designing operative strategies. This report indicates the delicacy and vulnerability of the intracranial and intracanalicular capillary network to traumatic disruption.

Key words:
optic nerve; vasa nervorum; neuroanatomy.

Uvod

Klasični udžbenici anatomije ne opisuju vaskularizaciju distalnog, odnosno intrakranijalnog i intrakanalikularnog dela vidnog živca, već se opisi odnose samo na proksimalni, odnosno intraorbitalni segment nerva [1, 2]. Francois i Neetens [3] prvi su opisali da je vidni živac celom svojom dužinom vaskularizovan grančicama pijalnog vaskularnog spleta. Oni navode da intrakranijalni segment vidnog živca vaskularizuju grane unutrašnje karotidne i prednje moždane arterije, formirajući pijalnu mrežu koja nastavlja duž celog nerva, ne spominjući oftalmičnu arteriju (AO) kao mogući izvor vaskularizacije. Ovu vaskularnu šemu kasnije su doradili drugi istraživači opisujući više grančica koje se odvajaju od OA tokom njenog puta kroz optički kanal [4, 5]. Ove arterije probijaju duralni omotač i završavaju se u nervu. Svoje rezultate autori nisu dokumentovali fotografijama.

Varijacije visine nastanka OA od unutrašnje karotidne arterije i odnos sa duralnim krovom kavernoznog sinusa, kao i pravac pružanja OA i njenih grana, od značaja je za poznavanje vaskularizacije vidnog živca. Vaskularna mreža na površini i u samom optičkom nervu izuzetno je fina i osetljiva. Mikroanatomsko istraživanje i poznavanje morfoloških i topografskih detalja vaskularizacije vidnog živca od velikog je značaja za planiranje i za pravilno odvijanje hirurških procedura [6-8]. Cilj našeg istraživanja bio je da se prouči šema arterijske vaskularizacije intrakranijalnog i intrakanalikularnog dela (distalni deo) vidnog živca kod čoveka.

Metode

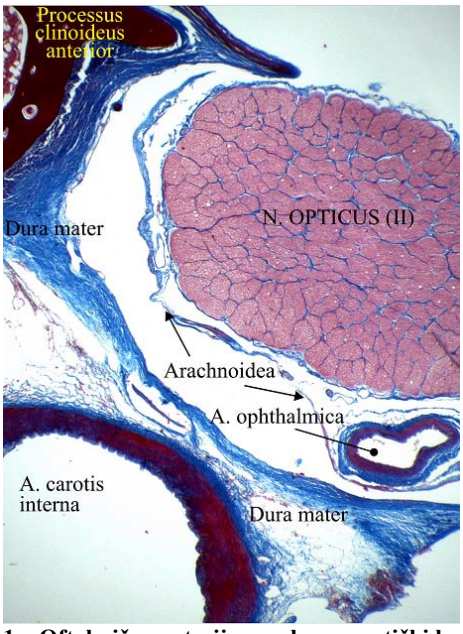
Istraživanje je obavljeno na 25 preparata intrakranijalnih i intrakanalikularnih delova humanih vidnih živaca i OA iz zbirke Instituta za sudsku medicinu, Instituta za histologiju i embriologiju i Instituta za anatomiju Medicinskog fakulteta u Beogradu. Korišćene su tri metode istraživanja: makroskopska disekcija, mikroanatomsko proučavanje pod stereomikroskopom i analiza preparata histološkim tehnikama.

Na preparatima celog mozga i blok preparatima vidnog živca i OA u intrakranijalni segment unutrašnje karotidne arterije i početni deo OA injicirana je 10% mešavina rastopljenog želatina i tuša. Mikrodisekcija injiciranih krvnih sudova optičkog nerva obavljena je pomoću mikroinstrumenata pod Leica MZ6 stereomikroskopom. Vaskularna mreža optičkog nerva i topografski odnosi sa okolnim arterijama i venama ucrtavani su u unapred pripremljenu šemu. Korišćena je metoda prosvetljavanja preparata prema Spalteholzu, koja se sastoji u provlačenju preparata, injiciranog tuš želatinom i fiksiranog u 10% formalinu, kroz seriju alkohola, ksilol- i metil-salicilat na kraju, sve u trajanju od oko mesec dana. Rezultat je potpuna prozirnost mekih tkiva i jasno ocrtavanje tušem obojene vaskularne mreže. Svi preparati su fotografisani digitalnim foto aparatom, a svi detalji pod stereo mikroskopom snimljeni su Leica DC 300 digitalnom kamerom.

Materijal za histohemijske metode bojenja pripreman je na standardan način. Blok-preparati vidnog živca i OA sa koštanim strukturama optičkog kanala fiksirani su u 4% neutralnom puferisanom rastvoru formaldehida tokom 24 časa u volumenu 20 puta većem od volumena tkiva koje se fiksira. Rutinskom procedurom, koja obuhvata dekalcifikaciju, dehidrataciju, prosvetljavanje, impregnaciju i kalupljenje, uzorci su pripremani za pravljenje preseka. Na rastojanju od 15 μm pravljeni su serijski tkivni preseci debljine 4-5 μm. Zatim je svaki preparat optičkog kanala i njegovog sadržaja bojen histohemijskim metodama: trihromno bojenje prema Massonu, Van Giesonu, Azanu i toluidin plavim.

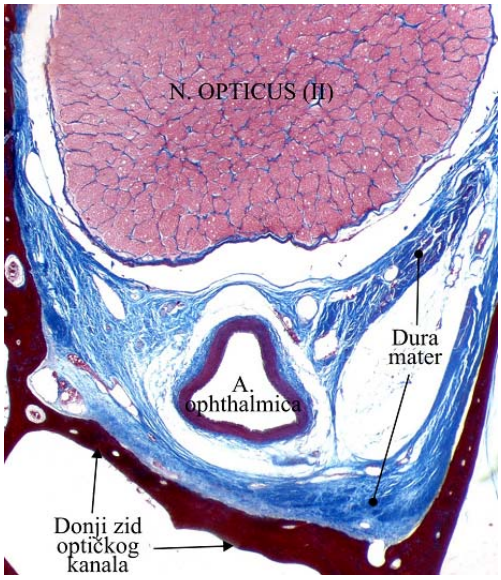
Rezultati

A. ophthalmica je na našem materijalu u svim slučajevima nastajala kao grana *a. carotis internae* (ACI). Po svom nastanku, AO, usmerena ka donjoj strani optičkog nerva, ulazi u optički kanal i uvlači se između dva lista tvrde moždanice koja oblaže kanal (slika 1). U nivou kranijalnog otvo-



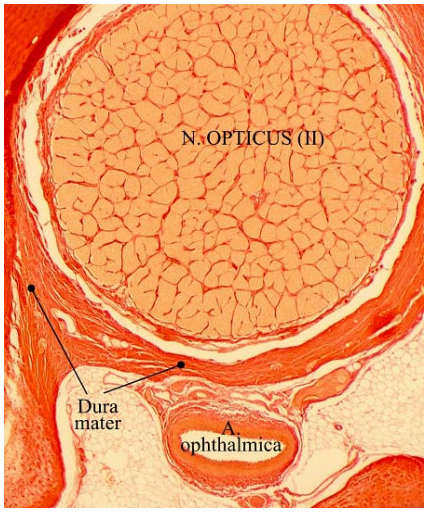
Sl. 1 – Oftalmična arterija na ulazu u optički kanal (Azan, 25×)

ra optičkog kanala AO je najčešće postavljena ispod i unutra od nerva kod 11 (44%) slučajeva, ispod nerva, kod 8 (32%) slučajeva ili ispod i spolja od nerva kod 6 (24%) slučajeva (slika 2). Tokom svog pružanja kroz optički kanal AO najčešće je blago usmerena upolje.



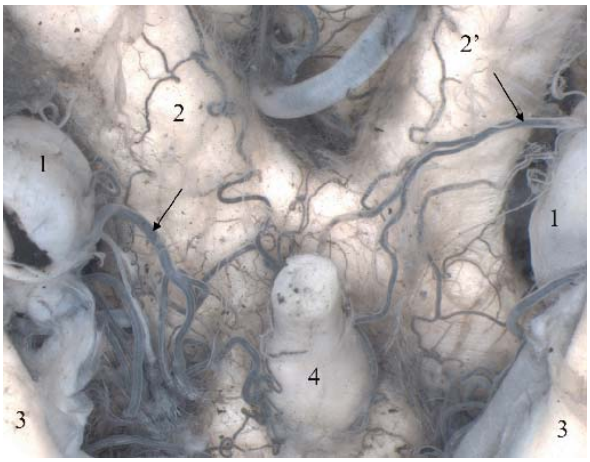
Sl. 2 – Intrakanalikularni segment oftalmične arterije (Azan, 25×)

Oftalmična arterija pruža se optičkim kanalom uvek između dva lista tvrde moždanice koja oblaže kanal. Na mestu orbitalnog otvora optičkog kanala AO izlazi iz optičkog kanala i duralnog omotača i najčešće je postavljena ispod i spolja od nerva kod 18 (72%) slučajeva, ispod nerva kod 5 (20%) slučajeva ili ispod i unutra od nerva kod 2 (8%) slučaja (slika 3).



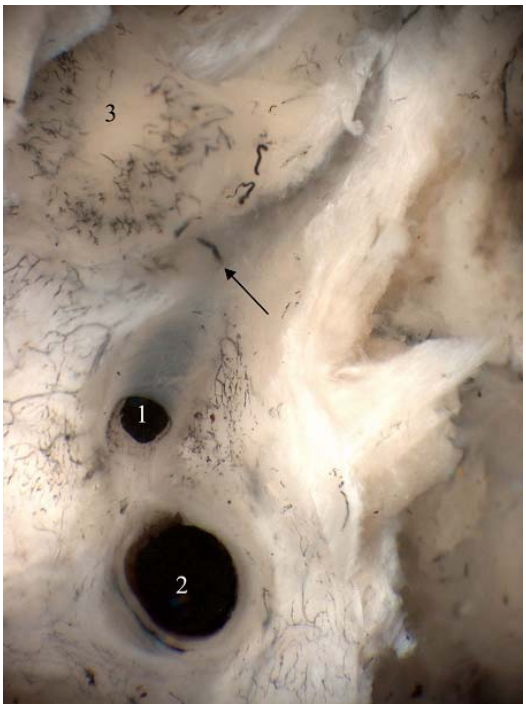
Sl. 3 – Intraorbitalni segment oftalmične arterije po izlasku iz optičkog kanala (Van Gieson, 20×)

A. carotis interna svojom hipofiznom granom, *a. hypophysialis superior*, vaskularizuje intrakranijalni deo optičkog nerva (slika 4). Ovaj segment vidnog živca ishranjen je isključivo penetrantnim granama koje polaze od pijalne arterijske mreže nastale na opisani način. Nismo uočili postojanje bilo kakvog aksijalnog krvnog suda ovog segmenta vidnog živca.



Sl. 4 – *A. carotis interna* (1) daje *a. hypophysialis superior* (strelica) od koje se odvajaju grane za eminenciju medijanu (4), za hijazmu i desni i levi *n. opticus* (2, 2'); *n. oculomotorius* (3) (tuš želatin)

Intrakanalikularni segment vidnog živca je vaskularizovan obično jednom arterijom kod 18 (72%) slučajeva ili sa dve grane oftalmične arterije na 7 (28%) nerava (slika 5).

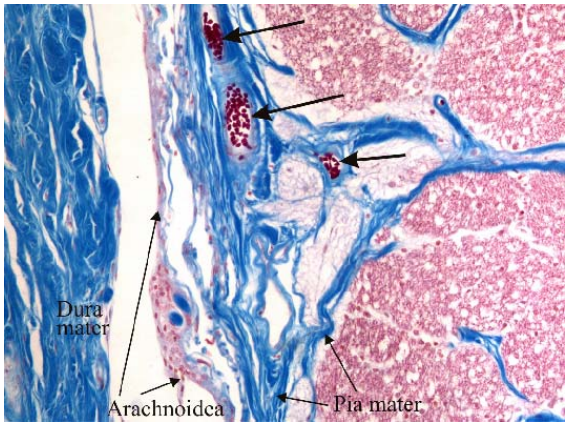


Sl. 5 – *A. ophthalmica* (1) koja se odvaja od *a. carotis internae* (2) daje malu granu (strelica) za intrakanalikularni segment *n. opticus*-a (3) (tuš želatin)

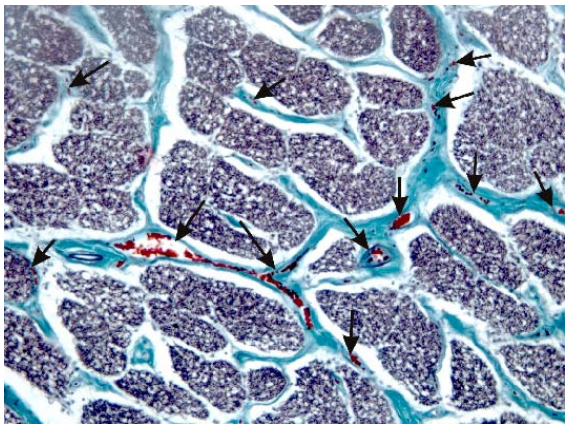
Opisana ekstraoptička arterijska mreža daje manje ogranke koji ulaze u optički nerv i vaskularizuju sve neuronske i paraneuronske strukture. U živcu smo zapazili male arterije, arteriole, prekapilare, kapilare, venule i male vene.

Male arterije su postojale gotovo isključivo u površinskom delu fascikulusa živca, tj. u samom vezivnom, pijalnom omotaču ili između njega i površinskih grupa mijelin-

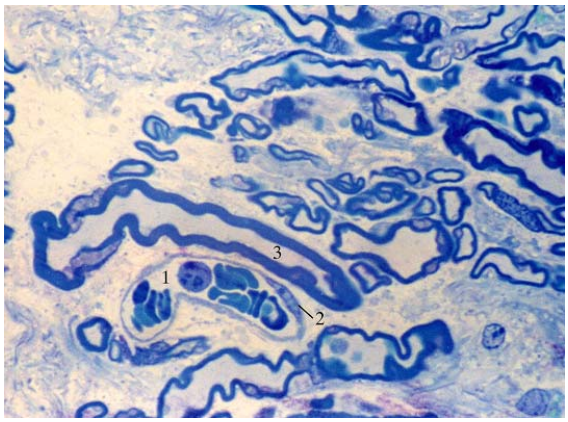
skih aksona fascikulusa (slika 6). Za razliku od arterija koje su imale površinsku lokalizaciju, arteriole su se pretežno nalazile interfascikularno u optičkom živcu (slika 7). Za vizuelizovanje intraoptičkih mikrosudova pod svetlosnim mikroskopom koristili smo polutanke isečke bojene toluidinom (slika 8). Kapilari vidnog živca su iregularno raspoređeni prateći raspored glijalnih pregrada. Na polutankim isečcima kapilara jasno se zapažao jedan red kontinuiranih endotelnih ćelija sa jako izduženim jedrom, kao i produžeci pericita. Kapilari su se često nalazili veoma blizu mijelinskih aksona.



Sl. 6 – Pijalna i fascikularna vaskularna mreža *n. opticus*-a (strelice) na poprečnom preseku (Azan, 25×)



Sl. 7 – Fascikularni kapilari *n. opticus*-a (strelice) na poprečnom preseku (Masson 200×)



Sl. 8 – Fascikularni kapilar *n. opticus*-a i okolni mijelinski aksoni: (1) lumen kapilara, (2) jedro endotelne ćelije, (3) akson sa mijelinskim omotačem (Toluidin blue)

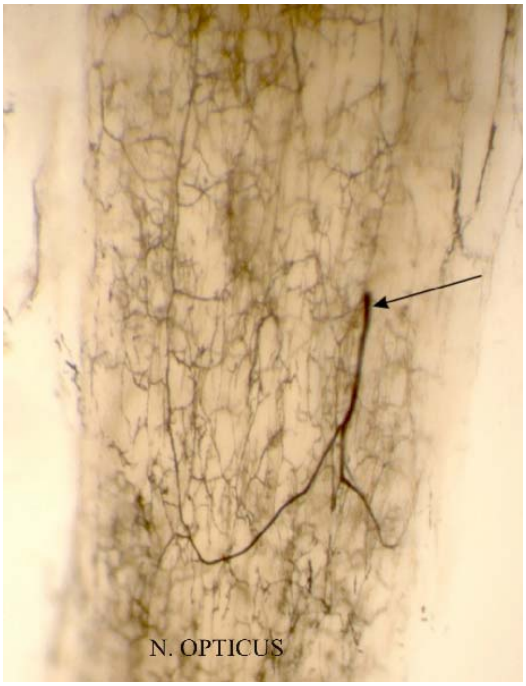
Diskusija

Intrakranijalni deo optičkog nerva vaskularizuje C4 segment *a. carotis internae* svojom hipofiznom granom, *a. hypophysialis superior*. Arterije namenjene vaskularizaciji ovog dela optičkog nerva prilaze ventralnoj strani nerva i hijazmi, usmerene rekurentno prema ulazu u optički kanal. Više grana gornje hipofizne arterije gradi gustu mrežu na donjoj strani hijazme i nerava, a svojim nastavcima prelaze i na gornju, dorzalnu stranu vidnih živaca. Gornja strana optičkog nerva dobija fine grane i iz *a. cerebri anterior*. Da su ovo predominantni izvori vaskularizacije navode i drugi autori [3, 9]. Oni nalaze da intrakranijalni segment OA direktno učestvuje u vaskularizaciji intrakranijalnog dela optičkog nerva što nismo mogli da potvrdimo na našem materijalu [10-12]. Novija istraživanja pokazuju da postoji značajan doprinos OA vaskularizaciji ovog dela optičkog nerva kod čak 4% slučajeva, što u našem istraživanju nismo uočili ni u jednom slučaju [13]. Ovaj segment vidnog živca ishranjen je isključivo penetrantnim granama koje polaze od pijalne arterijske mreže nastale na opisani način. Nismo uočili postojanje bilo kakvog aksijalnog krvnog suda ovog segmenta vidnog živca.

Kao što je napred spomenuto prvi opisi vaskularizacije intrakranijalnog segmenta vidnog živca potiču od Francois i Neetens [3], koji su za proučavanje vaskularizacije optičkog nerva koristili razne injekcione metode i histološke tehnike. Oni su prvi opisali da je živac celom svojom dužinom vaskularizovan grančicama pijalnog vaskularnog spleta. U svojim istraživanjima naveli su da ovaj segment vidnog živca vaskularizuju grane unutrašnje karotidne i prednje moždane arterije, formirajući pijalnu mrežu koja nastavlja duž celog nerva, ne spominjući OA kao mogući izvor vaskularizacije. Ovu vaskularnu šemu kasnije je doradio Hayreh [4], opisujući više grančica (jednu do tri) koje se odvajaju od oftalmične arterije tokom njenog puta kroz optički kanal. Ove arterije probijaju duralni omotač i završavaju se u nervu. Svoje rezultate autor nije dokumentovao fotografijama.

Naši nalazi u potpunosti potvrđuju ove opise. Intrakanalikularni segment vidnog živca bio je vaskularizovan obično jednom arterijom, kod 72% slučajeva, ili sa dve grane OA kod 28% nerava. Pošto se odvoje od OA, ove grane nastavljaju naviše i unazad, probijaju duralni pokrivač OA i granaju se po intrakanalikularnom segmentu vidnog živca usmerene ka orbitalnom otvoru optičkog kanala. Bogato se anastomozuju sa granama koje dolaze iz lobanjske duplje, kao i sa granama iz očne duplje formirajući pijalnu arterijsku mrežu ovog dela nerva (slika 9). Ni na ovom nivou nismo uočili postojanje bilo kakvog aksijalnog krvnog suda ovog segmenta vidnog živca.

Gracilnost intrakanalikularnog arterijskog sistema nerva može se uočiti samo na dobro injiciranim preparatima tuš želatinom. Optički živac može biti oštećen kompresijom različitog porekla [14, 15]. Prekid u vaskularizaciji intrakanalikularnog dela optičkog živca, bilo zbog povrede glave, koja izaziva kidanje pijalne arterijske mreže nerva, ili zbog direktne kompresije delovima kosti ili hematomom, najšire je prihvaćeno kao uzrok gubitka vida kod traumatske optičke neuro-



Sl. 9 – Grančica (strelica) *a. ophthalmicae* koja se grana u intrakanalikularnom segmentu *n. opticus*-a (tuš želatin, prosvetljen preparat)

patije. Walsh [16] u svojim kliničko patološkim poređenjima navodi da su hemoragije u nervu, duri i prostorima između omotača, kidanje nerva, kao i kontuziona nekroza nerva primarne lezije kod indirektne traume optičkog živca. Brojni su slični nalazi u literaturi [12, 17]. Svi ovi podaci pokazuju osetljivost intrakanalikularne kapilarne mreže vidnog živca na traumatsko oštećenje i potvrđuju naše nalaze.

Naši rezultati ultrastrukturnih proučavanja arterija i arteriola nervusa optikusa praktično se poklapaju sa opisima građe cerebralnih sudova [18, 19]. Endoneurijumski kapilari pružaju se longitudinalno duž živca, dakle paralelno sa aksonima. Isto tako, zalaze i transverzalno, formirajući gracilnu mrežu oko grupica mijelinskih aksona. U vidu potpunih ili nepotpunih prstenova okružuju nervne snopove koji tako postaju periodično obuhvaćeni, u pravilnim intervalima, celom dužinom nerva. Pojedini kapilari iz ove mreže zalaze i u ove male grupe aksona. Ovakva uređena struktura kapilarne mreže gubi se na poprečnim presecima intrakranijalnog dela vidnog živca, gde kapilari postaju pretežno longitudinalno postavljeni sa nepravilnim deljenjem. Očigledno je da promene u strukturi fascikulusa nerva i u rasporedu vezivnog tkiva dovode i do promene rasporeda kapilara. Ovi nalazi poklapaju se sa rezultatima drugih autora [3, 20].

Zaključak

Anatomski podaci dobijeni našim proučavanjima pružaju informacija važne za razumevanje patologije predela optičkog kanala i orbitokranijalnog prelaza, kao i za planiranje strategije operativnih zahvata. Naši nalazi ukazuju na gracilnu intrakranijalnu kapilarnu mrežu vidnog živca, poreklom iz *a. hypophysialis superior*, i intrakanalikularnu, poreklom iz obično jedne grane oftalmične arterije, posebno osetljivu na traumatska oštećenja.

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Faktori rizika od samoubistva kod profesionalnih vojnih lica u Vojsci Srbije

Suicide risk factors in the professional military personnel in the Army of Serbia

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Apstrakt

Uvod/Cilj. Poznavanje faktora rizika od samoubistva omogućuje preduzimanje odgovarajućih preventivnih mera u okviru Programa prevencije suicida kod profesionalnih vojnih lica (PVL) koji je uveden 2003. godine u Vojsci Srbije (VS). Cilj rada bio je utvrđivanje faktora suicidnog rizika kod PVL VS u periodu od 1998. do 2007. godine. **Metode.** Analiza faktora suicidnog rizika PVL rađena je na osnovu podataka dobijenih psihološkom autopsijom suicida. Kontrolnu grupu činila su PVL VS koja su se zbog različitih psihičkih problema javljala psihijatru. U radu je korišćena deskriptivna statistika. Značajnost razlika između grupa ispitanika utvrđena je *t*-testom. **Rezultati.** Ukupno 30 PVL, starosti od 22 do 49 godina života (prosečno 30,53 ± 6,24) u periodu od 1998 do 2007. godine izvršila su samoubistva. Distalni faktori suicidnog rizika PVL bili su: bračno stanje (neoženjen), pozitivan psihijatrijski hereditet, netraženje pomoći psihijatra, kockanje, redovno telesno vežbanje (*bodybuilding*), manji broj prekomandi, snižena motivacija za vojnu službu ($p < 0,001$), bez dece, gubitak oca u ranom detinjstvu, konzumiranje alkohola ($p < 0,005$), niska plata ($p < 0,01$), bez završene vojne škole, zaduženost porodice ($p < 0,05$). Najčešći proksimalni faktori suicidnog rizika PVL bili su: aktuelni porodični problemi (36,6%), aktuelne psihičke smetnje (13,3%), iscrpljenost adaptacionih kapaciteta (13,3%), negativan životni bilans (13,3%), problemi na radnom mestu (6,7%), model ponašanja, dok kod 10,0% PVL motivi za samoubistvo nisu mogli biti utvrđeni. **Zaključak.** S obzirom na prisustvo multiplih faktora suicidnog rizika, Program prevencije suicida kod PVL VS usmeren je na prevenciju i proksimalnih i distalnih faktora suicidnog rizika.

Ključne reči:
samoubistvo; faktori rizika; vojni kolektiv; preventivno-medicinska zaštita; srbija.

Abstract

Background/Aim. Recognition of suicide risk factors is important in taking adequate suicide preventive measures, Suicide Prevention Program for Professional Military Personnel (PMP) implemented in the Army of Serbia in 2003. The aim of our study was to establish suicide risk factors in PMP of the Army of Serbia. **Methods.** Analysis of suicide risk factors in PMP was carried out on the basis of data obtained by psychological suicide autopsy. The controls were demographically similar psychiatric outpatients with no history of suicidal behaviour. A descriptive statistics method was used for risk factors analysis. The *t*-test was used for testing statistical hypotheses. **Results.** A total of 30 PMP, aged 22-49 years (30.53 ± 6.24 on average) committed suicide within the period 1998-2007. Distal suicide risk factors in PMP were considered to be not being married, psychiatric heredity, having no outpatient psychiatric treatment, gambling, regular physical practice (bodybuilding), less transfer to a different post, low motivation for military service ($p < 0.001$), not having children, parental loss in early childhood, alcohol abuse ($p < 0.005$), low salary ($p < 0.01$) uncompleted military school, debts in the family ($p < 0.05$). The commonest proximal suicide risk factors were: actual family problems (36.6%), actual mental problems (13.3%), burnout (13.3%), negative balance of accounts (13.3%), professional problems (6.7%), behavioral model while for 10.0% PMP suicide risk factors could not be established. **Conclusion.** According to the presence of multiple suicide risk factors, Suicide Prevention Program for PMP in the Army of Serbia is directed to the prevention of both proximal and distal suicide risk factors.

Key words:
suicide; risk factors; military personnel; preventive health services; serbia.

Uvod

Savremeni modeli shvatanja suicidnosti idu u smeru integracije niza faktora rizika, od psiholoških i socijalnih s jedne strane, do bioloških s druge strane. Novu dimenziju psihološkog pristupa suicidu predstavlja oblast personologije, koja naglašava jedinstvenost svakog pojedinca, kao i stav da svaka osoba može da izvrši samoubistvo ako joj je uskraćena neka vitalna potreba [1].

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Utvrđeni su mnogobrojni faktori suicidnog rizika: pol (muškarci češće izvršavaju, žene češće pokušavaju samoubistvo), godine života (mlađe osobe), bračno stanje (separacija), biološka krizna stanja (adolescencija, nakon porođaja, starost), roditeljsko zanemarivanje ili odbacivanje, emotivno i seksualno zlostavljanje i zloupotreba dece, gubitak podrške prijatelja, psihičke smetnje (depresija, anksioznost, panični napadi, opsesivno-kompulzivni poremećaj, nesanica, šizofrenija, bipolarni afektivni poremećaj, zloupotreba alkohola i psihoaktivnih supstanci - PAS), psihijatrijski hereditet, prethodni pokušaji samoubistva, suicid u bližem socijalnom okruženju, organske bolesti infaustne prognoze, nedavni stresni događaj u životu, gubitak životnih ciljeva i besmislenost života, usamljenost, osećanje stida ili nepodnošljive krivice, pripadnost pojedinim etničkim i subkulturnim grupama [2-9]. Posebno su u riziku da izvrše samoubistvo pripadnici zanimanja koja koriste oružje ili imaju pristup oružju tokom obavljanja profesionalne dužnosti [10-14].

Svi nabrojani faktori suicidnog rizika mogu se klasifikovati na distalne i proksimalne. Distalni faktori odnose se na dugotrajnu i povećanu vulnerabilnost osobe da izvrši samoubistvo, dok proksimalni faktori utiču na neposrednu pojavu samoubistva. U odnosu na distalne faktore, proksimalni faktori se nadograđuju na njih [1].

Kod jedne osobe istovremeno može postojati jedan ili više distalnih i proksimalnih faktora suicidnog rizika. Prisustvo jednog od faktora suicidnog rizika samo povećava suicidni rizik jedne osobe, dok njihovo sadejstvo ukazuje na vrlo visok suicidni rizik. Važno je naglasiti da mnoge osobe mogu imati jedan ili više faktora suicidnog rizika, a da pri tom nisu suicidne. S obzirom na to da se faktori suicidnog rizika retko javljaju izolovano, prevencija je usmerena na utvrđivanje multiplih faktora suicidnog rizika [1, 2, 14].

Konceptualna razlika između distalnih i proksimalnih faktora suicidnog rizika ima praktični značaj u planiranju programa prevencije suicida s obzirom na strategiju koja se koristi i njen potencijalni efekat, što omogućuje da se napravi razlika u programu prevencije suicida, zavisno od prirode ciljnih faktora rizika. Kompleksna priroda samoubistva sugeriše da je potrebno formulisati kompleksni plan aktivnosti koje su neophodne za prevenciju.

U Odeljenju za mentalno zdravlje i vojnu psihologiju Vojnomedicinske akademije (VMA) od 1998. godine vrši se psihološka autopsija svakog samoubistva pripadnika vojne sredine: vojnika i profesionalnih vojnih lica (PVL) - starešina, vojnika po ugovoru, civilnih lica, kao i učenika i studenata vojnih škola sa ciljem utvrđivanja motiva za samoubistvo svakog pripadnika Vojske Srbije (VS) i preduzimanja odgovarajućih mera prevencije [15-17]. S obzirom na specifičan položaj VS u društvu u periodu tranzicionih promena, smatramo da je potrebno kontinuirano istraživanje faktora suicidnog rizika u vojnoj sredini kako za vojnike, tako i za PVL, kako bi se kontinuirano radilo na prevenciji njihove pojave. Cilj našeg rada bio je retrospektivna analiza i utvrđivanje najznačajnijih faktora suicidnog rizika izvršenih samoubistava PVL Vojske Srbije.

Metode

Podaci za istraživanje dobijeni su iz psiholoških autopsija samoubistva PVL VS (oficiri, podoficiri, vojnici po ugovoru) koji su u periodu od 1998. do 2007. godine izvršili samoubistvo. Istraživanje svakog slučaja suicida pripadnika VS izvršio je ekspertski tim Odeljenja za mentalno zdravlje i vojnu psihologiju VMA u sastavu psihijatar i psiholog, koji je odlazio u jedinicu u kojoj je suicidant radio i na osnovu heteroanamnestičkih podataka dobijenih od njegovih kolega i pretpostavljenih starešina, uz korišćenje medicinske i personalne dokumentacije o svakom suicidantu, kao i podataka dobijenih od članova njegove porodice, utvrđivao motive koji su doveli do suicida.

Dobijeni podaci uneti su u Upitnik suicida PVL koji sadrži 40 pitanja podeljenih u pet kategorija: sociodemografske karakteristike suicidanta, karakteristike vojne i porodične sredine i zdravstvene probleme suicidanta, kao i karakteristike izvršenog suicida. Pri konstruisanju Upitnika suicida PVL koristili smo pitanja koja uključuju najznačajnije faktore suicidnog rizika dobijenih podataka iz literature, ali i iz našeg iskustva praćenja suicida u vojnoj sredini od 1998. godine od kada se u Odeljenju za mentalno zdravlje i vojnu psihologiju VMA radi psihološko-psihijatrijska autopsija suicida [2-17].

Kontrolnu grupu činila su PVL VS koja su se, zbog različitih psihičkih problema koji nisu doveli do pokušaja suicida, javljala psihijatru u Odeljenje za mentalno zdravlje i vojnu psihologiju VMA. Ispitanici obe grupe bili su ujednačeni po godinama života, godinama radnog staža i činu.

U statističkoj obradi podataka korišćena je deskriptivna statistička metoda (srednja vrednost - $\bar{x}$, standardna devijacija - SD, frekvencije - f. Značajnost razlika između grupa ispitanika utvrđena je χ^2, *t*-testom, na nivou značajnosti $p < 0,05$.

Obrada podataka izvršena je u statističkom paketu programa SPSS (*Statistical Package for the Social Science version* 10 *for age* Windows (SPSS Inc. 2000).

Rezultati

Tabela 1 prikazuje sociodemografske karakteristike PVL koja su izvršila samoubistvo u periodu od 1998. do 2007. godine.

Prosečna starost PVL koja su izvršila samoubistvo iznosila je 30,53 ± 6,25 godina života, od toga najviše (60%) između 20 i 30 godina života, zatim trećina (33,33%) od 30 do 40 godina, dok je najmanje (6,7%) PVL bilo između 40 i 50 godina starosti.

Više od polovine (56,7%) PVL bili su niži oficiri, oko četvrtine (23,3%) viši oficiri, a petina (20%) vojnici po ugovoru. Prosečna dužina radnog staža PVL koja su izvršila samoubistvo iznosila je 7,08 ± 5,65 godina, dok je više od polovine (53,3%) imalo ispod pet godina radnog staža. Između PVL koja su izvršila samoubistvo i PVL kontrolne grupe nije bilo statistički značajne razlike u godinama života, činu i godinama radnog staža.

Više od polovine (53,3%) PVL bilo je neoženjeno, dok je decu imalo 40% PVL koja su izvršila samoubistvo. U odnosu na PVL kontrolne grupe bilo je više neoženjenih ($p < 0,001$) i bez dece ($p < 0,005$).

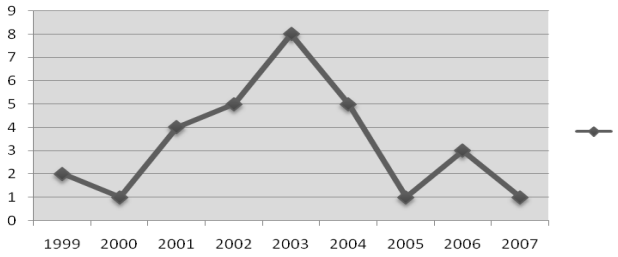
Tabela 1

Sociodemografske karakteristike profesionalnih vojnih lica koja su izvršila samoubistvo u periodu od 1998. do 2007.

Sociodemografske karaktersitike	Suicidanti			Kontrolna grupa			*p*
	x̄ ± SD	broj	%	x̄ ± SD	broj	%	
Godine života	30,53 ± 6,25			35,10 ± 5,20			0,139
20-30		18	60,0		6	20,0	
30-40		10	33,3		17	56,7	
40-50		2	6,7		7	13,3	
Bračno stanje							
neoženjen		16	53,3		6	20,0	0,001
oženjen (ima decu)		12	40,0		24	80,0	0,002
Čin							1,000
podoficir		17	56,7		17	56,7	
oficir		7	23,3		7	23,3	
vojnik po ugovoru		6	20,0		6	20,0	
Završena vojna škola		16	53,3		21	70,0	0,028
Godine radnog staža	7,08 ± 5,65			14,43 ± 6,46			0,154
<5		16	53,3		2	6,7	
5-10		9	30,0		7	23,3	
10-20		3	10,0		14	46,7	
20-30		2	6,7		7	13,3	

Manje PVL koja su izvršila samoubistvo imalo je završenu vojnu školu nego PVL kontrolne grupe, što je dalo statistički značajnu razliku između grupa ($p < 0,05$).

Na slici 1 prikazana je distribucija suicida PVL za period od 1999. do 2007. godine. U posmatranom periodu, godišnje jedan do osam PVL izvršilo je samoubistvo. Pri tom, uočavalo se povećanje broja suicida od 2001. do 2004. godine, s najvišom vrednošću 2003. godine.



Sl. 1 - Suicid profesionalnih vojnih lica Vojske Srbije za period od 1999. do 2007.

U tabeli 2 prikazani su faktori porodične sredine PVL koja su izvršila samoubistvo u periodu od 1998. do 2007. godine.

Oko četvrtina PVL koja su izvršila samoubistvo izgubila su jednog roditelja u ranom detinjstvu, a kod 10% roditelji su bili razvedeni. Više od četvrtine (26,7%) PVL u vreme izvršenja suicida imalo je roditelje koji su bolovali od raznih hroničnih somatskih bolesti. Psihijatrijski hereditet bio je prisutan kod 30% PVL koja su izvršila samoubistvo.

Između grupa ispitanika postojala je visoko statistički značajna razlika u psihijatrijskom hereditetu ($p < 0,001$) i u gubitku oca u ranom detinjstvu ($p < 0,005$).

Oko četvrtine PVL koja su izvršila samoubistvo imalo je problema u odnosima sa suprugom, 30% živelo je u teškoj materijalnoj situaciji u porodici, pri tom po 16,7% je podiglo kredite i imalo dugove. Više od polovine nisu imali rešeno stambeno pitanje, odnosno živeli su kao podstanari u vreme izvršenja samoubistva. Statistički značajna razlika između grupa ispitanika postojala je za dugove u porodici ($p < 0,05$).

U tabeli 3 prikazane su zdravstvene smetnje i navike PVL koja su izvršila samoubistvo. Trećina PVL imala su somatske bolesti (povišen krvni pritisak, ulkus, išijalgija), zbog čega se 16,7% javljalo lekarima odgovarajućih specijalnosti. Prijatelji i članovi porodice navodili su da su kod 40% PVL koja su izvršila samoubistvo uočili psihičke smetnje (anksioznost, sniženo raspoloženje), a prema njihovom

Tabela 2

Faktori porodične sredine profesionalnih vojnih lica koja su izvršila samoubistvo u periodu od 1998. do 2007.

Faktori porodične sredine	Suicidanti		Kontrolna grupa	
	n	%	n	%
Faktori primarne porodice				
gubitak majke u ranom detinjstvu	3	10,0	3	10,0
gubitak oca u ranom detinjstvu	4	13,3	9	30,0
razvedeni roditelji	3	10,0	5	16,7
bolest u porodici	8	26,7	5	16,7
psihijatrijski hereditet	9	30,0	1	3,3
Faktori sekundarne porodice				
bračni problemi	7	23,3	7	23,3
teška materijalna situacija u porodici	9	30,0	9	30,0
dugovi	5	16,7	2	6,7
kredit	5	16,7	3	10,0
nerešeno stambeno pitanje	16	53,3	19	63,3

Tabela 3

Zdravstvene smetnje i navike profesionalnih vojnih lica koji su izvršili samoubistvo u periodu od 1998. do 2007.

Zdravstvene smetnje i navike	suicidanti		kontrolna grupa		*p*
	n	%	n	%	
Somatske bolesti	10	33,3	11	36,7	0,598
Psihičke smetnje (anksiozno-depresivni poremećaj)	12	40,0	20	66,7	0,305
konzumiranje alkohola	7	23,3	3	10,0	0,005
lečenje kod psihijatra (ambulantno)	4	13,3	30	100,0	0,001
bolničko lečenje zbog psihičkih smetnji	4	13,3	6	20,0	0,172
Navike					
kockanje	5	16,7	1	3,3	0,001
redovno telesno vežbanje (bodibilding)	5	16,7	1	3,3	0,001

saznanju, manje od četvrtine (23,3%) koristila su sedative. Manje od četvrtine (23,3%) PVL konzumirala su alkohol. Ambulantno, kao i u Klinici za psihijatriju lečeno je po 13,3% PVL koja su izvršila suicid. Po 16,7% PVL kockala su se i bavila redovnim telesnim vežbanjem.

Između grupa ispitanika postojala je visoko statistički značajna razlika u kockanju, redovnom telesnom vežbanju i ambulantnom lečenju kod psihijatra ($p < 0,001$), kao i u konzumiranju alkohola ($p < 0,005$).

U tabeli 4 prikazane su karakteristike vojne službe PVL koja su izvršila samoubistvo u periodu od 1998. do 2007. godine. Više od polovine PVL koja su izvršila samoubistvo, a sva PVL kontrolne grupe imala su prekomande tokom službovanja, što daje visoko statistički značajnu razliku ($p < 0,001$) između grupa ispitanika. Trećina PVL koja su izvršila samoubistvo, a skoro polovina PVL kontrolne grupe bila je na jednom ili više ratišta u periodu 1991-1995. godine, odnosno tokom NATO agresije 1999. godine ili je kasnije radilo u Kopnenoj zoni bezbednosti (KZB). Tokom službovanja više od četvrtine (26,7%) PVL koja su izvršila samoubistvo kažnjena je, a dvostruko više (53,3%) nagrađivana je za obavljanje profesionalnih dužnosti. Snižen motiv za vojnu službu izražavalo je više od četvrtine (26,7%) PVL koja su izvršila samoubistvo, četiri puta više u odnosu na PVL kontrolne grupe, što daje visoko statistički značajnu razliku između grupa ispitanika ($p < 0,001$).

U tabeli 5 prikazane su karakteristike izvršenog samoubistva PVL za period od 1998. do 2007. godine.

Tabela 4

Karakteristike vojne službe profesionalnih vojnih lica koja su izvršila samoubistvo u periodu od 1998. do 2007.

Karakteristike vojne službe	Suicidanti		Kontrolna grupa		
	n	%	n	%	*p*
Prekomande	17	56,7	30	100,0	0,001
Kažnjavanje	8	26,7	9	30,0	0,575
Nagrađivanje	16	53,3	23	86,7	0,008
Snižena motivacija za vojnu službu	8	26,7	2	6,7	0,001
Boravak na ratištu	10	33,3	13	43,3	0,079
Hrvatska	5	16,7	5	16,7	
Bosna i Hercegovina	3	10,0	3	10,0	
Kosovo i Metohija	6	20,0	8	26,7	
Kopnena zona bezbednosti	6	20,0	3	10,0	

Tabela 5

Karakteristike izvršenog samoubistva profesionalnih vojnih lica za period od 1998 do 2007.

Karakteristike izvršenog samoubistva	n	%
Mesto izvršenja samoubistva		
kasarna - na dužnosti	7	23,3
kasarna - van dužnosti	2	6,7
teren	2	6,7
kuća/stan	14	46,7
van kuće	5	16,7
Način izvršenja samoubistva		
vatreno oružje	26	86,7
vešanje	3	10,0
skakanje sa visine	1	3,3
Mesec izvršenog samoubistva		
oktobar, novembar, decembar, januar,	13	43,3
maj,juni	8	26,7
februar, mart, avgust	6	20,0
april, juli, septembar	3	10,0
Vreme izvršenog samoubistva		
0 do 6 časova	4	13,3
6 do 12	10	33,3
12 do 18	5	16,7
18 do 24	7	23,3
nema podataka	4	13,3
Prisutan presuicidni sindrom	23	76,7
Ostavljeno oproštajno pismo	10	33,3

Oko polovine (46,7%) PVL izvršili su samoubistvo u svom domu (kuća ili stan), a zatim na radnom mestu, za vreme obavljanja dužnosti. Samoubistvo je najčešće izvršeno vatrenim oružjem (86,7%), ređe (10%) vešanjem i skakanjem sa visine (3,3%).

Postoje dva vremenska pika izvršenja samoubistva, tzv. „zimski“ (oktobar-januar) i „letnji“ (maj-juni). Što se doba dana tiče, trećina samoubistava izvršena je od 6 do 12 časova, a četvrtina od 18 do 24 časa.

Više od tri četvrtine PVL koja su izvršila samoubistvo, ispoljila su simptome presuicidnog sindroma, a trećina je ostavila oproštajno pismo.

U tabeli 6 prikazani su najčešći motivi za izvršeno samoubistva PVL u periodu od 1998. do 2007. godine.

U periodu od 1999. do 2007. godine, godišnje je 1-8 PVL izvršilo samoubistvo. Najveći broj izvršen je 2003. godine, što se može objasniti političkim događajima prethodnih godina i transformacijom vojske koja je usledila nakon toga, koju su pratile socijalno-ekonomske promene u društvu. Naglašavamo da nakon 2003. godine i uvođenja Programa prevencije suicida u VS, dolazi do naglog pada broja samoubistva PVL [16, 17].

Istovremeno, na osnovu podataka Instituta za informatiku i statistiku u Beogradu, u periodu od 1997. do 2004. godine, najveća stopa suicida za muškarce za grad Beograd zabeležena je 2000. godine i iznosila je 19,7, a najniža 2004. godine i iznosila je 9,1. Pri tom, muškarci najčešće izvršavaju samoubistvo vešanjem, davljenjem i gušenjem, a na drugom mestu je vatreno oružje [18].

Tabela 6

Motivi izvršenog samoubistva i motivi traženja psihijatrijske pomoći profesionalnih vojnih lica

Motivi	Suicidanti		Kontrolna grupa	
	n	%	n	%
Aktuelni porodični problemi	11	36,6	10	33,3
svađa sa suprugom/devojkom	4	13,3	2	6,7
razvod - prekid emotivne veze	5	16,7		
materijalni problemi	2	6,7	1	3,3
razdvojenost od porodice zbog posla			4	13,3
zdravstveni problemi u porodici			3	10,0
Problemi na radnom mestu	2	6,7	5	16,7
materijalno-finansijska kontrola	2	6,7		
konflikt sa pretpostavljenima			3	10,0
istek ugovora			2	6,7
Akutne psihičke smetnje	4	13,3	9	30,0
psihotični poremećaj	4	13,3		
neurotski poremećaj			9	30,0
Iscrpljenost adaptacionih kapaciteta (*burnout*)	4	13,3	3	10,0
Strah od osude okoline			3	10,0
Negativan životni bilans	4	13,3		
Model ponašanja	2	6,7		
Ostalo	5	10,0		
impulsivno	1	3,3		
zadesno	1	3,3		
nejasno	1	3,3		

Najčešći motivi za samoubistvo PVL u posmatranom periodu bili su aktuelni porodični problemi (36,6%). Podjednako su bile prisutne akutne psihičke smetnje (13,3%), iscrpljenost adaptacionih kapaciteta (*burnout*) (13,3%) i negativan životni bilans (13,3%). Suicid kao model ponašanja okoline i problemi na radnom mestu (6,7%) bili su najređi motivi. Motivi za samoubistva nisu mogli biti utvrđeni kod 10,0% PVL.

Diskusija

U 10-godišnjem periodu, od 1998. do 2007. godine, 30 PVL VS izvršilo je samoubistvo. Stopa suicida u VS za period do 1998. godine iznosila je 16 na 100 000, a od 2003. godine, nakon uvođenja Programa prevencije suicida u VS 13 na 100 000 [16, 17].

S obzirom na to da je samoubistvo u vojnoj sredini redak događaj, te da je veoma teško prikazati statističke podatke retkih događaja, u našem radu samoubistva PVL prikazujemo kao apsolutne brojeve.

Poređenjem stope suicida u VS odnosno bivše Jugoslovenske narodne armije (JNA) i Vojske Srbije i Crne Gore (VSCG) sa stopom suicida u opštoj muškoj populaciji za grad Beograd, uočavaju se značajne razlike u distribuciji stope suicida po godinama koje se mogu objasniti razlikom u dobnim skupinama suicidanata, koja u civilnoj populaciji obuhvata sve uzraste muške populacije, a u vojnoj samo uzrast od 20 do 49 godina.

U periodu od 1998. do 2007. godine najčešći način samoubistva PVL bio je vatrenim oružjem (86,7%), što je u skladu sa istraživanjima u stranim armijama, i može se objasniti time da PVL koja su izvršila samoubistvo koriste oružje ili imaju pristup oružju tokom obavljanja profesionalne dužnosti, što je značajan faktor suicidnog rizika u vojnoj sredini [19, 20].

Prema mestu izvršenja samoubistva PVL, najčešći je van radnog mesta, i to u svom domu (kuća ili stan), u popodnevnim časovima. Oko trećine samoubistava PVL izvršeno je za vreme obavljanja profesionalne dužnosti, od toga oko četvrtina na radnom mestu, odnosno za vreme radnog vremena.

U naše istraživanje faktora suicidnog rizika PVL VS koja su izvršila samoubistvo u periodu od 1998. do 2007. godine uključili smo kao kontrolnu grupu PVL koja su se zbog različitih psihičkih smetnji obraćala psihijatru u Odeljenju za mentalno zdravlje i vojnu psihologiju VMA u tom periodu. Ispitanici obe grupe bili su ujednačeni prema godinama života, činu i godinama radnog staža. Iako su obe grupe ispitanika imale slične porodične probleme, zdravstvene smetnje i probleme vezane za njihovo profesionalno funkcionisanje, ovi problemi kod PVL kontrolne grupe ipak nisu doveli do izvršenja samoubistva.

Najčešći motivi obraćanja psihijatru PVL kontrolne grupe bili su aktuelni porodični problemi nastali zbog razdvojenog života posle prekomande, bračne svađe, materijalnih problema u porodici, kao i zbog zdravstvenog problema člana porodice (bolest supruge/deteta, roditelja ili braće/sestara) zbog čega su ispoljavali psihičke smetnje u okviru anksiozno-depresivnog reagovanja. Motiv obraćanja psihijatru bio je ispoljavanje paničnih napada ili psihosomatskog poremećaja. Problemi na radnom mestu manje su bili zastupljeni (konflikt sa kolegama ili pretpostavljenim starešinom, istek ugovora). Iscrpljenost adaptacionih kapaciteta (*burnout*) i strah od osude okoline (otkriveni da koriste psihoaktivne supstance) bili su najmanje prisutni.

Uzimajući u obzir uticaj različitih faktora koji su prethodili samoubistvu, faktori suicidnog rizika najpre su organizovani unutar okvira koji pravi razliku između proksimalnih i distalnih faktora suicidnog rizika.

Sociodemografski podaci pokazuju da je prosečno PVL koje je izvršilo samoubistvo: niži oficir, starosti oko 30 godina, na početku vojne karijere, neoženjen, bez dece, što je u skladu sa istraživanjima u svetu kako u vojnoj, tako i u civilnoj populaciji [9-14].

Oko polovina PVL koja su izvršila samoubistvo nisu završili vojnu školu (srednju vojnu školu ili jednogodišnje specijalističko školovanje), što se može objasniti činjenicom da su se mnogi od mobilisanih rezervista, učesnika ratova na teritoriji bivše Jugoslavije, tokom angažovanja u ratu pokazali kao dobri borci, pa im je predloženo da se nakon završetka rata aktiviraju, što su oni i prihvatili. Pri tom, neki od njih su aktivirani u vojnu službu bez prethodne provere zdravstvenog stanja koja uključuje i psihološku procenu podobnosti za vojnu službu. Međutim, u radu se pokazalo da, iako su bili izuzetno uspešni u izvršavanju borbenih zadataka u ratu, ne tako retko su imali probleme u izvršavanju vojnih dužnosti u miru, što je uočeno kao faktor suicidnog rizika. Takođe, uočeno je da je samoubistvo neuporedivo češće među PVL koja su nakon završene vojne škole u civilstvu kasnije primljena u profesionalnu vojnu službu nakon jednogodišnjeg specijalističkog školovanja, jer su bili nedovoljno dorasli zadacima vojne službe, a, s obzirom da su bili u bliskom kontaktu sa vatrenim oružjem, bili su u prilici da izvrše samoubistvo.

Posmatrajući faktore primarne porodice, uočava se da je četvrtina PVL koja su izvršila samoubistvo odrasla bez jednog roditelja u detinjstvu ili mladosti. Ukoliko ovome dodamo i odrastanje uz jednog roditelja nakon njihovog razvoda, trećina PVL koja su izvršila samoubistvo, a više od polovine PVL kontrolne grupe odrasli su u nepotpunim porodicama. Iako je poznato da su osobe sa negativnim premorbidnim razvojem i iskustvima, organizacijom života i strukturom, posebno ona koja se odnose na poremećene interpersonalne odnose, traume, modele identifikacije, strukturu porodice, kvalitet života i sistem vrednosti u životu, u većem riziku da ispolje suicidno ponašanje u traumatizujućim situacijama, jer za njih nemaju odgovarajuće kapacitete u rešavanju, niti resurse da nauče da žive sa traumom, rezultati našeg istraživanja pokazuju obrnuto [22-24]. Ovako dobijeni rezultati mogu se objasniti češćim odvajanjem PVL kontrolne grupe u adolescentnom periodu od kuće radi školovanja u vojnim školama, gde su prihvatila nove modele formiranja smisla života, interesa, radnih navika i načina rešavanja konflikata, koji su bitni prediktori načina rešavanja problema i reagovanja u životno teškim situacijama. Takođe, ovome treba dodati da pozitivan psihijatrijski hereditet, prisutan kod 30% PVL koja su izvršila samoubistvo, predstavlja značajan faktor suicidnog rizika, koji se može prevenirati još u selekciji kandidata za vojne škole sprečavanjem njihovog prijema na školovanje i u vojnu službu.

Probleme u sekundarnoj porodici u odnosima sa svojom suprugom ima skoro četvrtina, a materijalne probleme skoro trećina PVL, kako onih iz kontrolne grupe tako i onih koji su izvršili samoubistvo, među njima češće PVL bez ratnog učešća [21]. Materijalni problemi u sekundarnoj porodici posledica su materijalnog položaja pripadnika VS u posleratnom periodu, posebno nakon NATO bombardovanja 1999. godine. Međutim, 16,7% PVL koja su izvršila samoubistvo u vreme izvršenja bili su u dugovima, sa podignutim kreditima, što je češće u odnosu na PVL kontrolne grupe. Za rešavanje materijalnih problema birali su neadekvatne načine ponašanja (igre na sreću, pozajmljivanje novca od kolega, podizanje kredita) koji su mogli samo privremeno rešiti probleme, ali sa psihološke strane sve više su se zaplitali u bespomoćnost, nezadovoljstvo i nesposobnost da reše probleme [21].

Konzumiranje alkohola značajan je faktor suicidnog rizika PVL. Iako su više godina pre izvršenog samoubistva konzumirali alkohol u uobičajenim socijalnim prilikama, sa povremenim opijanjem, zloupotreba alkohola nije bila manifestacija teže psihopatologije kod PVL koja su izvršila suicid, osim kod jednog PVL iz grupe učesnika rata, koji je zahtevao bolničko lečenje u Klinici za psihijatriju Vojnomedicinske akademije [21]. Slabija tolerancija na anksioznost i frustraciju ličnosti PVL koja su izvršila samoubistvo, uz prisutne neefikasne mehanizme suočavanja sa stresom, imala je za posledicu pojavu zloupotrebe alkohola koja bi se mogla shvatiti i kao njihov pokušaj „samolečenja“ u cilju redukcije trpljenja zbog psihičkih smetnji. Samoubistvo je rezultat njihovog udruženog delovanja, s obzirom na to da je poznato da depresija i alkoholizam povećavaju suicidni rizik, udruženi mnogo više [25-31]. Svega 13,3% PVL koja su izvršila samoubistvo lečeni su kod psihijatra ambulantno, kao i bolnički u Klinici za psihijatriju, a četvrtina je, prema izjavi njihovih prijatelja i porodice, koristila sedative. Iako su psihičke smetnje bile prisutne duže vreme pre izvršenja suicida, oni i pored toga nisu zatražili psihijatrijsku pomoć. Podatak da su se sva PVL kontrolne grupe javljala psihijatru, uglavnom zbog anksiozne simptomatologije, posledica je našeg izbora ispitanika kontolne grupe.

Kao kuriozitet koji je uočen u analizi samoubistva PVL je tzv. sindrom telesne okupiranosti, preokupiranosti telesnim funkcionisanjem. Redovnim telesnim vežbanjem, odnosno bodibildingom, značajnije su se bavila PVL sa ratnim iskustvom nego PVL bez ratnog iskustva koja su češće svoje slobodno vreme provodila vežbajući u teretani [21]. Okupiranost sopstvenim telom, potreba da ga izgrađuju („ulepšavaju“) fizičkim vežbanjem, je kompenzatorni mehanizam kod osoba slabijih ego-potencijala, što ukazuje na njihovu narcisoidnost i potrebu da spoljnim izgledom odaju sliku snažnog i neustrašivog ratnika.

Posmatrajući faktore vojne sredine, uočava se da su PVL kontrolne grupe imala češće prekomande, češće su nagrađivana na radnom mestu i, takođe, češće su bila učesnici ratova vođenih na teritoriji bivše Jugoslavije u odnosu na PVL koja su izvršila samoubistvo, što sve ukazuje na njihove bolje adaptacione sposobnosti tokom vojne karijere u odnosu na PVL koja su izvršila samoubistvo. Zbog neizvršavanja profesionalnih zadataka četvrtina PVL su kažnjena, značajnije oni sa učešćem u ratovima koji su se vodili na teritoriji bivše Jugoslavije [21]. Četvrtina PVL kažnjena je ukorom i novčanim kaznama, ali nijedno PVL nije izgubilo posao.

Trećina PVL koja su izvršila samoubistvo i manje od polovine PVL kontrolne grupe, bili su učesnici ratova koji su se vodili na teritoriji bivše Jugoslavije. Profesionalna vojna lica obe grupe u podjednakom broju učestvovali su na ratištima Hrvatske i Bosne i Hercegovine. Međutim, PVL kontrolne grupe češće su bila angažovana na teritoriji Kosova i Metohije za vreme NATO bombardovanja 1999. godine, dok je dvostruko više PVL koja su izvršila samoubistvo bilo na dužnosti u Kopnenoj zoni bezbednosti (KZB). Od svih PVL koja su izvršila samoubistvo, učesnika ratova na teritoriji bivše Jugoslavije, polovina su bili učesnici rata na teritoriji Hrvatske, trećina na ratištima Bosne i Hercegovine, a više od polovine na teritoriji KiM-a za vreme NATO bombardovanja, kao i u zoni KZB, pri tom su petina bila učesnici na dva ratišta, a trećina svih ratišta na teritoriji bivše Jugoslavije. Učešće na dva ili tri ratišta su karakteristični za PVL starijeg godišta i čina u vojsci. Takođe, ističemo da su i u vreme mira neke jedinice Vojske Srbije angažovane u KZB koja se graniči sa teritorijom Kosova i Metohije i u kojima su uslovi života i rada slični onima na ratištu. Napominjemo da je broj samoubistava PVL u Kopnenoj zoni bezbednosti u periodu od 2002. do 2007. godine bio identičan broju samoubistava PVL koja su bila učesnici ratova vođenih na hrvatskom i bosanskom ratištu u periodu od 1991-1995. godine. Dobijeni podaci ukazuju da je angažovanost PVL u izvršavanju borbenih zadataka za vreme rata na teritoriji bivše Jugoslavije imala uticaja na nastanak psihičkih problema od kojih su se neki mogli uočiti i u porodičnom i u profesionalnom funkcionisanju, a koje uz pozitivan psihijatrijski hereditet imaju uticaja na konačni ishod, odnosno samoubistvo [21].

Snižena motivacija za vojnu službu uočena je kod više od četvrtine PVL koja su izvršila samoubistvo. Ovakav nalaz može se objasniti, s jedne strane, činjenicom da je PVL učesnicima ratova na teritoriji bivše Jugoslavije po povratku sa ratnih područja bilo teško da se adaptiraju na mirnodopske uslove rada u kojima su se u sistemu komandovanja nalazili u podređenom položaju pretpostavljenim starešinama koji nisu bili učesnici rata. Takođe, skoro polovina PVL koja su izvršila samoubistvo nisu završila vojnu školu, a nekima je bio istekao ugovor na određeno vreme. Istovremeno, na smanjenje njihove motivacije za vojnu službu uticalo je i kažnjavanje zbog disciplinskih prestupa na radnom mestu.

Na osnovu heteroanamnestičkih podataka kolega sa posla i članova njihove najbliže porodice, možemo opisati dve grupe osobina ličnosti PVL koja su izvršila samoubistvo. U prvoj grupi su PVL koja opisuju kao introvertna, sa osiromašenim socijalnim kontaktima, rigidna u kontaktu, sa pojačanom emocionalnom kontrolom, sa visokim usvojenim moralnim standardima, profesionalno veoma uspešna, često sa sindromom *burnout*, sa skrivenim (latentnim) depresivnim simptomima. U drugoj grupi su PVL koja opisuju kao ekstrovertna, dobro adaptirana, sa oslabljenom emocionalnom kontrolom, nezrela, sa impulsivnim reakcijama, sklona igrama na sreću (kockanje) ili nekim kriminogenim aktivnostima [16].

Najčešći proksimalni motivi PVL koja su izvršila samoubistvo su prouzrokovani problematičnim interpersonalnim odnosom sa bračnim partnerom (suprugom), odnosno sa devojkom, bilo da je u pitanju separacija (razvod, prekid emotivne veze) ili svađa, koja ima značenje straha od separacije od voljene osobe. U činu samoubistva ubija se onaj deo sebe koji pripada voljenoj osobi, onaj deo koji nije mogao da se oslobodi internalizovanog objekta. U fantaziji se napada napušteni voljeni objekat, ne *Self*. Ubijajući sebe, suicidant se izjednačava sa voljenom osobom koja mu je prouzrokovala veliki bol. Na taj način samoubistvo postaje kazna usmerena ka voljenoj osobi. Voljena osoba i suicidant postaju jedna osoba, a samoubistvo kao čin odigravanja nasilja predstavlja bekstvo iz nepodnošljive situacije [32].

Materijalni problemi u porodici kao motiv za samoubistvo povezani su sa nedostatkom novca u porodici ili nemogućnošću da vrate dugove, što u njima izaziva bespomoćnost. S druge strane, materijalno dugovanje PVL na radnom mestu otkriveno je nakon obilaska materijalno-finansijske kontrole, koja je prethodila samoubistvu. Bez obzira na objektivnu težinu učinjenog zakonskog prestupa, niko nije izgubio posao zbog materijalnog duga na poslu. U psihološkom smislu, PVL su obe ove situacije doživela kao narcističku traumu, moralnu kaznu i povredu ugleda i časti. U okviru uticaja oba sistema vrednosti, pretegao je onaj deo ličnosti koji to nije mogao da prihvati, te u kombinaciji sa moćnim distalnim faktorima, uz dostupnost vatrenog oružja, kod njih su stvoreni povoljni preduslovi da izvrše samoubistvo.

Svako osmo samoubistvo PVL bilo je posledica deklanširanja psihotičnog poremećaja. Kod dva samoubistva PVL, radilo se o psihotičnom poremećaju koji se javio nekoliko godina ranije i zbog čega su već lečeni bolnički. Međutim, kod druga dva samoubistva PVL, psihološkom autopsijom utvrđeno je da su izvršena u vreme ispoljavanja prve psihotične epizode koja je do momenta samoubistva ostala neprepoznata. U prilog navedenog ukazuju i istraživanja prema kojima se kod 20-30% mladih ljudi samoubistvo može izvršiti u prodromalnoj fazi prve psihotične epizode, odnosno još pre postavljanja psihijatrijske dijagnoze [1].

Samoubistvo kao posledica akumulacije negativnih životnih događaja, gubitaka životnih ciljeva i besmislenosti ži-

vota vezanih za porodične (razvod, neslaganje sa roditeljima) ili profesionalne aktivnosti (nerealizovane profesionalne aspiracije, otkrivene kriminogene aktivnosti) vrši se nakon pravljenja životnog bilansa sa negativnom procenom aktuelne životne pozicije. Visoke ambicije i aspiracije koje su posedovali ukazuju na naglašen *Superego* i snažnu unutrašnju kontrolu, a nerazvijeni kapaciteti za bliskost i poverenje izostali su kao potporni mehanizmi u kriznim situacijama što je dovelo do sloma adaptacionih sposobnosti i slike o sebi, uz nemogućnost da promene sliku o sebi i konsekutivno promene međusobne odnose. Napred navedeno ukazuje da su i pre izvršenja samoubistva mehanizmi suočavanja sa stresom bili ispod prosečno efikasni što je uz „potrošenost" ljudskog materijala, tešku egzistencijalnu situaciju, neizvesnost, imalo za posledicu iscrpljenost adaptacionih kapaciteta. Samoubistvo je rezultat nedovoljno integrisane, emocionalno nestabilne strukture ličnosti koja je u sukobu sa povećanim zahtevima i nerazumevanjem sredine dospela u stanje dekompenzacije i neadekvatnog reagovanja [2, 22, 23].

Odluka za samoubistvo kod dva PVL doneta je kao imitacija samoubistava izvršenih u njihovoj najbližoj okolini. Jedan suicidant je kao i kolega sa posla izvršio samoubistvo zbog nerealizovanih motiva vezanih za profesionalne ambicije, dok je drugi u istim godinama života i na istom mestu na kojem je njegova rođaka (tetka) pre nekoliko godina izvršila samoubistvo.

Ukupno 10% samoubistava izvršeno je zbog nejasnih motiva. Nejasni motivi postoje kod impulsivnog suicida, kao posledica trenutne odluke i manifestovanog *acting out* ponašanja kada je u jednom slučaju okidač bila identifikacija sa glavnim likom serije koji se ubio zbog nesrećne ljubavi. Ne isključuje se ni zades, odnosno da je samoubistvo izvršeno slučajno, provocirano nesmotrenim reakcijama, uz povišenu alkoholemiju u tom trenutku.

Analiza suicida pokazala je da ni u jednom slučaju suicida PVL izvršenog u periodu od 1998. do 2007. godine nije postojala odgovornost vojne organizacije, kao da ni međuljudski odnosi ni postupanje u jedinici nisu bili neposredni uzrok nastanka vanrednog događaja. Takođe, ni obrnuto, vanredni događaj nije bitnije uticao na stabilnost komandovanja i izvršavanje namenskih zadataka u jedinici.

Heteroanamnestički podaci dobijeni od članova porodice i prijatelja, pokazuju da je kod tri četvrtine PVL koja su izvršila samoubistvo postojalo prisustvo psihopatoloških ispoljavanja u periodu koji je prethodio suicidu, koji je tek retrogradnom analizom prepoznat kao presuicidni sindrom. Prema navodima familije i prijatelja, 40% PVL koja su izvršila samoubistvo u periodu pre izvršenja ispoljavala su anksiozno-depresivnu simptomatologiju kao posledicu intenzivnog emocionalnog distresa. Kao najupadljiviji simptom i promenu u ponašanju koje je registrovala okolina, porodica i prijatelji bilo je usamljivanje. Nažalost, sve ove promene u ponašanju nisu protumačene kao mogućnost da se može intervenisati, te da se pravovremeno upute psihijatru na pregled i time spreči suicid koji su kasnije izvršili. Pojava aktuelnih stresnih situacija uz pojačanu vulnerabilnost ličnosti koja je posledica njihove smanjene sposobnosti da ostvare stabilne profesionalne i porodične odnose imala je za posledicu bihejvioralne manifestacije usled visokog stepena subjektivne patnje, što je značajno uticalo na poremećaj socijalnog ili profesionalnog funkcionisanja i dezorganizaciju ličnosti.

U prilog navedenom i obraćanje lekarima opšte prakse u garnizonskim ambulantama pre izvršenja suicida ukazuje na apel osoba koje su u krizi i traže pomoć, ispoljavajući simptome tzv. „malih oboljenja" zbog čega njihovo depresivno raspoloženje (larvirana, „maskirana depresija") lekari u garnizonskim ambulantama nisu prepoznali i nisu ih uputili psihijatru. S druge strane, ovako dobijeni podaci ukazuju na mogućnost da upravo lekari opšte prakse mogu prepoznati simptome presuicidnog sindroma, što ukazuje na potrebu da se Program prevencije suicida u vojnoj sredini usmeri na edukaciju lekara opšte prakse u smislu obnavljanja znanja iz depresije i pomoći osobi u krizi, što je u skladu sa programom prevencije suicida u svetu [21].

Trećina PVL ostavila su oproštajno pismo. Uprkos mnogobrojnim ograničenjima, oproštajno pismo je mogućnost da se otkrije sadržaj razmišljanja osobe u trenutku kada je izvršila samoubistvo. Istraživanja mađarskih autora pokazuju da postoje dve vrste poruka koje ostavljaju osobe koje nameravaju da izvrše samoubistvo [33]. Prva vrsta oproštajnih poruka su upućene poznanicima, i u sadržaju poruka se nalazi sadržaj u kojem govore o nepodnošljivom psihološkom bolu, osećanju beznadežnosti, iscrpljenosti. Ove poruke su, uglavnom, pozitivne, pune emocija upućenih ženi i deci, kojima izražavaju ljubav.

Ređe su ove poruke negativne i u njima optužuju sebe, manje druge osobe. Najčešće objašnjavaju razloge zbog kojih su „morali" da izvrše samoubistvo („Zbog ovoga što ću uraditi, nemojte nikog da krivite, niko nije odgovoran. Slušajte majku i oprostite mi").

Oproštajne poruke najčešće su u vidu pisma: „Neka bude što biti ne može... Do viđenja druže, do viđenja", ili dnevnika koji su vodili nekoliko dana pre izvršenog samoubistva, ali ima i SMS poruka: „Ne mogu više! Izvinite... Zbogom!" Ti si bila nešto najbolje u životu i želim ti sve najbolje, uvek ću te voleti!!! Odoh ja..." Postoje i kao verbalne izjave koje je suicidant uputio kolegi sa posla, 20 minuta pre nego što je izvršio suicid: „Nema veze, svi ćemo i mi pod zemlju".

U porukama često daju uputstva prijateljima i rođacima da izmire njihove dugove, ili ostavljaju broj kućnog telefona da obaveste porodicu o tome šta je učinio.

Drugu vrstu oproštajnih poruka ostavljaju osobe koje su narcistički ozlojeđene i šalju negativne poruke poznanicima i članovima porodice, optužujući ih posredno za samoubistvo. Oproštajne poruke mogu biti upućene i državnim institucijama (crkva i vojska), prema kojima ispoljavaju verbalnu agresiju.

Mere prevencije suicida prvenstveno su usmerene na značaj redovnog vojnog školovanja PVL, kako bi se nakon višegodišnjeg vojnog školovanja s obzirom na složenost svakodnevnih zadataka i značaj angažovanja, jedinice popunile kvalitetnim i obrazovanim starešinama. U tome bi poseban značaj trebalo da ima rad na poboljšanju selekcije ljudstva. Takođe, veoma je važan preventivni rad sa PVL koja se angažuju na specifičnim zadacima koji zahtevaju pojačana psi-

hofizička opterećenja (specijalne jedinice, jedinice u posebnim stresogenim i psihofizički iscrpljujućim uslovima KZB) radi sprečavanja eventualnih negativnih efekata na emocionalnu stabilnost i mentalno zdravlje.

Mere prevencije suicida PVL spovode se putem rada primarnih mentalnohigijenskih timova koji bi trebalo da rade na zdravstvenom prosvećivanju PVL i otklanjanju straha od stigmatizacije zbog traženja stručne psihijatrijske pomoći.

U tom smislu, preporučuje se obuka članova primarnih mentalnohigijenskih timova uključivanjem u programe kontinuarane medicinske edukacije (KME), radi što ranijeg prepoznavanju osobe u krizi. Značaj ima i holisitički pristup trupnih lekara u prepoznavanju prvih simptoma depresije i ranog otkrivanja presuicidnog sindroma.

Zaključak

Iako su faktori suicidnog rizika PVL VS u 10-godišnjem periodu (1998-2007) vezani prvenstveno za ličnost PVL koje je izvršilo samoubistvo, motiv samoubistva PVL treba tražiti u interakciji više faktora koji su uticali na njegovo izvršenje, koji idu u smeru integracije više faktora rizika, klasifikovanih kao distalni i proksimalni, što ukazuje na prisustvo multiplih faktora suicidnog rizika PVL.

Stoga, program prevencije suicida PVL VS treba usmeriti ka prevenciji i proksimalnih i distalnih faktora suicidnog rizika. Profesionlanim vojnim licima koja imaju visok suicidni rizik, stvaraju se mogućnosti da se u sistemu koherentnosti i podrške vojne sredine, umanje proksimalni faktori suicidnog rizika. Poznavanje distalnih faktora suicidnog rizika profesionalnih vojnih lica daje mogućnost da se interveniše još tokom selekcije i da se eliminišu kandidati za prijem u vojnu službu, kada se uoče vojnospecifični faktori suicidnog rizika.

Smatramo da je potrebno nastaviti sa istraživanjem problema suicida u vojnoj sredini i u narednom periodu s obzirom na transformaciju vojske koja je u toku kako bi se na najbolji način sprečilo njegovo ispoljavanje među PVL.

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Principles of surgical treatment of congenital, developmental and acquired female breast asymmetries

Principi hirurškog lečenja kongenitalne, razvojne i stečene asimetrije ženskih dojki

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Abstract

Background/Aim. There is a natural asymmetry in normal female brests. When the difference in the shape, size or position of the breast and nipple-areola complex is visible, surgical correction is the only treatment option and presents one of the greatest challenges for a plastic surgeon. Based on the Nahai classification presented in details, the aim of the study was to present the possibilities of plastic surgery to correct primary (congenital), secondary (developmental) and tertiary (acquired) brest asymmetries. **Methods.** We conducted a retrospective analysis of female breast asymmetry surgeries performed in the Clinic for Plastic Surgery and Burns, Military Medical Academy (MMA), Belgrade over the last seven years (January 2002 – January 2009). **Results.** During the above mentioned period, 82 female patients, 18 – 65 years of age, underwent surgery for breast asymmetry. The most frequent asymmetries were developmental, "pubertal" (n = 43); acquired asymmetries as a consequence of tumor surgery were found in the other 22 patients, while 7 patients were diagnosed with primary asymmetries such as congenital chest-wall asymmetry (Sy. Poland), accessory and tuberous breasts. All patients underwent preoperative ultrasound examination, while hormone status was determined in those with developmental, "pubertal" asymmetries. The selection of surgical procedure for correction of breast asymmetry depended upon clinical examination findings and patient's wish relating to the shape and size of the breasts. The most of breast asymmetries were corrected by a combination of surgical procedures including primary and secondary reconstruction, reduction, suspension or augmentation mammoplasty. Having combined different surgical procedures, we managed to achive satisfactory results. The hypertrophic scar formation after reduction mamoplasty was seen in some cases, however, they caused no significant patient's discomfort. **Conclusion.** Application of plastic, reconstructive and aesthetic surgical principles can considerably contribute to achieving excellent results in corrective surgery for breast asymmetries. In addition to most suitable breast asymmetry surgical procedures choice, motivation of a patient is also very important for achieving satisfactory results.

Key words:
breast; nipples; congenital abnormalities; reconstructive surgical procedures.

Apstrakt

Uvod/Cilj. Sve ženske dojke su prirodno asimetrične. Kada je razlika u obliku, veličini ili položaju dojke i bradavice upadljiva, hirurška korekcija jedino je rešenje i predstavlja jedan od najvećih izazova za hirurga plastičara. Pridržavajući se detaljno opisane klasifikacije po Nahaiju, cilj rada bio je da se prikažu mogućnosti plastične hirurgije u rešavanju primarnih (kongenitalnih), sekundarnih (razvojnih) i tercijarnih (stečenih) asimetrija dojke. **Metode.** Izvršena je retrospektivna analiza hirurških procedura za korekciju različitih vrsta asimetrija dojki kod žena koje su u poslednjih sedam godina korišćene u Klinici za plastičnu hirurgiju i opekotine VMA. **Rezultati.** Tokom poslednjih sedam godina u Klinici za plastičnu hirurgiju i opekotine VMA operisane su 82 bolesnice starosti od 18 do 65 godina. Najveći broj asimetrija bio je iz grupe razvojnih, „pubertetskih asimetrija", čak 43. Operisano je sedam bolesnica sa primarnom asimetrijom: urođena asimetrija grudnog koša (Sy. Poland), prekobrojne i tuberozne dojke. Sve bolesnice bile su preoperativno ultrazvučno pregledane, a kod razvojnih asimetrija rađen je i hormonski status. Izbor hirurške tehnike za korekciju asimetrije diktirao je klinički nalaz i želja bolesnice za budućim izgledom dojki. Najveći broj asimetričnih dojki korigovan je primenom kombinovanih hirurških procedura: primarna i sekundarna rekonstrukcija, redukciona, suspenziona ili augmentaciona mamoplastika.

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Kombinacijom hirurških procedura postigli smo veoma zadovoljavajuće rezultate. Kod nekoliko bolesnica zabeleženi su hipertrofični postoperativni ožiljci nakon redukcionih mamoplastika, koji nisu uzrokovali značajne smetnje. **Zaključak.** Primena principa plastične, rekonstruktivne i estetske hirurgije može značajno da doprinese postizanju veoma dobrih rezultata u rešavanju asimetrija dojki. Pored odgovarajućeg izbora operativnih procedura za rešavanje asimetrije dojki, od izuzetnog značaja je i motivisanost bolesnica za postizanje što boljih rezultata.

Ključne reči:
dojka; dojka, bradavice; anomalije; hirurgija, rekonstruktivna, procedure.

Introduction

Female breasts go through three stages of development. During the intrauterine fetal growth, the nipple is formed between the 8th and 10th week, while the primitive milk dusts are formed by the 5th month of fetal life. Breast development is definitely completed at puberty under the influence of female gonadal hormones when lobules are formed [1]. There is a smaller or larger natural asymmetry in normal female breasts which may be in the shape, position and size of the breasts or in the projection of the nipples; however, these differences are almost invisible and do not require any esthetic-surgical correction. Nahai [2] has given a detailed description of the causes leading to the breast asymmetry and divided them into 3 groups.

Breast asymmetry is not a rare phenomenon and it presents one of the greatest challenges for a plastic surgeon, particularly in terms of surgical technique selection. Correction surgery for breast asymmetry falls into the sphere of cosmetic surgery.

Once an examination has been completed and diagnosis established, female patient is thourougly informed about the possibilities, advantages and disadvantages of some surgical procedures. Upon reaching an agreement, the patient and the doctor decide on the surgical technique that would allow for achieving optimal results. Sometimes, it would be needed to combine one or more surgical techniques.

However, all surgical procedures, the number of which is large, for correction of breast asymmetry using either patient's own tissue or artificial material, require complete preoperative preparation of the patient.

Depending on the type of asymmetry, additional diagnostic procedures may be indicated such as chest radiography, breast ultrasound examination, hormone status, color Doppler, mammography and basic laboratory analyses, as well as anesthesiology consultation prior to the surgery.

Surgical correction of breast asymmetry is a demanding surgery and it is often performed in several stages. Congenital asymmetries are usually corrected after the puberty, developmental in the adolescence period and acquired even in the advanced ages [3].

The aim of the study was to present the importance of knowing various surgical techniques for correction of female breast asymmetries. Possessing a good knowledge of these surgical procedures ensures the most adequate treatment of some types of asymmetry.

Methods

This paper presented a retrospective study of female patients with asymmetric breasts admitted to the Clinic for Plastic Surgery and Burns, Military Medical Academy in Belgrade, for correction surgery over the period from January 2002 to January 2009. Based on the data obtained from patients medical records, all surgical techniques chosen for each type of breast asymmetry were analyzed and their effectiveness in achieving functional and esthetic results evaluated.

Results

Based on the data obtained from medical records of surgically treated female patients for breast asymmetry, it was possible to divide them into three groups depending on the type of asymmetry classified by Nahai (Table 1). The group I included the patients with congential breast asymmetry, those with developmental asymmetry were in the group II, while the patients with acquired asymmetries felt into the group III.

Surgical methods used for correction of breast asymmetries included reduction mammaplasty, breast augmentation and mammaplasty, reconstruction of the missing breast using local flaps and silicone gel implants, as well as the combination of the above mentioned techniques.

The patients from the group I with the primary (congenital) asymmetries were treated for Poland's syndrome characterized by the defficiency of a large pectoral muscle by combination of the muscle flap and implant. Those with tuberous breasts were treated using the Muti-type technique [4]. Accessory breasts were excised without the need for additional correction of the exisitng breasts [5].

The group II of patients with secondary (developmental) asymmetries was the largest. Ultrasound examination of both breasts were conducted and hormone status determined in all the patietns. Prior to a specific surgical procedure, they all underwent endocrinological examination. Asymmetries were mostly corrected by augmentation mammaplasty, silicone gel implants "Mentor" of various sizes [6], and various techniques of reduction or suspension mammaplasty such as Motturi- , Pitanguy- , McKissock- , Lassus- , or Lejour-type mammaplasty techniques [7–13].

Acquired breast asymmetries in the patients from the group III were mostly a consequence of a previous surgical treatment for benign or malignant breast tumor. Upon clinical examination, the patients were presented to the conciliar commission, which then indicated breast reconstruction and/or subcutaneous mastectomy. In patients with such condition arising out of unilateral mastectomy, color Doppler of the blood vessels in the scapular and axillary region was performed prior to the surgical procedure to exclude the injury of *a. thoracodorsalis* that could happen during the primary surgery.

Table 1

Distribution of patients in dependence on breast asymmetry and surgical technique applied

Nahai classification of breast asymetry	Number of pts	Applied surgical technique
Primary breast asymmetry – congenital		
defficiency of the gland tissue	–	
absence of the nipples	–	
Sy. Poland	2	Siltex implant "Mentor"
accessory breasts	2	Accessory breast excision
accessory nipples	–	
tuberous breast	3	Augmentation, Reduction *sec* Muti
chest-wall asymmetry	–	
Secondary breast asymmetry – developmental		
unilateral hypoplasia	19	Augmentation (siltex prosthesis "Mentor")
unilateral hypothrophy	21	Combination of reduction mammaplasty and augmentation (siltex prosthesis "Mentor")
asymmetry of the areoal-mammary complex	3	Partial excision - reposition
asymmetry of the base and submammary region	–	
Tertiary breast asymmetry – acquired		
breast tumors	21	*Latissimus dorsi* + siltex prosthesis "Mentor"
trauma – burns	1	siltex prosthesis "Mentor"
iatrogenic	–	
after pregnancy and breastfeeding	10	Combination of suspension and augmentation mammaplasty
Total	82	

These types of asymmetries were corrected using myocutaneous *m. latissimus dorsi* flaps and silicone gel implants of the approapriate size. Asymmetries acquired after pregnancy and breastfeeding were treated by the breast augmentation or suspension mammaplasty [13–15].

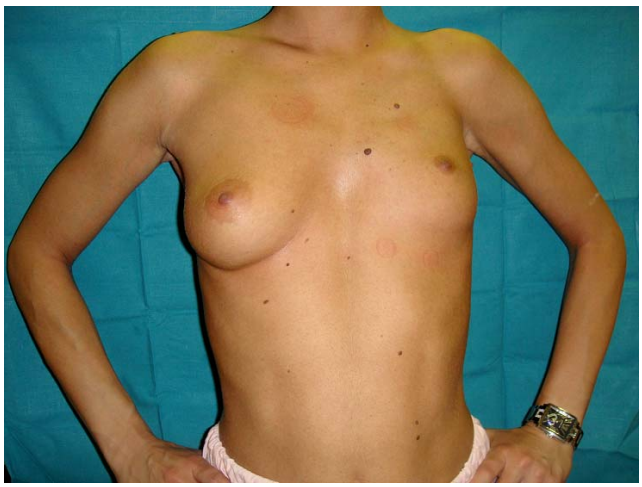
All the procedures were performed under general endotracheal anesthesia. Functional status of the surgically treated breasts and satisfaction of the patients with the visual outcome were scored to evalute the overall achieved results. From the functional and esthetic aspects, the results achieved with congenital breast asymmetry corrections were satisfactory. Among the patients from the group I, there were two patients with Poland's syndrome. The absence of pectoral muscle, hypoplastic milk glands and the nipples in a lateral position inclined to the ipsilateral were found in both of them. Asymmetry in the first patient was corrected by unilateral augmentation mammaplasty using silicone gel implant "Mentor" of an adequate size and shape, because the size and shape of the contralateral breast was satisfactory. The defficiency of pectoral muscle in the second patient was rebuilt using the ipsilateral *latissimus dorsi* muscular flap on the vascular pedicle and implants of various size because the contralateral breast was also hypoplastic (Figures 1 a-e).

Corrections were performed as one-stage procedures using implants which were placed subglandularly in both cases. Tuberous asymmetry in 3 patients was treated by the Muti-type technique. Due to the particularly pronounced breast deformity in the areola complex region in those patients, breast asymmetry reduction and suspension was required. Augmentation mammaplasty was performed in the second stage. There were also two other patients with bilateral accessory breasts which were asymmetric and extended lateraly towards the axilla. The accessory breasts were excised, the wounds were sutured directly with intradermal suture leaving a minimal post-operative scar. Hystopathological examination revealed that the milk gland tissue was affected.

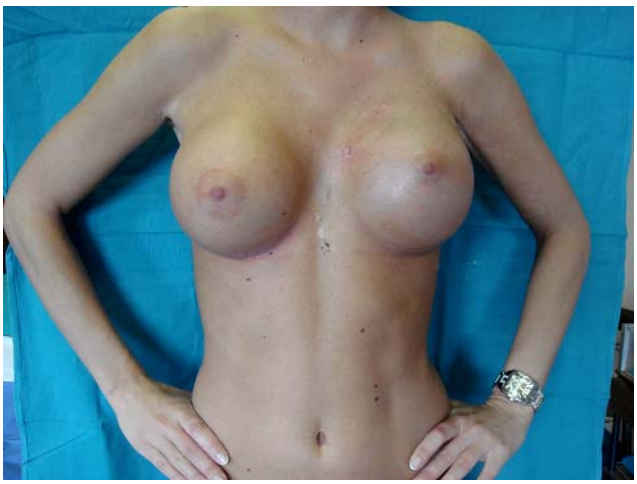
The group II included the largest number of patients with breast asymmetry, so various surgical techniques had to be used. The difference in the shape of the developmental asymmetric breasts was corrected in 19 patients using silicone gel implants "Mentor" of various size and shape (Figures 2 a, b).

The most adequate of too many breast reduction surgeries was chosen in the case of 14 patients with one breast more ptotic due to a large volume of fatty tissue in relation to the contralateral breast of satisfactory size and shape (Figures 3 a, b, and 4 a, b).

The other patients from the group, seven of them, with developmental breast asymmetries required the combination of two surgical procedures, augmentation and reduction mammaplasty (Figures 5 a, b). To place silicone gel implants, we used a submammary approach in all these cases. A skin incision was made in the submammary fold and the implant was inserted subglandurally in 70% of cases and submuscularly in 30% of cases. The functional results achieved with correction surgery of inverted nipples in the patient who underwent augmentation mammaplasty were absolutly satisfactory. In the case of other patient with lactation definitely complete, unilateral correction surgery was performed using the method by which milk ducts in the nipple were cut off.



a)



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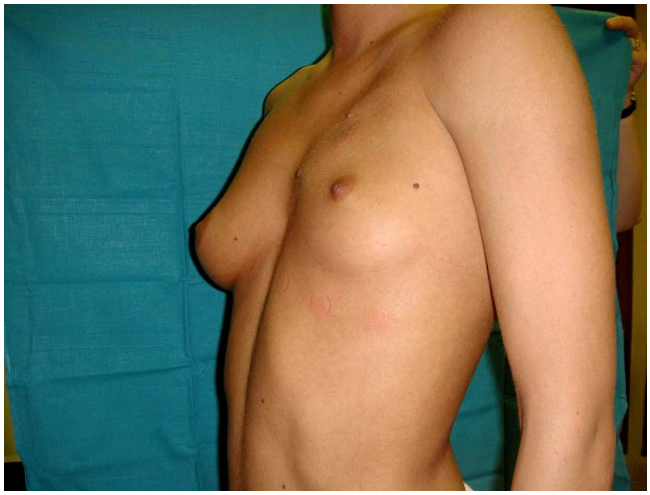

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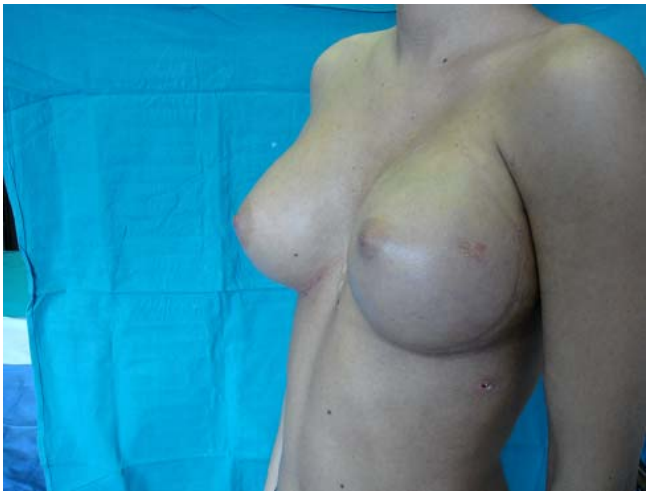

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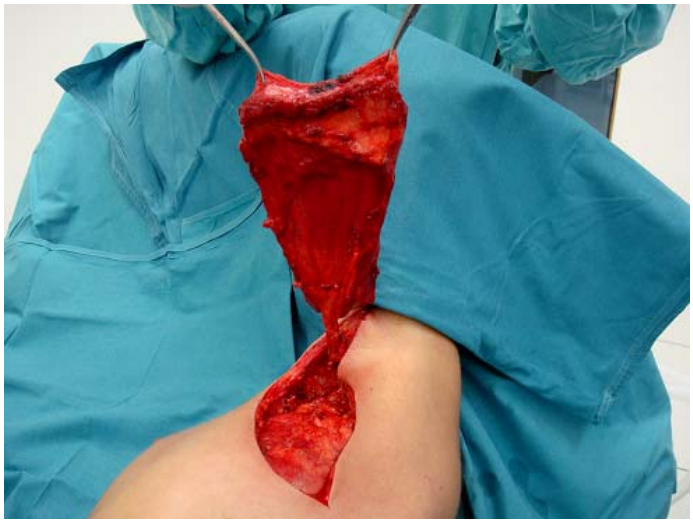
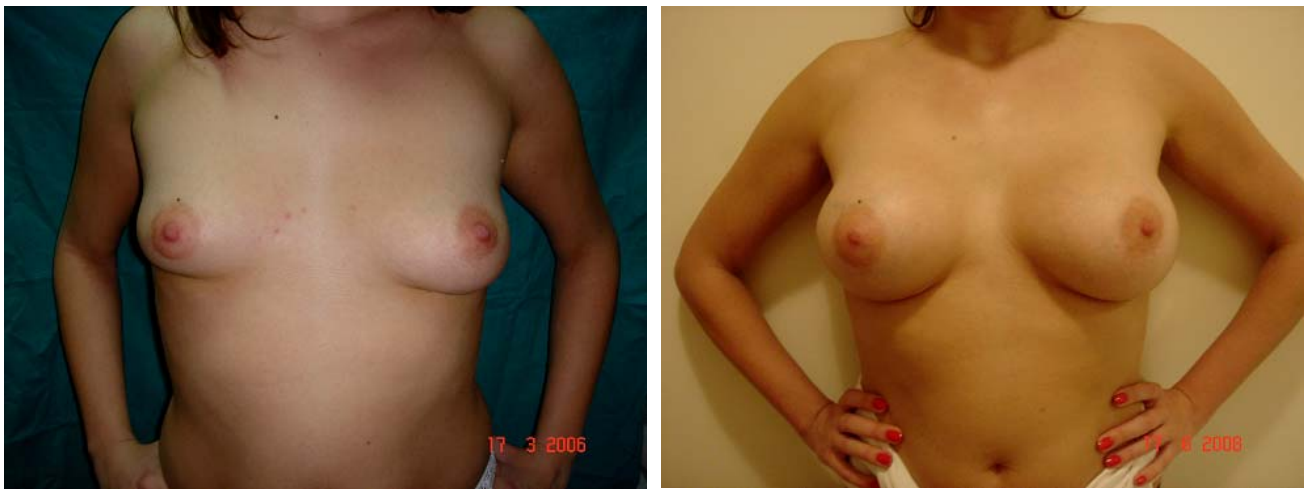


e)

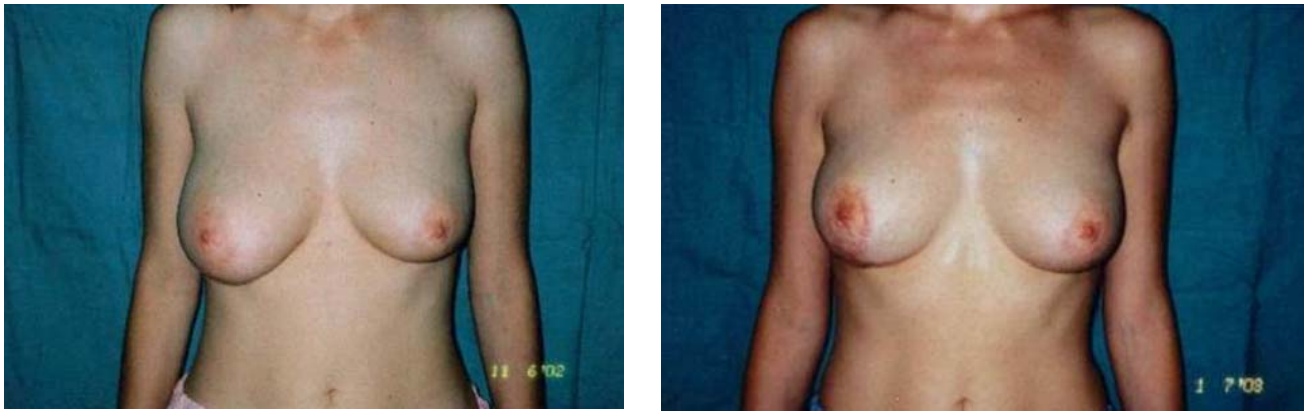
Fig. 1 – Poland's syndrome

a) anterior – preoperative view
b) anterior – postoperative view
c) lateral – preoperative view
d) lateral – postoperative view
e) harvested pedicled *latissimus dorsi* muscle flap at the left side



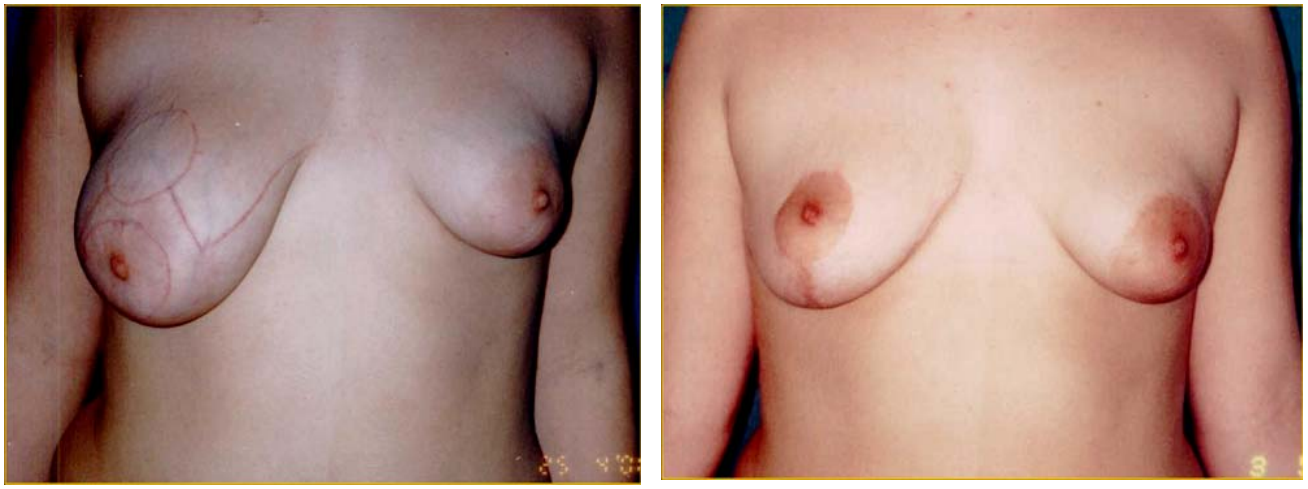
a) b)

Fig. 2b – Secondary breast asymmetry – developmental
a) anterior – preoperative view
b) anterior – postoperative view



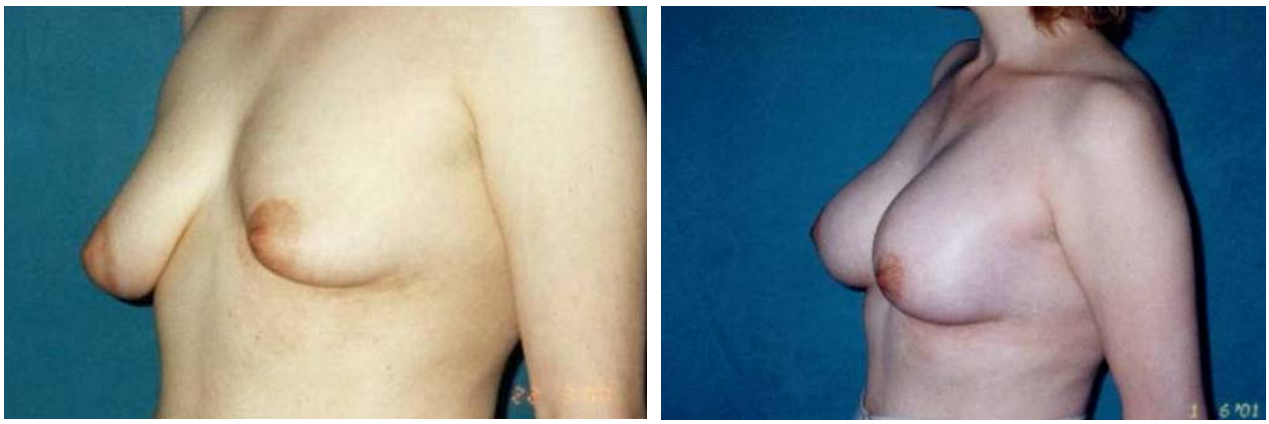
a) b)

Fig. 3 – Secondary breast asymmetry – developmental, with ptosis
a) anterior – preoperative view
b) anterior – postoperative view



a) b)

Fig. 4 – Secondary breast asymmetry – developmental, with hypertrophy and ptosis
a) anterior – preoperative view
b) anterior – postoperative view



a) **b)**

Fig. 5 - Secondary breast asymmetry – developmental
a) lateral – preoperative view
b) lateral – postoperative view

In 21 patients from the group III with acquired breast asymmetry who previously underwent unilateral mastoctomy, secondary breast reconstruction surgery was performed. *Latissimus dorsi* myocutaneous flap in combination with the silicone gel implant of adequate size was used in these cases (Figures 6 a, b).

In 50% of the patients from this group, the areola-mammary complex reconstruction was simultaneously performed. Subcutaneous mastectomy of the fibrocystic contralateral breast primarily reconstructed by the silicone gel implant was required in 10% of the cases.

There were also 10 patients in this group with breast asymmetry occuring after the pregnancy and breastfeeding. The post-operative recovery lasted 14–21 days in 95% of the cases.

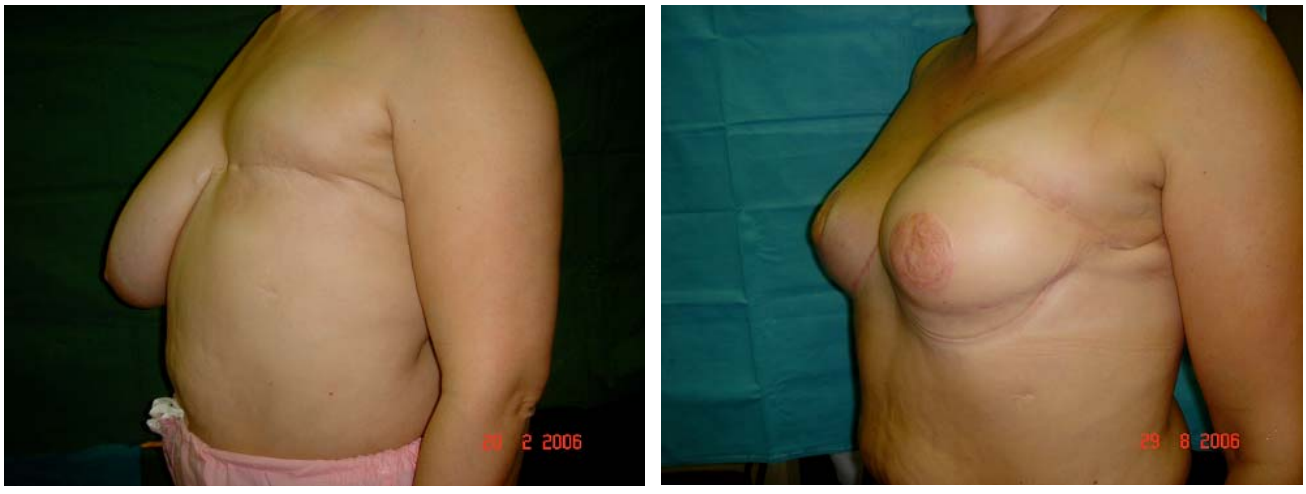
Complications of the above mentioned surgical procedures were negligible as compared with the achieved successful results. They were presented in Table 2.

Table 2

The most often complications in patients subjected to breast asymmetry surgical corrections

Complications	Incidence (%)
Hematomas	10.0
Seromas	3.0
Disorder of the mammillary sensibility	5.0
Capsule contracture	10.0
Partial necrosis of the mammilla	2.5
Hypertrophic scars	2.5
Marginal necrosis of the flap	2.5

The complications which were occasionally associated with reconstruction surgeries by local myocutaneous island flaps were manifested as early post-operative venous congestion and marginal necrosis of the flap, and were treated by necroctomy and secondary sutures. The complications of



a) **b)**

Fig. 6 - Acquired breast asymmetry (after unilateral mastectomy)
a) lateral – preoperative view
b) lateral – postoperative view

this type accompanied by radiodermitis and atrophic scar as a consequence occured in two patients who underwent radiation therapy after the primary surgery.

Discussion

The results of this analysis showed that giving importance to a detailed preoperative evaluation of asymmetry and the possibilities of esthetic surgical methods can ensure complete symmetry of surgically treated breasts with the certainty of female patients satisfaction.

Discussions on this issue is inevitable in terms of continuous advancements in the field of esthetic surgery. It is also neccessary to score the differences in the volume of the breasts, position of the submammary fold, the position, the size of the nipple and the shape of the bazal area of the breast.

The patients were informed about the advantages and disadvantages of axillary, periareolar and submammary pattern augmentation mammoplasty, as well as the shape and size of the scar arising out of the reduction or suspension mammoplasty. A special consideration was given to the choice of technique for patients who had not breastfed. The submammary approach was always used to insert the implant in those patients, and it was placed subglandularly to avoid additional traumatizing of the the breast gland tissue. In patients with lactation period definitely completed, the choice of surgical procedure was much more facilitated. However, highcohesive silicone gel implants were used in all the cases because they provided the best optimal results in our clinical practice in terms of a decreased percentage of infections and refusal of the implant as a foreign body. Our experinces gained in female patients undergoing augmentation mammoplasty by silicone gel implants correspond to those of Araco [16].

A correction of congenital chest-wall deformities accompanied by a marked breast asymmetry was feasible by a perforator or microvascular free flaps. Gautam et al. [17] favor perforator flaps, but our patient with Poland's syndrome chosen a muscular island flap primarily because of a scar that occurs as a consequence of the secundary defect [18, 19].

Persichetti et al. [20] studied both tuberous and tubular brests in their paper and proposed modifications of already described techniques. Their observations were of a great significance to us in selecting surgical techniques, and our knowledge of more similar techniques ensured greater intraoperative certainty.

Our choice of treatment with accessory breasts was excision even though liposuction allows for achieving equally successful esthetic results [5].

In choosing reconstruction method, we followed reconstruction ladder which means that desired outcome was to be achieved with a simplier method. Reconstruction by some of perforator flaps, DIEP (epigastric flaps) or TRAM (transverse rectus abdominis myocutaneous flaps) or distant *m. gracillis* or *m. glutealis* flap, was considered as a possible treatment option in the case of eventual ischemic post-operative complications that require complete necrosis after the primary reconstruction [21–23].

We think that breast reconstruction surgery with the *m. latissimus dorsi* myocutaneous island flap on the vascular pedicle along with the primary reconstruction of the mammila-areola complex [24–26] is the method of choice. According to our experience, complex, *m. latissimus dorsi* myocutaneous flap has many advantages such as the length of vascular pedicle, the possibility of taking a large dermal island, as well as esthetically acceptable secondary deffect-associated scar that may be hidden by a bathing suit [27].

In addition, general endotracheal anesthesia provided the best possible comfort for both a surgeon and a patient, although reduction mammaplasty may be performed under local infiltration anesthesia [2].

Over the last years, a great significance has been given to the preventive and early detection of the brest tumor, and in that sence, the relationship between breast asymmetry and more often occurence of breast malignant diseases was found [28, 29].

All breast asymmetry correction surgeries performed in our patients were preoperatively planned in details depending on the type of asymmetry (Table 1) [30].

There are other classifications available but like other authors, we followed a classification of asymmetric brests by Nahai as a very precise, clear and most comprehensive [31, 32].

Conclusion

Following the principles of plastic, reconstructive and aesthetic surgery and wishes of female patients with breast asymmetry as well, provide more successful dealing with the dilemma on selecting the most appropriate surgical technique.

Knowledge and the availability of a large number of surgical techniques for breast asymmetry corrections provide the possibility of selecting one or more surgical procedures that would allow for achieving optimal functional and aesthetic results for each patient.

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A K T U E L N E T E M E

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Portosistemski šant u lečenju portne hipertenzije

Portosystemic shunt in the treatment of portal hypertension

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Ključne reči:
portalni pritisak; portosistemski šant, hirurški; lečenje, ishod.

Key words:
portal pressure; portosystemic shunt, surgical; treatment outcome.

Uvod

Portna hipertenzija (PH) je klinički sindrom koji se definiše patološkim povećanjem pritiska u portnoj veni. Najčešći uzrok koji dovodi do portne hipertenzije jeste ciroza jetre. Direktno merenje portnog pritiska je invazivno, nepraktično, pa se danas određuje gradijent pritiska hepatičnih vena. Kada gradijent pritiska hepatičnih vena poraste iznad 10 mmHg (normalno iznosi 1-5 mmHg) nastaju komplikacije. Najčešće korišćeni parametar za određivanje gradijenta pritiska hepatičnih vena je razlika između zaglavljenog i slobodnog pritiska hepatičnih vena [1]. Necirotična portna hipertenzija (NCPH) je uopšteni naziv za heterogenu grupu bolesti intrahepatične ili ekstrahepatične etiologije. U principu, lezije kod NCPH su vaskularnog porekla. Necirotična portna fibroza i ekstrahepatička opstrukcija vene porte najčešće predstavljaju jedine uzroke portne hipertenzije pri čemu ne postoji disfunkcija parenhima jetre [2].

Patofiziologija

Godinama je u medicini vladala dogma da je kod nastanka portne hipertenzije poremećaj arhitekture jetre jedini faktor koji dovodi do povećanja otpora protoku krvi kroz jetru.

Mnoge pojave nisu se mogle objasniti ovako jednostavnim objašnjenjem, pa su se tako pojavile i druge teorije koje su imale uporišta u zapažanjima i eksperimentima s kraja 19. veka. Naime, još je Banti [3] 1894. primetio da povećanje protoka kroz slezinu izaziva povećanje protoka kroz venu portu.

Po novoj teoriji, kod ciroze jetre portna hipertenzija predstavlja kombinaciju povećanja intrahepatičnog vaskularnog otpora i povećanja protoka kroz splanhnični krvotok [4]. Primenom Omovog zakona pritisak u portnoj veni (P) posledica je vaskularnog otpora u jetri (R) i krvnog protoka u sistemu vene porte (Q) što se može predstaviti obrascem $P = R \times Q$[5]. Intrahepatični otpor zavisi od dve komponente: mehaničke i dinamičke [6]. Kod mehaničke komponente razvojem fibroznih promena u arhitekturi jetre dolazi do povećanja otpora na nivou mikrocirkulacije jetre. Poremećaji arhitekture uslovljeni su pojavom fibroze, regenerativnih nodula i kolagenskih depozita u Diseovim prostorima [7]. Dinamička komponenta koja dovodi do povećanja intrahepatičnog pritiska rezultat je vazokonstrikcije portnih venula usled delovanja endogenih vazokonstriktora poput noradrenalina, endotelina I, angiotenzina II, leukotrijena, tromboksana A2 koji kod bolesti jetre postaju dominantni u odnosu na endogene vazodilatatore. Vazokonstrikcija portnih venula nastaje aktivnom kontrakcijom portnih i septalnih miofibroblasta, zvezdastih ćelija jetre i glatkih mišićnih ćelija [8-10].

Portna hipertenzija karakteriše se povećanjem minutnog volumena srca, splanhničkom i sistemskom vazodilatacijom i smanjenjem sistemskog vaskularnog otpora, što rezultuje stanjem hiperdinamičke cirkulacije [11]. Splanhnička arterijska vazodilatacija vodi povećanju krvnog protoka kroz portni sistem i dalje ka mnogo ozbiljnijoj portnoj hipertenziji. Sama splanhnička vazodilatacija nastaje zbog ekscesivnog lučenja endogenih vazodilatatora poput azot-oksida, glukagona i vazointestinalnog aktivnog peptida [12]. Iako se većina poznatih vazoaktivnih supstanci/sistema aktivira u portnoj hipertenziji, odlučujuću ulogu imaju endotelni faktori kao što su NO, CO, i drugi medijatori nastali delovanjem ciklooksigenaze [13, 14].

Komplikacije

Pravilno razumevanje etiopatogeneze PH može biti korisno u prevenciji i tretmanu komplikacija kao što su ezofagusni variksi (kod 90% bolesnika), hepatička encefalopatija (39%), ascites (73%), hipersplenizam (48%), hepatorenalni sindrom (12%) [15].

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Težina portne hipertenzije i njenih komplikacija kao i mogućnost njihovog rešavanja određena je Child-Turcotte-Pugh (CTP) skorom (tabela 1) [16, 17]. U ovu skalu uključeni su klinički i laboratorijski podaci koji se odnose na funkcionalni status i raspoloživu rezervu jetre, sa predviđanjem morbiditeta i mortaliteta [18]. Skalu je modifikovao *United Network for Organ Sharing* (UNOS) kao uputstvo za određivanje neophodnosti transplantacije jetre. Iako je u početku korišćena za procenu potencijalnog uspeha hirurške intervencije, danas se koristi za prognozu kod bolesnika kod kojih postoji disfunkcija jetre.

Tabela 1

Stepen težine portne hipertenzije i predviđeno preživljavanje

Child-Turcotte-Pugh klasifikacija	Skor	Preživljavanje (%)	
		jednogodišnje	dvogodišnje
A	5 – 6	95	90
B	7 – 9	80	70
C	10 – 15	48	38

Poslednjih godina pored CTP skora, koristi se i MELD skor, na osnovu koga se bolesnici mogu podeliti u tri grupe: 1) 8; 2) 9-16; 3) ≥ 17. Ove vrednosti se dobijaju za svakog bolesnika na osnovu proračunavanja vrednosti bilirubina, INR i kreatinina:

$$MELD = 3{,}8 \times \log_e(\text{bilirubin mg/dL}) + 11{,}2 \times \log_e(\text{INR}) + 9{,}6 \times \log_e(\text{kreatinin mg/dL}).$$

MELD skor verodostojno predskazuje rani (jednomesečni) i kasni (tromesečni) postoperativni mortalitet kod bolesnika sa cirozom jetre koji su podvrgnuti hirurškim procedurama u opštoj anesteziji. Mortalitet se uvećava progresivno sa pogoršanjem funkcije jetre. Takođe, jasno predviđa razliku preživljavanja bolesnika koji su podvrgnuti urgentnim hirurškim procedurama u odnosu na one koji su podvrgnuti elektivnim [19].

Krvarenje iz ezofagusnih variksa je komplikacija portne hipertenzije koja životno ugrožava bolesnika. To su proširene vene koje se najčešće nalaze u završnih 5 cm ezofagusa. Kod normalnog ezofagusa, venski pleksus se nalazi submukozno, a u distalnom ezofagusu je postavljen površnije, u lamini propriji [20, 21]. Površna lokalizacija u distalnom ezofagusu uzrok je čestom krvarenju variksa. Istovremeno, kod 10-15% bolesnika sa ezofagusnim variksima mogu se naći variksi i u želucu. Kod nekih bolesnika sa cirozom jetre i PH upotrebom endoskopske kapsule kod 15,8% identifikovani su variksi tankog creva, dok je kod 89,5% identifikovan izvor potencijalnog krvarenja, tako da i ova metoda može uspešno zameniti enteroskopiju tankog creva i angiografiju koje su invazivne, a mogu biti neadekvatne [22].

Pritisak u portnom sistemu predstavlja važnu determinantu za pojavu variksa [23].

Kada hepatični venski gradijent pređe 10 mmHg postoji rizik od nastanka variksa, a kada hepatični venski gradijent pritiska naraste preko 12 mmHg može nastati krvavljenje [24]. Ipak, povećanje pritiska u portnoj veni preko 10 mmHg neće kod svih bolesnika dovesti do pojave variksa, tako da verovatno imaju uticaja i drugi, nedeterminisani faktori. Mnoge studije pokazale su da se variksi javljaju kod 90% bolesnika sa cirozom [25]. Od tog broja krvarenje se javlja kod 25-30%, sa velikim rizikom tokom prve godine posle dijagnoze [26]. Od onih koji prežive prvu epizodu krvarenja, 30% ima ponovno krvarenje tokom 6 nedelja, a 70% tokom prve godine [27]. Stopa mortaliteta za krvarenje iz variksa kreće se od 5 do 50% u zavisnosti od vrednosti Child-Pugh skora [28].

Hepatička encefalopatija je neuropsihijatrijski sindrom koji se karakteriše varijabilnim stanjem mentalnog statusa koji se može rangirati samo kao utvrđivanje postojanja deficita, pa do konfuzije, letargije i na kraju, kome.

Mnogi autori smatraju da produkti koji nastaju u digestivnom traktu, a koji se obično metabolišu u jetri, poput amonijaka, predstavljaju uzročnike ovog sindroma. Amonijak produkuju bakterije koje metabolišu proteine iz hrane. Tako nastali amonijak iz creva apsorbuje se u portni krvotok i obično se nakon toga ekstenzivno degradira u jetri [29]. Kod bolesnika sa cirozom, uporedo sa akumulacijom amonijaka u krvi, povećava se propustljivost moždane barijere za amonijak [30].

Drugi etiološki faktori koji se navode kao mogući uzroci za nastanak hepatičke encefalopatije uključuju γ-aminobuternu kiselinu, endogene benzodozepine, neurotoksične masne kiseline kratkog lanca, triptofan, merkaptane, fenole i endogene opijate [31-35].

Ascites podrazumeva akumuliranje serozne tečnosti u abdominalnoj duplji i pojavljuje se kod uznapredovale ciroze i teške portne hipertenzije. Iako PH ima značajnu ulogu u razvoju ascitesa, potrebno je prisustvo i drugih faktora za razvoj ascitesa: sniženje onkotskog pritiska plazme, povećano stvaranje limfe, povišeni pritisak u limfnom sistemu jetre i izmene renalnih i hormonskih mehanizama [36]. Kod ciroze, ascites je posledica kombinacije poremećaja renalne funkcije i portne i splanhničke cirkulacije. Glavni patogenetski faktor je retencija natrijuma. Polovina bolesnika sa cirozom razvija ascites tokom 10 godina praćenja, od čega više od 50% umire tokom dve godine. Internacionalni ascites klub usvojio je preporuku gradacije ascitesa [37]: gradus 1 – blagi ascites koji se registruje samo ultrasonografijom, gradus 2 – umereni ascites koji se manifestuje umerenom simetričnom distenzijom abdomena, gradus 3 – veliki ascites sa značajnom abdominalnom distenzijom.

Ako ascitna tečnost sadrži više od 25 g/L proteina i specifična težina iznosi više od 1016 radi se o eksudatu, dok transudat sadrži manje od 25 g/L i specifična težina mu je manja od 1016. Krajnji stadijumi ascitesa su refraktorni ascitesi, hepatorenalni sindrom i spontani bakterijski peritonitis. Blagi ascites može biti supklinički, registruje se ultrasonografijom i nije potrebno nikakvo specifično lečenje. Ordinira se redukcija dnevnog unosa soli (manje od 90

mmol/dan) i redukcija unosa vode. U slučaju umerenog ascitesa, renalna funkcija je obično očuvana, a lečenje bolesnika može se sprovoditi ambulantno. Pored redukcije unosa soli (do 90 mmol/dan) primenjuje se spironolakton bez ili sa diureticima Henleove petlje. Bolesnici sa velikim ascitesom imaju značajne abdominalne teškoće, u njihovom lečenju koriste se visoke doze diuretika i povremene paracenteze u kombinaciji sa ekspanderima volumena plazme [38, 39]. Ako se ukloni više od 5 L ascita trebalo bi primeniti albumin u dozi od 8 g/L uklonjenog rastvora [40].

Hepatorenalni sindrom (HRS) predstavlja krajnji stadijum redukovane renalne perfuzije kod bolesnika koji imaju uznapredovalu bolest jetre, cirozu, teški alkoholni hepatitis ili ređe, metastatske tumore, ali se može pojaviti i kod bolesnika sa fulminantnom hepatičkom insuficijencijom bilo kog uzrasta [41, 42]. Splanhnička vazodilatacija igra značajnu ulogu u razvoju bubrežne insuficijencije kod bolesnika sa hepatičnom bolesti. Hepatorenalni sindrom manifestuje se oligurijom, veoma niskom ekskrecijom natrijuma, i progresivnim povećanjem koncentracije kreatinina u plazmi. Na osnovu brzine razvoja renalne slabosti opisujemo dve forme HRS [43, 44]: tip 1 HRS koji se definiše kao najmanje 50% sniženjenje klirensa kreatinina do vrednosti ispod 20 mL/min u periodu kraćem od dve nedelje, ili dvostruko uvećanje kreatinina u serumu do nivoa većeg od 221 μmol/L i tip 2 HRS, sa blažim oblikom renalne insuficijencije, karakteriše se ascitesom koji je rezistentan na diuretike.

Hepatorenalni sindrom javlja se kod 18-39% bolesnika sa cirozom i ascitesom tokom pet godina [45]. Mortalitet bolesnika sa hepatičnom insuficijencijom najviši je ako se razvija HRS [46]. Ishod obolelih čvrsto je povezan sa reverzibilnošću hepatične slabosti, bilo da ona nastaje spontano, medikamentno ili nakon uspešne transplantacije jetre [47].

Dekompresija portnog sistema

Terapijski modaliteti koji se danas primenjuju u lečenju portne hipertenzije i njenih komplikacija su farmakoterapija, endoskopske procedure, transjugularni intrahepatični portosistemski šant (TIPS) i šant hirurgija [48]. Svaki od ovih modaliteta ima svoje prednosti i mane. Njihova primena zavisi od individualnih karakteristika svakog bolesnika, uzroka portne hipertenzije, funkcije jetre, bolničke infrastrukture i razvoja programa multidisciplinarnih timova.

Farmakološka terapija primenjuje se kod akutnog krvarenja, ali i za primarnu i sekundarnu profilaksu. Kod akutnog krvarenja dominantno se koriste vazopresin i nitroglicerin, ali nakon dobrog početnog odgovora javlja se visok procenat recidivantnog krvarenja posle prekida terapije. Glipresin pokazuje dugotrajniji efekat na vazodilataciju splanhničkih krvnih sudova i sinusoida jetre od vazopresina, dok oktreotid ima dugotrajniji efekat od somatostatina u smislu vazokonstrikcije, a pojedini radovi opisuju i efekte u inhibiciji angiogeneze [49]. Beta blokatori koriste se široko kod primarne i sekundarne profilakse, mada se kod njih javlja visoka učestalost ponovnog krvarenja [50]. Randomizovane studije pokazale su da kombinovanje vazodilatatora i transendoskopskog ligiranja daje obećavajuće rezultate u primarnoj, a dobre rezultate u sekundarnoj profilaksi [51, 52].

Transendoskopska skleroterapija primenjuje se za lečenje akutnog krvarenja, kod primarne i sekundarne profilakse. Ipak, ovaj tip terapije dominantno se koristi za sekundarnu profilaksu, mada postoji visok procenat ponovnog krvarenja (između 30 i 50%) [53]. Transendoskopsko ligiranje variksa u kombinaciji sa lekovima pokazalo se kao bolja opcija u odnosu na skleroterapiju, pošto se postižu isti rezultati, ali sa manjim procentom komplikacija [54-56].

Transjugularni intrahepatični portosistemski šant (TIPS), laterolateralni venskovenski šant, široko se koristi u razvijenim zemljama. Ova procedura je skupa i zahteva visoki kvalitet infrastrukture bolnice. Uspeh plasiranja je visok (98%), može se koristiti u lokalnoj anesteziji/sedaciji, kod bolesnika starijeg doba, masivnog ascitesa, kompromitovane funkcije jetre i urgentnih stanja, postiže se dekompresija ezofagusnih i gastričnih variksa, odlaganje transplantacije jetre [57, 58]. Kontraindikacije za primenu TIPS su postojanje fokalnih promena u jetri (tumori, ciste, hemangiomi), okluzije bilijarnog trakta, tromboza portne vene, tromboza splanhničkih vena, postojanje AV fistula u jetri i van jetre, sistemska infekcija, popuštanje desnog srca, hronična plućna hipertenzija. Mortalitet posle plasiranja stenta tokom mesec dana od procedure iznosi između 10 i 15%, a registrovana je i visoka incidencija encefalopatije (preko 40%). Posle šest meseci od intervencije kod 50% slučajeva javlja se opstrukcija kao posledica proliferacije epitela i tromboze [59, 60]. Pojedine serije u kojima je TIPS upoređivan sa dekompresivnim hirurškim šantom koji je postizao parcijalnu dekompresiju portnog sistema, pokazale su da TIPS iziskuje više intervencija i vodi ka češćoj pojavi rehemoragije, ireverzbilnoj okluziji, transplantaciji i smrti (tabela 2) [61]. Praćenje u dužem vremenskom periodu pokazalo je da bolesnici nakon hirurškog šanta duže žive. Naročito oni koji su klasifikovani u CTP klasu A i B sa MELD skorom manjim od 13 imaju značajno bolje preživljavanje nakon H-graft portokavalnog šanta (H-PCS) u poređenju sa TIPS (tabela 3) [62].

Tabela 2

Uporedni prikaz komplikacija transjugularnog intrahepatičnog portosistemskog šanta (TIPS) i H-grafta portokavalnog šanta (H-PCS)

Vrsta komplikacija	Učestalost komplikacija (%)	
	TIPS	H - PCS
Stenoza i tromboza	49	11
Rehemoragija	30	7
Ascites	40	28
Encefalopatija	4	3
Mortalitet (posle 10 god)	82	74

Tabela 3

Preživljavanje bolesnika sa transjugularnim intrahepatičnim portosistemskim šantom (TIPS) i H-graftom portokavalnog šanta (H-PCS)

Child-Turcotte-Pugh klasifikacija	Preživljavanje (meseci)	
	TIPS	H-PCS
Svi bolesnici	29	56
A	29	73
B	21	68
C	47	36

Poslednje dve decenije razvoj konzervativnih metoda lečenja dovodi do smanjenja indikacija za primenu šant hirurgije, pa se sada postavlja pitanje gde je mesto portosistemskog šanta u lečenju portne hipertenzije pored medikamentne terapije, endoskopske skleroterapije, TIPS i transplantacije jetre.

Prvi portokavalni šant kod ljudi prezentovao je 1903. godine Vidal. Bolesnik je imao neuravnotežen postoperativni tok i umro je posle dve nedelje od posledica pileflebitisa [61]. Do 1945. godine bilo je više pojedinačnih pokušaja kreiranja šanta, a tada su Blakemore i Lord [62] objavili seriju od 5 portokavalnih šantova gde su u kreiranju anastomoze koristili Blalock principe vaskularne anastomoze. Iste godine Whipple je prezentovao centralni splenorenalni šant što je označilo početak ere šantova. Početni dobri rezultati doveli su do popularizacije ove operacije koja je odmah prepoznata kao najbolja procedura za prevenciju ponovnog variksnog krvavljenja.

Posle početnog oduševljenja usledio je period kritičke refleksije. Početkom 60-ih godina počele su da se pojavljuju studije gde je dokumentovno prisustvo kliničkih i metaboličkih sekvela kod šant hirurgije – poput hepatične encefalopatije i popuštanja jetre. Komplikacije su bile posledice skretanja celokupnog portnog krvotoka u sistemsku cirkulaciju pri čemu je dolazilo do gubitka portne perfuzije jetre.

Šantovi mogu biti totalni (totalno skretanje portnog krvotoka u sistemsku cirkulaciju), parcijalni (delimično skretanje portnog toka plasiranjem uske proteze u portokavalni ili mezokavalni položaj i selektivni (distalni splenorenalni, koronarokavalni, splenokavalni).

Primenu hirurškog šanta možemo analizirati kroz tri modaliteta primene, a u sklopu najčešće i najopasnije komplikacije: kao profilaksu prvog krvarenja iz ezofagealnih variksa, kao urgentni šant kod akutnog krvarenja iz variksa i kao prevenciju ponovnog krvarenja iz variksa.

Preventivni šant

S obzirom na visoku smrtnost posle prve epizode krvarenja, ideja vodilja mnogim hirurzima bila je da kreiranje portosistemskog šanta nedvosmisleno dovodi do preveniranja variksnog krvarenja. Početna istraživanja utemeljena na malom broju bolesnika, gde nisu bili mogući jasni naučni rezultati, pokazala su sniženje smrtnosti kod šantovanih bolesnika u odnosu na smrtnost od krvarenja u prvoj epizodi. Međutim, kasnije su sprovedene četiri kontrolisane studije u Americi sprovedene na 292 bolesnika (dve 1968, 1969. i 1972.) Metaanalizom ovih serija, koju su sproveli Collins i sar. [63] 1985, pokazano je da profilaktički šant značajno smanjuje rizik od krvarenja. Ovaj zaključak nije se odnosio i na preživljavanje s obzirom da je smrtnost u grupi sa šantom neznatno porasla. Dobijeni rezultati objašnjavani su niskim rizikom od krvarenja u kontrolnoj grupi i visokim rizikom za popuštanje jetre kod šantovanih bolesnika.

Zaključak ovih studija bio je da preventivna intervencija nije preporučljiva pošto nije moguće pouzdano identifikovati bolesnike koji imaju visok rizik od krvavrenja iz variksa, a kod kojih postoji veća verovatnoća popuštanja jetre nakon šant hirurgije.

Šant procedura zbog ovih razloga postala je nepoželjna kod većine autora kao profilaktičko rešenje [64].

Zbog ovih nedoumica Beppu i sar. [65] 1981. godine pokušali su da definišu izgled variksa koji bi bio značajan za preventivno korišćenje hirurgije. Opisali su „crveni znak“, veličinu variksa i boju koji predstavljaju realnu opasnost od pojave krvarenja iz variksa u japanskoj studiji (Japansko društvo za istraživanje portne hipertenzije, 1980), što je otvorilo nove perspektive.

Inokuchi je primenom kriterijuma po Beppu i sar. [66] za rizike u kombinaciji sa nedekompresivnom hirurgijom dobio vrlo dobre rezultate. Hirurgija je značajno redukovala incidenciju krvarenja i značajno je produžila petogodišnje preživljavanje.

Severnoitalijanski endoskopski klub (NIEC) postavio je nove selekcione kriterijume za bolesnike sa visokim rizikom od prvog krvarenja iz ezofagusnih variksa. Bolesnici sa visokim rizikom za prvu epizodu krvarenja, identifikovani ovom klasifikacijom, najčešće su klase C, i oni su *per se* kontraindikovani za operaciju. Bolesnici A i B CTP klase imaju nizak rizik od krvarenja (oko 10% godišnje), tako da im se invazivna procedura ne preporučuje [67, 70].

Na osnovu ovih istraživanja kreiranje profilaktičkih šantova se ne preporučuje.

Urgentni tretman

Bez profilaktičke terapije oko 18% cirotičnih bolesnika sa portnom hipertenzijom krvare unutar godine, a oko 50% njih umre zbog hemoragije. Otkako je ustanovljena efikasnost šant hirurgije u zaustavljanju krvarenja, logično je bilo očekivati napredak u preživljavanju nakon njenog korišćenja kao urgentne terapije. Iskustva Spina i sar. [69] govore da se krvarenje zaustavlja kod 97% bolesnika, sa operativnim mortalitetom od 9%. Napredak u preživljavanju bio je evidentan već posle godinu dana praćenja. Ovakve rezultate autor je objasnio primenom agresivnijeg pristupa, tj. operacija je rađena tokom 32 sata od hospitalizacije, poboljšanjem anestezije i boljim izborom bolesnika.

U sedam studija analizirana je upotreba urgentnog šanta nakon primene konzervativne terapije, ali nijedna nije pokazala značajne prednosti [71-77]. Izdvaja se studija Orloffa i sar. [71] iz 90-ih godina u kojoj je upoređen urgentni šant (urađen tokom 6 sati od hospitalizacije) sa konzervativnom terapijom koja prethodi elektivnoj operaciji. Ovi rezultati favorizuju hitni šant. Ipak, ne postoje randomizovane studije koje bi sa sigurnošću potvrdile prednost primene urgentnog šanta u odnosu na onaj koji se primenjuje posle neuspeha skleroterapije. U principu, zaustavljanje krvarenja konzervativnim metodama daje vreme za izbor najboljeg elektivnog tretmana, dok je hitna hirurgija put bez povratka [73, 77].

Dugo je postojala dilema u slučaju neizbežne primene šanta, koju vrstu treba izabrati: selektivni ili totalni.

Totalni šant garantuje trenutno i bezbedno zaustavljanje krvarenja, a selektivni veliku verovatnoću da će očuvati funkciju jetre. Logično je da će kod masivne hemoragije primena totalnog šanta biti korisnija, dok je selektivni šant rezervisan za manje ozbiljne hemoragije koje ne zahtevaju trenutnu

dekompresiju variksa. Neke novije studije pokazuju i odstupanje od ovog stava, tj. da kod selektivnih šantova dolazi do prestanka krvarenja kod 80% bolesnika [78, 79].

Urgentno kreiranje šanta treba koristiti tek nakon neuspeha skleroterapije. Ipak, ne treba predugo čekati jer odluka o operativnom lečenju mora biti doneta u pravo vreme pošto bolesnici bolje tolerišu šant hirurgiju pre nego što nastupi pogoršanje izazvano perzistentnim, pa makar i malim, krvarenjem.

Elektivni tretman

Entuzijazam za elektivnim operacijama u početku poticao je od boljeg izbora bolesnika i samog tipa operacije. Taj entuzijazam je potpomognut i studijama koje su upoređivale totalni šant i konzervativnu terapiju, u kojima je kod šanta značajno manji procenat variksne rehemoragije (5-20% prema 64-75%), ali nije značajno bolje preživljavanje, a sama šant hirurgija uzrokuje dva efekta: pogoršanje funkcije jetre (smrtnost kod bolesnika sa šantom prouzrokovana popuštanjem jetre iznosi 51-81% prema 10-48% kod konzervativnog lečenja) i povećanje procenta hronične hepatične encefalopatije [80-83]. Kao rezultat ovog zaključka, šant hirurgija je u mnogim centrima napuštena, sve dok nije shvaćeno da se regulacijom kalibra anastomoze mogu postići mnogo bolji rezultati [84].

Rešenje problema pronašli su Warren i sar. [83] 1967. analizirajući splenoportogram bolesnika sa spontanim splenorenalnim šantom. Kreiranje distalnog splenorenalnog šanta (DSRS) bazira se na ligiranju spleničnih, koronarnih, gastroepiploičnih i piloričnih vena pri čemu se održava visok pritisak u portomezenteričnom području, a nizak pritisak u gastrospleničnoj zoni garantuje dekompresiju gastroezofagusnih variksa [85].

Selektivni šantovi opisani 1967. imaju prednost što kod većine bolesnika održavaju portni krvotok, jer se formiraju dve odvojene zone cirkulacije. Ezofagogastrosplenična zona derivira se kroz anastomozu u sistemski krvotok. Uopšteno, postiže se niska stopa ponovnog krvarenja (manje od 5%), niska stopa encefalopatije (manje od 10%) i dobar kvalitet života u postoperativnom periodu. Nijedna druga opcija ne nudi tako dobre rezultate u kratkom roku.

Encefalopatija ima povećanu incidenciju u kasnom postoperativnom periodu (između 7 i 10 postoperativnih godina). To je posledica transformisanja selektivnog u totalni šant, a rezultat je povećanog otpora u hepatičnom sinusoidu.

Ovaj povećani otpor posledica je napredovanja oboljenja jetre koje povećava sinusoidni otpor i mezoportalni pritisak. Kolaterlne zone niskog pritiska razvijaju se i javlja se gubitak portne perfuzije. Pošto ovi šantovi ostavljaju hepatični hilus intaktnim, dobra su opcija kandidatima za transplantaciju jetre i izvanredni su kao dugoročni most do transplantacije [86, 87].

Ablativne procedure (devaskularizacije) koriste se kao alternativan izbor za bolesnike kod kojih se ne može uraditi šant. Neke grupe, uglavnom u Japanu, koriste ih kao prvi terapijski izbor pošto imaju nižu incidenciju encefalopatije. One imaju višu stopu ponovnog krvarenja nego hirurški šantovi i izgleda da je to povezano sa ekstenzijom devaskularizacije. Što je ekstenzivnija devaskularizacija, niža je stopa ponovnog krvarenja [88].

Devaskularizacija se obavlja uključujući aferentne i eferentne vaskularne elemente, kao i ezofagusnu transekciju sa splenektomijom. Operacija Sugiura Futagave (SFO) i njene verzije (Hassab, Paquet) u najširoj su upotrebi.

Kompletna portoazigosna diskonekcija je operacija koja se zasniva na proceduri Sugiura Futagava, ali sa varijantama koje proceduru olakšavaju i čine je bezbednijom. U abdominalnoj fazi čuva se slezina. Slezina se uklanja jedino ako se nađe velika splenomegalija (kao kod prehepatične portne hipertenzije) i/ili težak hipersplenizam (broj trombocita ispod 20×10^3/dL) [87].

Važan korak u tome je prekidanje aferentnih arterijalnih grana koje dolaze do razvijenih variksa.

Devaskularizacijske procedure daju dobre rezultate sa niskom stopom ponovnog krvarenja (10-15%) i niskom stopom encefalopatije (2-4%) i dobrim dugoročnim preživljavanjem. Primenom samo diskonekcije ostvaruje se petogodišnje preživljavanje od 71-94%, učestalost rehemoragije je 6-13%, a incidencija hepatične encefalopatije 2,2-4,1%. Mortalitet kod ove procedure iznosi 1,66-5,1% [87, 88]. Neki autori uspešno su primenili diskonekciju laparoskopskom tehnikom [89].

U razvijenim zemljama transplantacija jetre je rutinska procedura lečenja krajnjih stadijuma bolesti jetre. Jednogodišnje preživljavanje kod bolesnika sa transplantiranom jetrom je 85%, sa dužinom preživljavanja i do 29 godina [90].

Zaključak

Hirurgija šantova u dekompresiji portnog sistema tehnički se tokom vremena značajno menjala. U toku evolucije lečenja izgubila je primat u tretmanu portne hipertenzije. Do devedestih godina prošlog veka hirurgija gotovo da nije imala alternativu, ali pojavom novih lekova, endoskopske sklerozacije, TIPS i transplantacije jetre izbor za hirurgiju je znatno sužen.

U profilaksi prvog variksnog krvarenja šant hirurgija nije indikovana zato što je teško sa apsolutnom sigurnošću odrediti bolesnika koji ima visok rizik od krvarenja iz variksa, očuvanu funkciju jetre tako da bez rizika može podneti šant.

Bolesnik sa dobrom funkcijom jetre (A i B klasa po CTP klasifikaciji) kandidat je za šant hirurgiju, a samo u izuzetnim slučajevima i bolesnik sa ozbiljnim oštećenjem jetre.

Selektivni šant je opcija koja obezbeđuje dobru variksnu dekompresiju i zadovoljavajuće održavanje funkcije jetre. Rezultati kod ovog šanta umnogome zavise od veštine hirurga.

Kod urgentnih krvarenja iz variksa prvo treba pokušati sa primenom lekova i skleroterapijom, a u slučaju neuspeha neophodno je primeniti šant hirurgiju, pri čemu se mora voditi računa o opštem stanju bolesnika kako bi se iskoristilo optimalno vreme.

Šant može poslužiti kao odličan dugoročni most do transplantacije jetre za bolesnike sa očuvanom hepatičnom rezervom.

Primena šantova u dekompresiji portnog sistema još uvek igra važnu ulogu u tretmanu pažljivo selektovanih bolesnika sa variksnim krvarenjem koji u budućnosti neće biti u prilici da im se uradi transplantacija jetre.

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New nutrition recommendations for healthy aging

Nove preporuke o ishrani za zdravo starenje

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Key words:
aging; aged; preventive health services; diet.

Ključne reči:
starenje; stare osobe; preventivno-medicinska zaštita; ishrana

Introduction

Population aging shows a global rising trend. The World Health Organization (WHO) foresees that 1.2 billion elderly will live on Earth in 2025, two thirds of them in underdeveloped regions [1]. Actual studies have confirmed that most prevailing diseases in adults and/or elderly result from inadequate nutrition, that nutritional risk factors influence aged persons falling ill still in their early years and that risks only accumulate in time and affect synergistically the physiological changes in aging [2-4]. Also, the WHO experts consider that nutrition risk prevention is a vital investment into the future [1].

Nutrients important for old age

Elderly have special nutritional problems and requirements, in the first place due to involutionary physiological processes but also to metabolic changes synergistically affecting, together with social medical factors and nutritional status [5]. The results of a well-known SENECA study (Survey in Europe on Nutrition and the Elderly, a Concerted Action) showed that nutritional factors qualitatively influence mortality, more than 25% [6].

This refers especially to energy intake, protein, vitamin D and vitamin B12 intakes. The most recent dietary recommendations for healthy people – DRI (report by the Food and Nutrition Board of the National Academies developed jointly by American and Canadian scientists) gave separately, for the first time, recommended values for adults aged 50 to 70 and those aged over 70 [7].

Excessive energy intake contributes to the greatest extent to obesity; its prevalence is 4 times higher among elderly within the last few decades [2]. Body mass index (BMI) as main obesity indicator increases with aging regardless the level of physical activity; subsequently, higher BMI values are followed by higher morbidity and mortality rates [2, 8, 9]. In elderly, the quantity of visceral adipose tissue represents a disease risk much more important than BMI values. However, it is desirable to monitor BMI values in order to prevent risk and undesirable body mass fluctuations, and permanently maintain BMI values stable even if not within optimal limits (18.5–24.9 kg/m^2) [3, 9].

Assessment of cardiovascular morbidity showed that physical fitness, i.e. "readiness" of cardiovascular system, is essential. An important effect in aged persons' body mass reduction is achieved by exercise only, regardless a reduction diet [10, 11]. Although dietary treatment contributes to the reduction of visceral adipose tissue, physical exercise improves cardio-respiratory state, reduces overall and intra-abdominal fat tissue, thus increasing muscular strength and endurance; it also reduces insulin resistance [12].

Reduced and insufficient protein intake will result in sarcopenia and even osteopenia appearance in the elderly. Sarcopenia, as an age-related progressive process, occurs already after 30 years of age by 3-8% reduction in skeletal muscle mass every ten years. A comprehensive current research has examined the mechanisms of its occurrence, as well as the prevention possibilities. Latest studies have confirmed that muscular restoration and preservation in elderly depend on qualitative and quantitative protein content in food, as well as appropriate physical activity [13-15]. In order to maintain anabolism in skeletal muscles it is necessary that each meal (of usual three daily meals) contains an adequate quantity of proteins. It is important that anabolic effect is maintained with respect to the content of essential amino acids [16]. Daily intake should also adequately provide proteins of animal and plant origin: 60 g of protein daily intake should be divided into three even meals where the content of essential amino acids should be 5–8 g, thus obtaining their

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minimum daily intake of 10–15 g necessary for anabolic effect in elderly. There is no effect if protein intake is 10 g through first, 40 g through second and 10 g through third meals. It is very important to know that protein intake exceeding 30 g per meal is undesirable regarding protein synthesis, energy balance, and especially glomerular filtration and renal function disorders. Intake of 20-25 g proteins of high biological value per meal results in 10 g essential amino acids which maximally stimulate protein synthesis in skeletal muscles [17]. Intake of essential amino acids can also be obtained by supplements. Leucine intake through adequate protein meals is suggested if there is no insufficiency of renal function. Such combination will potentially contribute to sarcopenia prevention and protein synthesis stimulation to the greatest possible extent [13, 17].

Mobility of many elderly is limited due to disease or inability. Therefore, regardless the fact that physical activity largely contributes to sarcopenia prevention, protein synthesis in muscles and muscular preservation – adequate protein intake and/or supplementing by essential amino acids remain the only solution.

Protein deficiency in elderly diets increases the risk of osteoporosis, lowers the IGF-1 (insulin-like growth hormone-1) level and reduces bone mass; simultaneously, it stimulates the synthesis of inflammatory cytokines such as TNF-α which increases bone resorption [15]. It is therefore considered that supplementing with proteins is useful, since levels of IGF-1 in the serum, albumin, prealbumin and IgM increase, with the probability of bone mass reduction in the proximal part of femur decreases [15]. With respect to these considerations an increased daily intake of proteins should be suggested to elderly because of their sarcopenia and osteopenia preventing role, results of large research studies proposed a moderate increase of protein intake: latest recommendations of WHO elderly nutrition expert group are that protein intake should amount 0.9–1.1 g/kg body mass [2]. On the other hand, latest DRI nutrition recommendations do not suggest adults and elderly any increase of protein daily intake which is still 0.8 g/kg body mass [7]. Therefore, it is not necessary for elderly to increase protein intake, but only ensure sufficient daily intake, its quality and uniformity within the three main meals.

A potentially insufficient nutrient intake in elderly is possible for calcium, vitamin D, potassium, vitamin E, vitamin K and dietary fibres. These deficits are explained by the fact that elderly consume less milk and dairy products (which are the best source of calcium) probably because of lactose intolerance syndrome. According to the Centre for Disease Control, liquid milk is also, of all foodstuffs, the most reliable source of vitamin D [18-20]. Lesser milk consumption, insufficient exposure to Sun, and a reduced level of endogenous vitamin D due to a reduced skin capacity to synthetize it, are reasons for its deficit in elderly population. It is important to underline that obesity contributes to vitamin D deficit, since vitamin D precipitation in adipocytes occurs in obese elderly and its bioavailability thus becomes insufficient. Vitamin D deficit occurs in a average 40% elderly and results in worsening of physical functions and muscular weakness. Newer dietary recommendations therefore suggest vitamin D daily intakes of 10 and 15 micrograms for persons aged 50 to 70, and over 70, respectively [18, 19].

New recommendations and their application

A disease in old age can be influenced by nutrition still in early childhood. It seems that diet changes affect the level of risk factors during life. Intake of minimum 1-2 portions daily of fruits and vegetables could reduce the cardiovascular disease risk by around 30%.

In 1999 (International Year of Elderly), the first dietary pyramid for elderly was proposed. It was intended for persons over 70, in order to point out the need to move the previous old age limit of 65 years [13].

A modified model of elderly dietary pyramid was proposed in January 2008 (Figure 1) that was harmonized with

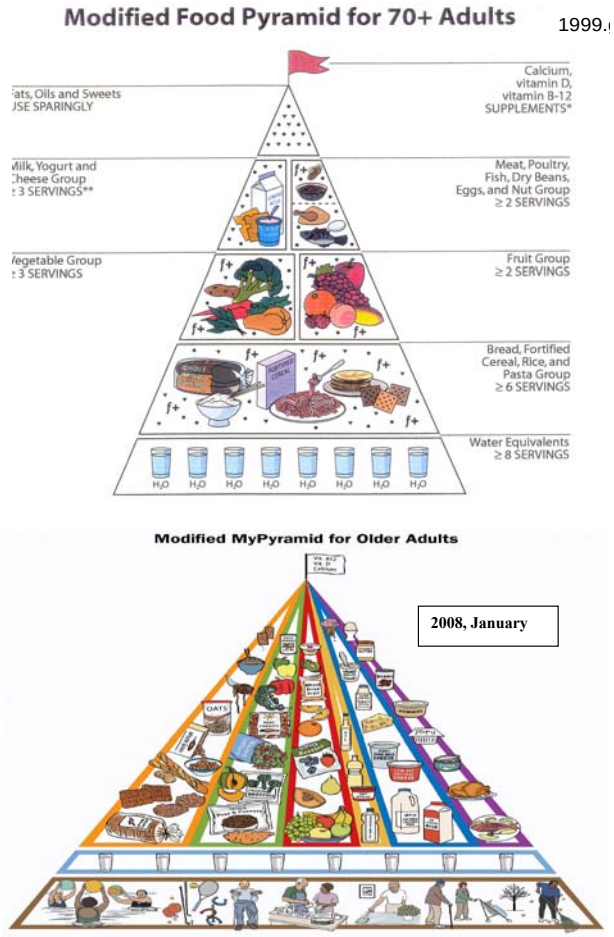

Fig. 1 - Previous and new food guide pyramid for the elderly [13, 20]

new nutrition recommendations of 2006 [20]. It was designed to represent a proper nutritional guide since it ilustrates the importance of individual diet, physical activity and gradual improvement of all lifestyle habits.

This modern pyramid model is oriented towards elderly who live an independent active life and are of relatively good

health. The pyramid's design is a direct presentation of latest dietary recommendations that are not only to provide necessary nutrient intake but also to prevent dietary deficits and chronic non-communicable diseases where nutrition has an etiologic role in elderly.

The pyramid emphasizes the importance of nutritional adequacy, achieved by a proper choice of foodstuffs of greater nutritional density, rich in dietary fibers, with reduced content of total fats, saturated fats and trans-fatty acids, or containing no fats. It shows that diets should contain whole grain cereals and their products, fruit, vegetables, vegetable oils, lactose-free milk, products which are the source of vegetable proteins, as well as enriched and fortified products.

Regular intake of vegetables and fruits fresh, canned or frozen – is suggested to provide sufficient potassium, vitamin E and vitamin K. A required nutritional density and most suitable forms of foodstuffs are thus achieved. The importance of nutrient intake from foodstuffs, not from supplements, also becomes evident; however, supplementing is possible for vitamin B12, vitamin D and calcium (as indicated also in the previous pyramid model). Optimal fluid intake is important for elderly: this recommendation figures in the pyramid's second row.

The pyramid base, suggesting physical activity, is absolutely new. It conforms to recommendations given in 2007 by the Cardiologists Association which integrate preventive and therapeutic programs [21]. These suggest aerobic exercise, muscle strengthening and stretching exercise, as well as balance exercise. It is suggested to elderly to extend a daily duration of chosen activity.

Conclusion

Life duration has almost doubled within the past 200 years. There is a rising trend of elderly population increase, especially those older than 85. However, such increase is not followed by improvement of the quality of life: old age is full of disease. Growing old is successful only if active – it is not sufficient to influence only the nutritional and morbogenic factors, but also to promote regular physical activity of this population. Activities promoting health and preventing chronic non-communicable diseases should be long-term ones. However, lifestyle factors are important also because they exert influence on physical functioning, mental health and well-being. It is never late to correct bad habits when health is concerned. Longer life is possible by an adequately balanced diet.

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Neuroendocrine gastric carcinoma in a young patient

Neuroendokrini karcinom želuca kod mlađeg bolesnika

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Abstract

Background. Neuroendocrine tumors cover a spectrum of neoplasms showing wide variations in their clinicopathological and pathogenetic features, as well as prognosis. They may develop throughout the whole gastrointestinal tract. **Case report.** We described a case of gastric neuroendocrine carcinoma in a 29-year-old male. The patient presented with chronic continuous abdominal pain and weight loss over a 6-month period. Preoperative diagnosis, operative findings, histology and immunohistochemistry of the tumor confirmed the diagnosis of the rare neuroendocrine gastric carcinoma, stage T2N1. **Conclusion.** Case reports of this rare tumor are important, because of the paucity of studies noted in the gastrointestinal literature as a result of poor identification prior to the advent of modern immunohistochemistry. Significance of accurately diagnosing gastrointestinal neuroendocrine tumors is crucial for an appropriate treatment.

Key words:
neurosecretory systems; neoplasms; stomach; immunohistochemistry; gastrectomy.

Apstrakt

Uvod. Neuroendokrini tumori (NET) karakterišu se mnogobrojnim varijacijama u kliničkopatološkoj i patogenetskoj slici, kao i prognozi. **Prikaz slučaja.** Prikazali smo bolesnika, starog 29 godina, sa neuroendokrinim karcinomom želuca. U kliničkoj slici dominirali su hronični stalni bol u predelu stomaka koji je bio praćen gubitkom telesne mase u trajanju od šest meseci. Preoperativna dijagnostika, operativni nalaz, histološke i imunohistohemijske analize tumora potvrdile su dijagnozu retkog neuroendokrinog karcinoma želuca stadijuma T2N1. **Zaključak.** Prikazi slučajeva ovog retkog tumora veoma su važni, jer su bili retki u ranijoj gastroenterološkoj literaturi pre pojave moderne imunohistohemijske dijagnostike. Blagovremeno dijagnostikovanje NET odlučujuće je za adekvatno lečenje i prognozu bolesti.

Ključne reči:
neurosekretorni sistem; neoplazme; želudac; imunohistohemija; gastrektomija.

Introduction

Distinguishing between neuroendocrine carcinoma and adenocarcinoma may be difficult. According to the World Health Organization (WHO) classification of 2000, gastric neuroendocrine tumors (NETs) are classified as well-differentiated NETs with benign or uncertain malignant potential (classic carcinoids), well-differentiated NETs with low-grade malignant behaviour (malignant carcinoids), and poorly differentiated NECs with high-grade malignant behaviour, which can be subdivided into small cell and large cell variants based on morphological characteristics [1, 2]. It was recognized that gastric neuroendocrine tumors cover a spectrum of neoplasms showing wide variations in their clinicopathological features, prognosis and pathogenetic mechanisms [3, 4]. According to the literature, they usually develop in the seventh decade [5]. We reported a case of large cell neuroendocrine carcinoma diagnosed in a young patient.

Case report

A 29-year-old male presented to our hospital due to continuous epigastric pain and a weight loss of 15 kg. At the time of referral, he had been symptomatic for approximately 6 months. His medical history revealed duodenal ulcer disease with hemorrhage and hemorrhagic shock four years ago. Physical examination demonstrated pallor, distress and discomfort with epigastric palpation. Laboratory testing consisting of complete blood count, biochemistry, and tumor markers showed no abnormalities, iron defficiency, anemia (hemoglo-

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bin 90 g/L, Fe^{2+} 3 μmol/L), as well as serum normal gastrin levels. The patient subsequently underwent a routine gastrointestinal work-up. Ultrasonography demonstrated a "pseudo kidney" sign in the epigastrium. According to the radiographic examination, a ventricular ulcer disease was diagnosed. Esophagogastroduodenoscopy revealed a large ulcerovegetating tumor on the lesser gastric curvature to the posterior wall, which was covered with necrotic detritus and hemorrhage, callous and rigid. Tissue samples for patohistology examination were taken. Endoscopic ultrasound revealed involvement and thickening of the mucosa, submucosa and muscularis propria, while the serosa was preserved (T2 stage) in posterior wall of the stomach body. The regional lymph nodes were markedly enlarged (N1stage) (Figures 1 and 2).

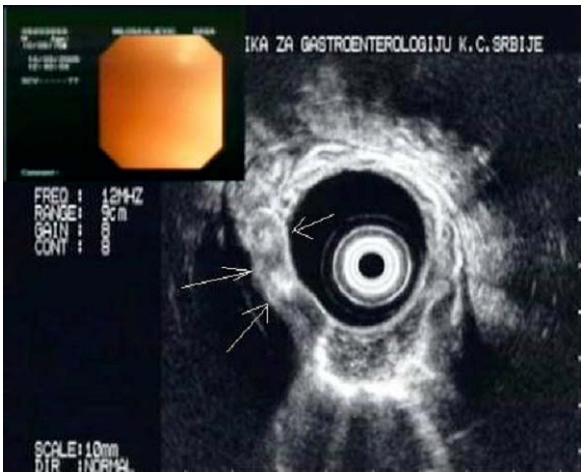

Fig. 1 – Ultrasound image: T2 tumor of the stomach wall

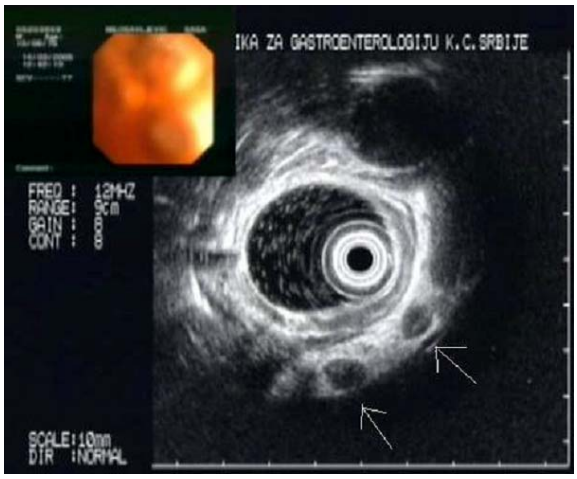

Fig. 2 – Ultrasound image of enlarged lymph nodes around the tumor (see white arrows)

With the exception of the apparent thickening of the gastric wall in the antral region, no other abnormalities were detected on computerized tomography. Explorative laparotomy was appropriately performed. A mass lesion located corporally within the gastric wall was easily identified. This was consistent with preoperative findings. Following exploration, total gastrectomy was performed. Histology evaluation demonstrated trabecula and islet of round cells with rare eosinophilic cytoplasm. The nuclei were atypical, hyperchromatic, moderately pleomorphic, without prominent nucleolus. The stroma was edematous. Vascular invasion in mucosa and submucosa was detected (Figure 3). Cytological immunophenotypes included: marked and diffuse immunoreactivity in the

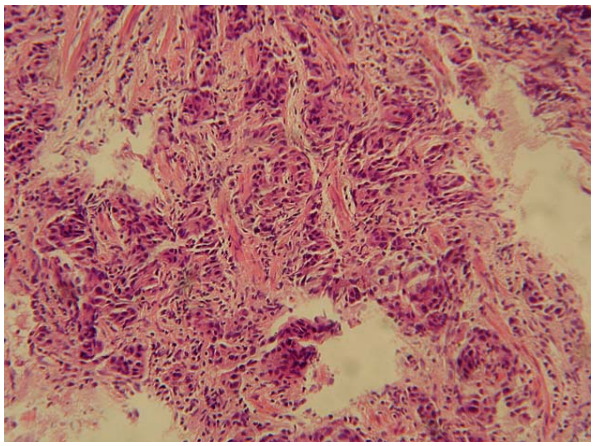

Fig. 3 – Vascular invasion in gastric mucosa and submucosa (HE, ×400)

majority of the cells to neuron specific-enolase (NSE), chromogranin A and synaptophysin (Figures 4 and 5). Immunore-

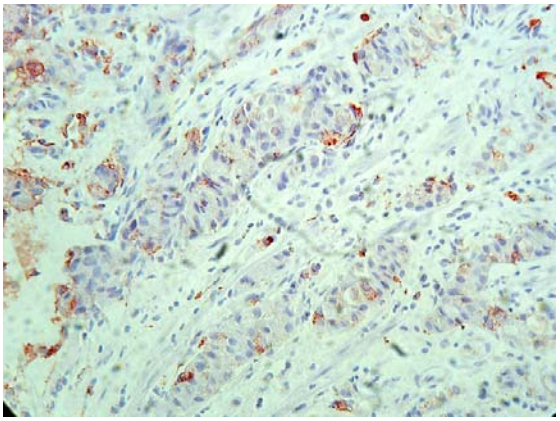

Fig. 4 – Neuroendocrine tumor cells of the stomach wall immunostaining – neuron-specific enolase (LSAB+, ×200)

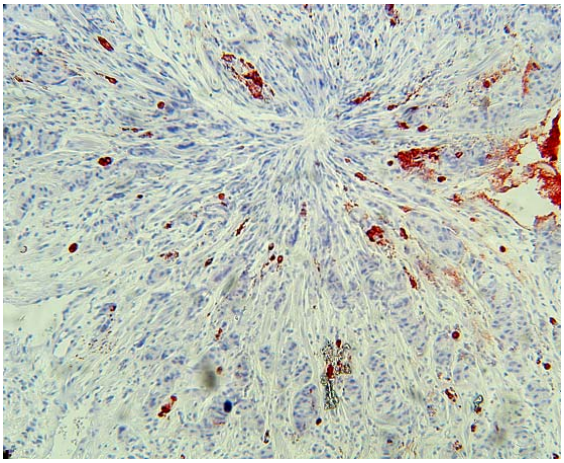

Fig. 5 – Neuroendocrine tumor cells of the stomach wall immunostaining - chromogranin A (LSAB+ , ×200)

activity to other markers was not significant. The mitotic index was 1/10 per microscopic High Power Field (HPF). Our pathologist diagnosed neuroendocrine gastric carcinoma – a large cell type.

The patient denied any postoperative treatment and died six months after the operation.

Discussion

Since Hamperl [6] described argentaffin or argyrophil cells in gastric adenocarcinomas in 1927, neuroendocrine differentiation in gastric carcinomas has been repeatedly reported [7–15]. However, the prevalence of neuroendocrine differentiation in gastric carcinomas still remains undefined.

As already mentioned, these tumors are usually diagnosed in the seventh decade, but we recognized it in this case much earlier (29-year-old patient). There is no significant sex prevalence. Neuroendocrine (NE) gastric carcinomas are generally large (mean size 4.2 cm), fungating or annular lesions, found most frequently in the body/fundus, as it was in our presented case. At the time of diagnosis, most of the tumors were already in advanced stage. Presenting symptoms (weight loss, vomiting, abdominal pain, loss of appetite) were similar to those seen in our patient [16].

Neuroendocrine tumors are neoplasms that consist of relatively uniform cells. Histologically, NE carcinomas are solid, organoid, trabecular, pseudoglandular, spindle cell, or rosette-like [3]. The tumor of the patient related in this report was composed of malignant cells having a moderately pleomorphic aspect and exhibiting vascular and perineural invasion as detected in practically all NE carcinomas [2]. Based on both cell size and morphologic features, Matsui et al. [3] subdivided NE carcinomas into two variants, namely, small and large cell NE carcinoma. Comparing with small cell NE carcinomas, large cell NE carcinomas have a higher mitotic index, larger polygonal cells, a decreased nuclear-cytoplasmic ratio, coarser nuclear chromatin, and more frequently conspicuous nucleoli. In relation to small cell NE carcinoma, large cell NE carcinoma, as presented in this case report, is a more aggressive tumor with a very poor prognosis.

Four types of "pure" NETs can be distinguished in the stomach. Type 1 is the most common, occurring in 70–80% of all cases. In most cases, type 2 NETs of the stomach are small (0.1–1 cm in diameter), multifocal tumors, mainly limited to the mucosa and submucosa, with no metastasis, affecting women more than men, and always occurring in the background of chronic atrophic gastritis. Type 3 (sporadic and solitary) is the second most common NET of the stomach, not associated with any significant clinicopathological condition; these tumors have mostly solitary growth, or are larger than type 1 and type 2 in size, and are deeply invasive with metastase, whereas types 2 (occurring in association with Zollinger-Ellison syndrome and multiple endocrine neoplasia type 1) and 4 (undifferentiated solid neuroendocrine carcinoma) are considered rare [1]. According to this, we classified our patient's tumor into NET type 3.

The main immunohistological feature of NETs are cells strongly positive for endocrine markers in the major part of the tumor (> 50%). In this case, neoplastic cells expressed immunoreactivity to chromogranin A, synaptophysin, and neuron-specific enolase. Neuron-specific enolase and chromogranin A are most frequently expressed. Several reports have shown that the most useful immunohistochemical marker of NE differentation is chromogranin A, followed by Leu-7 and synaptophysin. Other authors have suggested that neuron-specific enolase could be unreliable because it also stains in up to 60% of non-NETs. Use of panel rather than a single NE marker appeared to be more valuable [3, 17, 18].

Although rare, gastric NE carcinomas deserve particular attention, as they are aggressive and have an extremely poor prognosis. Surgical resection is the most appropriate form of treatment for this type. The usefulness of multi-drug chemotherapy remains to be evaluated in larger clinical studies [3]. Mean survival rates of 6.5–14.9 months have been reported with a 1-year survival rate of 58% [16, 19]. As the patient reported in this study, the majority of the patients die due to extensive metastatic disease [20].

Conclusion

Neuroendocrine tumors of the stomach cover a spectrum of neoplasms showing wide variations in their clinicopathological features, prognosis, and pathogenetic mechanisms. It can, however, appear in much younger age as we described, than previously reported.

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Contralateral eyelid metastasis of uveal melanoma with further systemic dissemination

Metastaza malignog melanoma uvee u kontralateralnom kapku sa naknadnom sistemskom diseminacijom

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Abstract

Background. The usual way of dissemination of an uveal malignant melanoma comprises hematogenous metastases to various organs, liver in the first place. Uncommon development of the disease is always possible, while unusual ways of dissemination and secondary deposits in the unexpected sites have been observed. We presented an unusual case of a patient with uveal melanoma metastatic to the contralateral eyelid with very fast further dissemination in the manner typical for primary malignancies. **Case report.** This observational case report included a 70-year-old male, enucleated for uveal melanoma in his left eye, appeared again 2.5 years later with a fast growing contralateral eyelid metastasis, followed by submandibular lymph node involvement on the same side and further systemic dissemination. **Conclusion.** The firts revealed solitary contralateral eyelid metastasis of uveal melanoma is extremely rare, such as an uncommon secondary deposit with a strange way of further dissemination.

Key words:
melanoma; uveal neoplasms; eyelid neoplasms; neoplasm metastasis; treatment outcome.

Apstrakt

Uvod. Po pravilu maligni melanom uvee metastazira hematogeno, pri čemu se sekundarni depoziti prvo javljaju u jetri. Neuobičajen tok bolesti uvek je moguć, a neobični načini metastaziranja, kao i prvi registrovani sekundarni depoziti neočekivanih lokalizacija već su uočeni. Autori prikazuju nesvakidašnji slučaj malignog melanoma uvee koji je najpre dao metastazu u kontralateralnom kapaku, a potom se dalje diseminovao načinom karakterističnim za primarni tumor kapka. **Prikaz slučaja.** Kod muškarca, starog 70 godina, kod koga je 2,5 godine ranije učinjena enukleacija desne očne jabučice zbog malignog melanoma uvee, registrovan je brzorastući sekundarni depozit u donjem kapku levog oka. Potom su se pojavile metastaze u regionalnim limfnim čvorovima levo, a kasnije sistemska diseminacija bolesti. **Zaključak.** Prva registrovana metastaza malignog melanoma uvee u kontralateralnom kapku ekstremna je retkost, kao što je i izneti dalji put diseminacije maligniteta apsolutno neuobičajen.

Ključne reči:
melanom; uvea, neoplazme; kapak, neoplazme; neoplazme, metastaze; lečenje, ishod.

Introduction

Uveal malignant melanoma is the most common primary intraocular malignancy in adults. The clinical course is unpredictable and metastatic disease may occur after a prolonged disease-free interval [1]. The liver is the sole site or the initial site of metastases in more than 50% of cases, followed by lungs, bone and skin [2]. Unexpected behavior or an uncommon development of the disease is always possible [3], as well as strange and unusual ways of dissemination: contralateral choroids [4], ipsilateral orbit [5], contralateral orbit [6], brain [7, 8], brest [9], heart [10] or adrenal gland [11]. The mechanisms of the peculiar modes of dissemination sometimes are really difficult to explain. Unusually located metastases may appear as solitary or as a part of a metastatic disease. Life prognosis in patients with metastatic disease is always poor, with a median survival between 2 and 9 months after detection of metastases [12]. A solitary metastasis of a choroidal melanoma to the contralateral eyelid has been reported, too [13]. In this paper, we described a case of uveal melanoma metastatic to the contralateral eyelid with very fast further dissemination in an unusual way.

Case report

A 70-year-old male patient was first admitted with clinical signs of an intraocular tumor in his left eye. A large uveal melanoma was found both clinically and by ultra-

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sound, without detectable signs of dissemination. The function of the eye being reduced to light perception, an enucleation was performed. Malignant melanoma of the choroid and the ciliary body was confirmed by histology. The same patient appeared again 30 months later, with a large, fast growing tumor of his right lower eyelid. The lesion was not pigmented, it was red colored, with fleshy appearance, bilobar in shape, with subcutaneous and a subconjunctival part (Figure 1). At the time of admission, a huge submandibular lymph node was already present (Figure 2). The patient stated that the eyelid tumor appeared one month previously, but that he had not paid very much attention until he noted the lymph node enlargement soon after that. General checkup revealed secondary deposits in the lungs and in the liver. Removal of the eyelid lesion was advocated for diagnostic purposes, so that a surgical excision was done. Malignant melanoma was found by histology, once again. There was no further treatment and the family notified us informally when he died at home 3 months later.

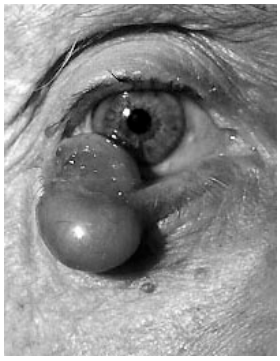

Fig. 1 – Clinical appearance of eyelid tumor

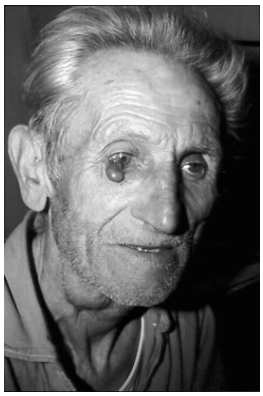

Fig. 2 – The patient on second admission with eyelid tumor and enlarged submandibular lymph node on the same side (Note anophthalmus and an artificial left eye)

In the first specimen, after enucleation, there was an eyeball of a normal size and shape. On vertical section, an irregularly pigmented choroidal and ciliary body tumor filled the inferior half of the globe, with partial retinal detachment (Figure 3). Microscopically, a moderately pigmented malignant melanoma of the mixed cell type (Figure 4), with a predomination of the epitheloid cells, with a number of bizarre, multinucleated or giant ones was found. There were no signs of extrabulbar penetration. The second one was a 15 mm wide full thickness eyelid resection specimen, with a tumor and the surrounding skin. The tumor was whitish and flashy on cross section. Microscopically (Figure 5), a non- pigmented, epitheloid cell type malignant melanoma was found (Figure 6). Neither conjunctival nor cutaneous origin of the tumor could be traced on serial sections. Positive immunostains for S-100 and HMB-45 confirmed the diagnosis.

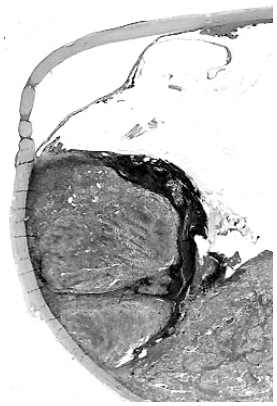

Fig. 3 – Uveal melanoma – histological section of the enucleated left eyeball

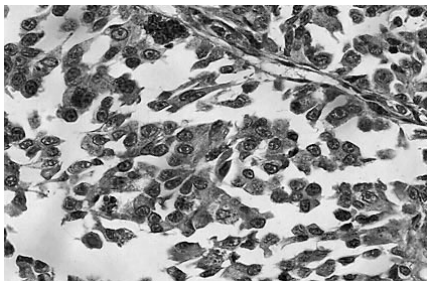

Fig. 4 – The same section. Uveal melanoma, mixed cell type (HE, original magnification 400×)

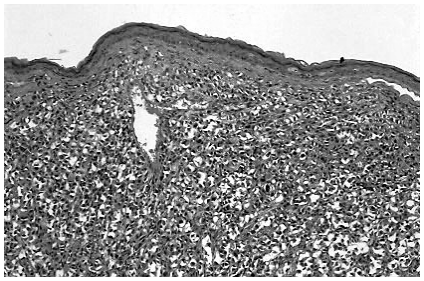

Fig. 5 – Subcutaneous part of the eyelid tumor, low power histologicval appearance (HE, original magnification 40×)

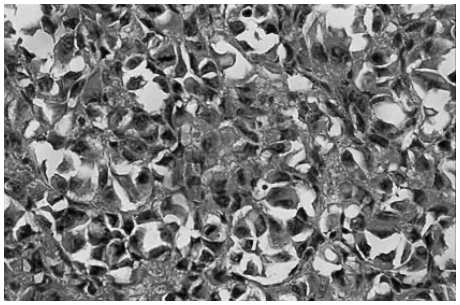

Fig. 6 – The same section. Melanoma, epitheloid cells (HE, original magnification 400×)

Discussion

Regional lymph node involvement with subsequent further dissemination is typical for primary malignancies of the conjunctiva and the eyelids. A second primary melanoma would be an exceptional rarity. Even if it was a new tumor, what had it developed from? Without convincing histological evidence of neither cutaneous nor conjunctival origin of the eyelid tumor in serial sections, we are prone to rule out the possibility of an independent second primary tumor in our case. A solitary contralateral eyelid metastasis being an extreme rarity itself [13], such an uncommon secondary deposit with very fast further evolution and systemic dissemination typical for primary tumors made us believe that, among other cases of atypical or uncommon metatases of the uveal malignant melanoma, this one is worth publishing, too.

Conclusion

The first revealed solitary contralateral eyelid metastasis of uveal melanoma is extremely rare, such as an uncommon secondary deposit with a strange way of further dissemination.

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I S T O R I J A M E D I C I N E

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Pedeset godina od smrti akademika dr Đorđa P. Nešića

The 50th anniversary of death of Academician Đorđe P. Nešić

Rade R. Babić*, Gordana Stanković Babić†

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Niš, Srbija

Ključne reči:
medicina, vojna; istorija medicine, XX vek; oftalmologija; hirurgija, oftalmološka, procedure; literatura; srbija.

Key words:
military medicine; history, 20th century; ophtalmology; ophtalmologic surgical procedures; serbia.

Uvod

U oktobru prošle godine navršilo se 50 godina od smrti akademika, prof. dr Đorđa P. Nešića (slika 1), oftalmologa, profesora Medicinskog fakulteta Univerziteta u Beogradu i člana Srpske akademije nauka i umetnosti (SANU).

Prof. dr Nešić Đorđe rođen je 15. juna 1873. godine u Šapcu, a umro je 24. oktobra 1959. u Beogradu [1, 2]. Osnovnu školu i gimnaziju učio je u Loznici i Šapcu. Maturirao je 1890. godine kao najbolji učenik šabačke gimnazije. Po nagovoru svoje rođake, koja je bila udata za profesora oftalmologije dr Krjukova, Đorđe Nešić upisao se 1890. godine na medicinski fakultet u Moskvi, na kojem je diplomirao 1896. godine. Na istom fakultetu, 1897. godine, mladi dr Đorđe Nešić završio je specijalizaciju iz očnih bolesti.

Dr Đorđe Nešić uporedo je studirao dva fakulteta – medicinu i fiziku u Moskvi. Znanje koje je stekao iz fizike kasnije mu je dobro došlo u lekarskoj praksi, posebno u konstrukciji elektromagneta za uklanjanje metalnih stranih tela iz oka i očne duplje.

Stekavši zvanje specijaliste za očne bolesti, dr Đorđe Nešić se iz Moskve vratio u Beograd (1897) i započeo privatnu lekarsku praksu. Kao lekar – oftalmolog dr Đorđe Nešić kraći vremenski period radio je honorarno, da bi kasnije započeo lekarski staž u okviru vojne oftalmološke službe.

U vreme kada je Đorđe P. Nešić otpočeo oftalmološku praksu, u Srbiji su bila svega dva očna lekara koji su imali pravo da kao putujući specijalisti obavljaju lekarsku praksu. Jedan od njih bio je dr Pavle Popović (1854–1937), rodom iz Velikog Bečkereka (Zrenjanin), a drugi dr Dragoljub Đorđević (1866–1942) koji je službovao u Nišu [1].

Godine 1901. dr Đorđe Nešić imenovan je za šefa Očnog odeljenja Opšte državne bolnice u Beogradu (danas u ulici Džordža Vašingtona 19), da bi od 9. jula 1921, od osnivanja Očne klinike, do 1955. bio postavljen za njenog upravnika, sa prekidom za vreme Drugog svetskog rata (1941–1944) [1–3].

Sl. 1 – Đorđe P. Nešić
(Šabac, 15. jun 1873 – Beograd, 24. oktobar 1959)

Ukazom od 30. juna 1921. dr Đorđe Nešić imenovan je za redovnog profesora oftalmologije na Medicinskom fakultetu u Beogradu, a 1947. izabran je za redovnog člana SANU.

Prof. dr Đorđe Nešić osnivač je beogradske oftalmološke škole poznate po doprinosu oftalmologiji u Srbiji i Jugoslaviji i šire.

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Bio je član ruskog, poljskog, češkog i bugarskog oftalmološkog društva.

Prof. dr Đorđe Nešić napisao je dva udžbenika, više od deset knjiga, više od 50 naučnih radova i nekoliko studija, objavljenih u zemlji i inostranstvu.

Udžbenik „Očne bolesti“ koji, je doživeo nekoliko izdanja, napisao je sa prof. dr Aćimom Markovićem (slika 2) [4].

Sl. 2 – Naslovna strana udžbenika „Očne bolesti“ koji su napisali Đorđe P. Nešić i Aćim Markovića (izdanje Srpska akademija nauka i umetnosti u Beogradu, 1955)

Od knjiga koje je napisao izdvajaju se: „Način ispitivanja vida“ (1899), „Optičke i mehaničke osobine savremenog mikroskopa“ (1906) i „Trahom u Srbiji“ (1914).

Zbog velikih zasluga prof. dr Đorđa P. Nešića za razvoj oftalmologije u Srbiji, Jugoslaviji i u svetu, Institut za oftalmologiju Kliničkog centra Srbije nosi njegovo ime. Ovo ime dotadašnja Očna klinika dobila je 1970. godine prilikom proslave 50 godina rada Medicinskog fakulteta u Beogradu, kao znak priznanja profesoru dr Đorđu Nešiću za njegov doprinos unapređenju medicinske nauke i struke [1–3, 5].

Za prof. dr Đorđa Nešića vezana je i jedna anegdota [2] prema kojoj je on nakon brižljivog pregleda cara Haila Salasija, zbog sumnje na trahom, odlučno rekao: „To nije trahom!“, a zatim je dugo prao ruke četkom, sapunom i toplom vodom i isprao ih alkoholom. Videvši šta profesor radi, jedan od bliskih saradnika upitao ga je: „Zašto ste, toliko dugo prali ruke kada nije trahom“. Profesor mu je odgovorio: „Za svaki slučaj“.

Učešće u balkanskim ratovima i Prvom svetskom ratu

Prof. dr Đorđe P. Nešić učestvovao je od 1912. u svim ratovima Srbije. U balkanske ratove dr Nešić otišao je 1912. sa činom rezervnog sanitetskog majora, a iz I svetskog rata izašao je kao sanitetski potpukovnik. U tursko-srpskom ratu, dr Đorđe Nešić bio je lekar zavojišta, da bi u bugarsko-srpskom ratu bio imenovan za komandira poljske bolnice [1].

Na pragu I svetskog rata dr Đorđe Nešić bio je komandir zavojišta Dunavske divizije drugog poziva, na Solunskom frontu komandir I srpske hirurške bolnice u Dragomancima, a kraj I svetskog rata dočekao je kao sanitetski potpukovnik.

Za vreme I svetskog rata, ofanziva na Solunskom frontu koju je započela srpska vojska 1916. godine (septembar/decembar) odjeknula je osvajanjem Kajmakčalana i oslobađanjem jednog dela otadžbine (uključujući Bitolj). Srpska vojska nanela je neprijatelju gubitak od preko 68 000 ljudi od kojih 8 685 je bilo zarobljeno, ali je i sama imala gubitak od 27 965 ljudi. Bez obzira na to što je neprijatelj imao znatno veće gubitke, takvi gubici srpske vojske postali su neprihvatljivi. Usledila je reorganizacija u redovima srpske vojske. Na liniji fronta formirana je srpska bolnica koja je u početku bila pod ingerencijom savezničkih saniteta, a kasnije naših iskusnih ratnih hirurga (dr Đorđe Nešić, dr Mihailo Petrović i dr), internista i mladih, sposobnih lekara i medicinara, od kojih su mnogi postali poznati profesori Medicinskog fakulteta u Beogradu. Već 14. juna 1916. godine osnovana je u Vasilici Prva hirurška poljska bolnica, a 30. jula još dve poljske hirurške bolnice [6, 7].

U našoj ratnoj sanitetskoj literaturi najpoznatija je I srpska hirurška bolnica u Dragomancima na čijem su čelu bili pukovnik dr Mihailo Petrović kao glavni hirurg, i major dr Đorđe Nešić, kao njen komandir od 1. januara 1917, pa do kraja rata.

Pre imenovanja za komandira I srpske hirurške bolnice, dr Đorđe Nešić u Mikri kraj Soluna, bio je postavljen za komandira 3. rezervne bolničke čete pri Vrhovnoj komandi, a potom za referenta saniteta Glavne vojne stanice [6, 7].

Dr Đorđe P. Nešić dijagnostikovao je hemeralopiju (kokošje slepilo) kod srpskih vojnika na Solunskom frontu, objašnjavajući to kao posledicu avitaminoze nastale jednoličnom ishranom. Ove rezultate dr Nešić objavio je u radu „*Étude sur l,héméralopie*“, u francuskom časopisu *Annale d,oculistique* (Pariz, 1918, 25. strana) [2, 3]. Na kraju separata stoji „*par Georgas Néchitch, ophtalmologiste en chef de l,hòpital général de l,Etat â Belgrade, médicin – chef de l,hòpital chirurgical d,une armées serbs*“ [1].

Dr Vojislav Subotić koji je na liniji Solunskog fronta sarađivao sa dr Nešićem, zapisao je: „Za vreme naših ratova od 1912. do 1918. godine bio je g. Nešić neumoran u pomaganju našim vojnicima. Njegova stručna sprema, njegovo požrtvovanje, kao i njegove organizacione sposobnosti, spasili su mnogim našim vojnicima, često pod teškim prilikama očni vid. I u tom ratnom vremenu, on nije prekidao naučno obrađivanje okulističkih problema“ [1].

Dr Mihailo Petrović govorio je: „Mi smo na Solunskom frontu radili, ako bi smeo da to nazovem, donekle, improvizirali. Tako smo improvizirali udlage (dr N. Nikolić, dr Petrović), improvizirali sterilizatore i aparate za destilaciju vode (dr Nešić). Isto tako i patološko-anatomski materijal nije

mogao biti stručno razmatran, jer u bolnici osim mene i dr Nešića kao komandira i specijaliste za očne bolesti, u tome vremenu nije bilo ni jednog lekara koji bi pomagao“ [1].

Treba istaći da je francuski inspektor istočnih armija general Furnije, koji je nekoliko dana pažljivo posmatrao pripreme srpske vojske, rekao dr Nešiću i dr Petroviću: „Francuski ranjenici biće upućeni sa fronta isključivo u vašu bolnicu, nikuda dalje“ [1].

Vojvoda Stepa Stepanović, komandant Druge Armije, pismeno je pohvalio dr Đorđa P. Nešića za vršenje vojne dužnosti upravnika Prve poljske hirurške bolnice u selu Dragomancima na Solunskom frontu [1–3]. Na predlog sanitetskog referenta puk. dr Save Popovića, vojvoda Stepa Stepanović je rekao: „Komandir Prve poljske hirurške bolnice, rezervni sanitetski major, dr Đorđe Nešić, kao upravnik Armijske poljske bolnice, pokazao se za sve vreme njenog rada kao jedinstven organizator i njen tvorac. Njegovoj dovitljivosti, umešnosti i neobičnom razumevanju i improvizovanju svega što je neophodno za poljsku bolnicu, ima se zahvaliti što je bolnica najbolje odgovorila svom ratnom zadatku. Ista bolnica služila je na Moglenskom odseku fronta i služiće u istoriji srpskog ratnog saniteta, kao model i škola“ [1]. Interesantan je podatak da je ova bolnica po proboju Solunskog fronta prebačena u Niš, gde je preformirana u Moravsku stalnu vojnu bolnicu naredbom Vrhovne komande br. 32187 od 5. novembra 1918. godine.

Svoje ratno iskustvo dr Đorđe Nešić izneo je u radu „O povredama i bolestima oka za vreme naših ratova“ [1].

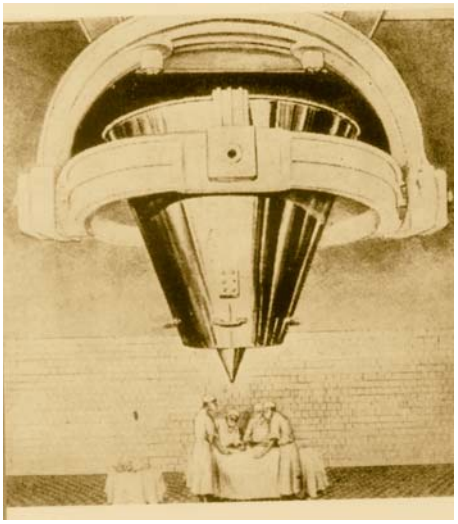
Malo se zna da je dr Đorđe Nešič bio dobrovoljac u rusko-japanskom ratu 1904 –1905. godine. Za učešće u ovom ratu dr Đorđe Nešić je od Crvenog krsta Rusije u Petrogradu 17. marta 1906. dobio znak i medalju Crvenog krsta. Svoja oftalmološka iskustva u ovom ratu dr Nešić je objavio u radu „Projektili u rusko-japanskom ratu. Njihov uticaj na očni vid. Naočari za zaštitu od projektila“ objavljen u Srpskom arhivu (br. 11, 1905, str. 445–450) [1].

Inovacije u otfalmologiji

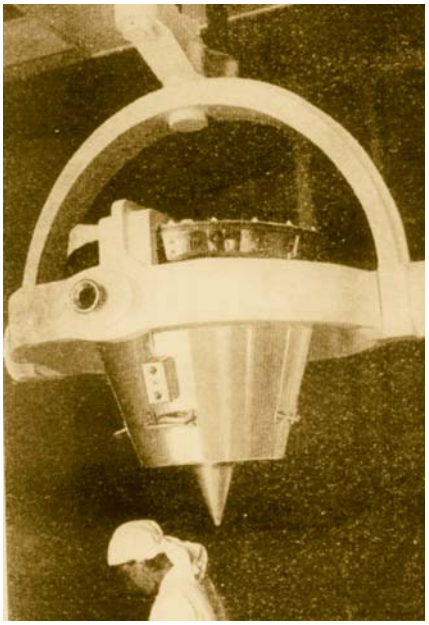
Godine 1937, prof. dr Đorđe P. Nešić konstruisao je elektromagnet za uklanjanje metalnih stranih tela iz oka i očne duplje i nazvao ga „džinovski elektromagnet“ (slika 3). Taj elektromagnet, težak oko 5 t, bio je smešten u Klinici za očne bolesti, koja tada postaje jedan od vodećih centara u zemlji i svetu [1–5].

Prema instrukcijama profesora Nešića, izrađena su dva džinovska (slika 4) i pet prenosnih elektromagneta, a njihov rad shematski je prikazan na slici 5. Prema mišljenju profesora Nešića ovi elektromagneti mogli su se „usprešno primeniti radi udaljenja stranih tela iz mozga i drugih delova organizma“ [4]. Ovaj postupak profesor Nešić opisao je na sledeći način: „pomoću električnog magneta, projektil je privučen iz dubine mišićnog tkiva pod kožu koju podiže u kupu. U ovom slučaju dovoljno je napraviti mali rez kože na vrhu kupe da bi se pušćano zrno odstranilo“ [4].

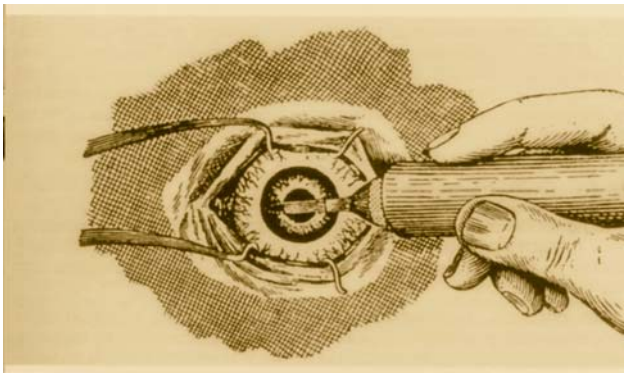
Nakon preseljenja Očne klinike u Pasterovu ulicu sačuvan je samo jedan magnet koji se nalazi u zgradi Srpskog lekarskog društva (Beograd, Džordža Vašingtona 19).



Sl. 3 – Džinovski elektromagnet Očne klinike u Beogradu za vađenje legura i stranih tela sa slabo izraženim magnetskim osobinama i za potrebe velike hirurgije (ovaj elektromagnet bio je presvučen niklovanom košuljicom radi sterilizacije plamenom)



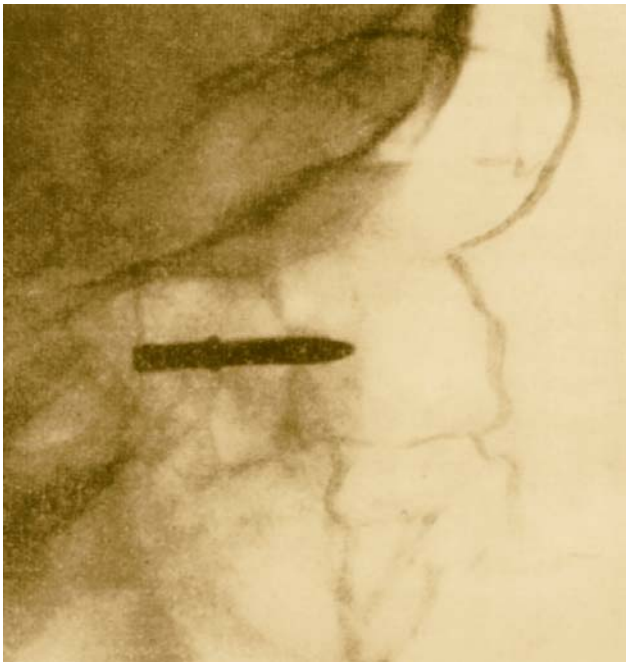
Sl. 4 –Manji elektromagnet oklopljen niklovanim pancirom koji se nalazio u Očnoj klinici u Beogradu, izrađen po nacrtima prof. dr Đorđa P. Nešića



Sl. 5 – Izvlačenje stranog tela iz oka pomoću malog elektromagneta (ilustracija profesora Nešića) [4]

Na našim prostorima prof. dr Đorđe P. Nešić prvi je dao rendgenološki opis radiografski stranog tela u oku i očnoj duplji i prvi uveo novu hirušku tehniku za odstranjivanje metalnog stranog tela iz oka [3, 4].

Na slici 6a prikazan je rendgenogram leve orbite sa metalnim stranim telom koji je opisao profesor Nešić [4]. Bio je to čelični fragment koji se nakon eksplozije puščane cevi zario u dno leve orbite. Uz pomoć elektromagneta i nove hirurške tehnike, profesor Nešić metalno strano telo iz leve orbite odstranio je istim putem kojim je i ušlo (slika 6b) [4]. Zdrastveno stanje ovog bolesnika popravilo se tako da je on petog dana posle ekstrakcije stranog tela imao oštrinu vida 1,5 (slika 7) [4].



a)

b)

Sl. 6. – Na našim prostorima profesor Đorđe P. Nešić prvi je dao rendgenološki opis radiografskog stranog tela u oku a) bio je to čelični fragment koji je nakon eksplozije puščane cevi okrznuo glabelu, prošao duž unutrašnjeg orbitalnog zida i zario se u dno leve orbite, b) ekstrakcija čeličnog fragmenta iz leve orbite pomoću elektromagneta koji je konstruisao prof. dr Đorđe Nešić

Sl. 7 – Izgled bolesnika posle pet dana od ekstrakcije metalnog stranog tela, sa oštrinom vida 1,5.

Prof. dr Đorđe P. Nešić ovako je opisao hiruršku tehniku za odstranjivanje stranog tela iz oka (slika 8): „Pošto je napravljen kao što je pomenuto, razrez u limbusu rožnjače, ne vrši se više iridektomija, taj deo operacije otpada, no se odmah uvlači u ranu vrh ručnog magneta iznad stranog tela koje se nalazi ispod dužice. Kao što se vidi, pol ručnog elektromagneta nije u direktnom kontaktu sa stranim telom, no se između njega i magnetskog vrha nalazi tkivo dužice, koje ih razdvaja. Pri aktivisanju ručnog magneta strano telo se pripija uz vrh magneta priljubljujući uz njega i dužicu, koja se nalazi između njih, tako da se pri izvlačenju magnetnog vrha izvlači zajedno sa stranim telom i odgovarajući mali deo dužice u kome se nalazi i strano telo. Ovaj deo se odseca.

Sl. 8 – Ilustracija rada sa ručnim elektromagnetom pri izvlačenju stranog magnetnog tela iz zadnje i prednje komore oka (ilustraciju je uradila naša eminentna umetnica Emilija Ognjanov)

Na taj način se vrši se jednovremeno i iridektomija i ekstrakcija stranog tela bez opasnosti da vrh magneta povredi kristalno sočivo, jer je ono zaštićeno dužicom.

Sa ovom novom metodom do koje se došlo na našoj klinici, i koja se danas sa uspehom primenjuje, ne samo da je uprošćena do krajnih granica sama operacija, no je skraćeno vreme njenog trajanja i dobivena maskimalna sigurnost u jednom ovakvom komplikovanom i punom odgovornosti operativnom poduhvatu.

Posle završene ekstrakcije ostaje u gornjem delu dužice uzan kolobom, koji se prekriva gornjim kapkom“ [4].

Prof. dr Đorđe P. Nešić, između ostalog, dao je opis jedne koliko korisne, tako i proste tehnike fiksacije stranog tela koja se primenjivala u Klinici za očne bolesti, a sastoji se u sledećem: „Pošto je strano telo kroz zonulu dovedeno u zadnju komoru i lako fiksirano u perifernom delu dužice i pošto je izvršen razrez i ispuštena tečnost iz prednje komore, dužica odmah prileže uz zadnju površinu rožnjače, usled pozitivnog pritiska staklastog tela. Tada se ili pojačava magnetska snaga puštanjem u njega veće količine struje ili se magnet bliže primiče oku pošto više ne postoji opasnost da se tkivo dužice pokida, jer ono leži sad uz rožnjaču“ [4].

Stvaralački i pronalazački duh prof. dr Đorđa Nešića ogleda se i u pronalasku i konstrukciji brizgalice sa pritiskom i biogenog stimulatora sa analizom njihovog uticaja na ćelijski metabolizam (tzv. tkivna terapija - implantant placente konzervisane šest dana i potom i autoklavirane na 120 °C tokom jednog časa, za čiju primenu je konstruisao posebnu metalnu brizgalicu), kao i načina ispitivanja vida kod kandidata za vojne lekare [2–5].

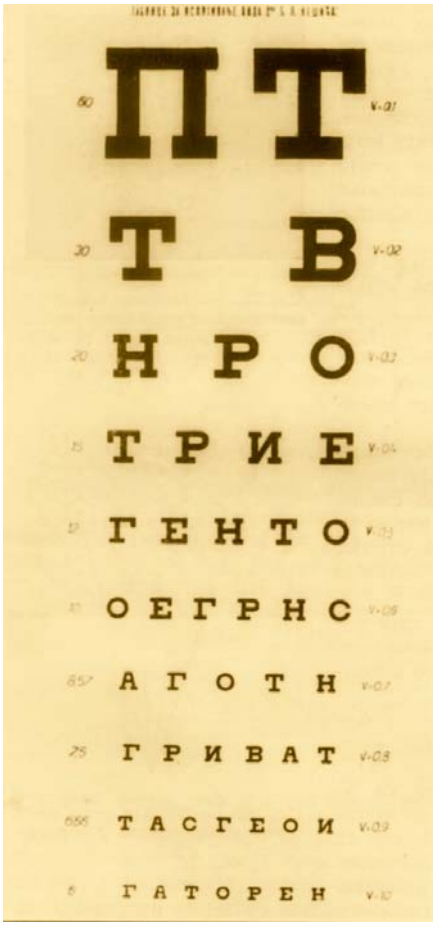
U radu na biogenom stimulatoru i njegovom uticaju na ćelijski metabolizam pomagali su mu prof. dr Filatov iz Odese i tadašnji asistenti na Medicinskom fakultetu u Beogradu dr Olga Litričin i dr Milivoje Radovanović [1–3].

Prof. dr Đorđe P. Nešić izradio je tablicu za ispitivanje oštrine vida koja se sastojala od slova ili brojeva različite veličine (slika 9), za nepismene od znakova, a za decu od slika poznatih predmeta [1–4] .

Zbog uspeha u suzbijanju trahoma (slika 10) [4] u Mačvi, Podrinju i Sremu, Svetska zdravstvena organizacija usvojila

Sl. 10 – Trahom kod bolesnika koji je dijagnostikovao prof. dr Đorđe Nešić u trećem periodu blefarofimoze (ivice kapaka uvrnute na rožnjačama ožiljci)

je plan prof. dr Đorđa Nešića na suzbijanju trahoma u svetu, dok je SANU izdala monografiju u kojoj su prikazani njegovi rezultati rada na suzbijanju trahoma u periodu od 1948. do 1956. godine [2–5].



Sl. 9 – Tablica za ispitivanje oštrine vida po akademiku Đorđu P. Nešiću

Književni i sportski rad

Prof. dr Đorđe Nešić, između ostalog, bio je i književnik i pesnik.

Napisao je pesme: Surogati i Osjek, Crv sumnje u jabuci razdora, kao i knjige: Bolnica u Dragomancima i njene improvizacije – Istorija srpskog vojnog saniteta i Konji Vuka Brankovića [2, 3, 5].

Prof. dr Đorđe P. Nešić bio je jedan od inicijatora osnivanja Biciklističkog saveza Srbije [1–3] (prvo Srpsko velosipedsko društvo osnovano je u Beogradu 23. decembra 1884.). Za vreme studija u Moskvi, učestvovao je na mnogobrojnim biciklističkim takmičenjima i pobeđivao najbolje bicikliste Rusije, Francuske, Austrije i Italije. Godine 1896, dr Đorđe P. Nešić bio je šampion Rusije u biciklizmu, a iste godine u Lođu, pobedio je tadašnjeg aktivnog svetskog prvaka, Nemca Lera.

Odlikovanja

Za hrabrost i vojne zasluge, kao lekar-ratnik, prof. dr Đorđe Nešić odlikovan je Medaljom kralja Petra I za hrabrost pod Jedrenom - dva puta, Bugarskim ordenom svetog Aleksandra V reda sa mačevima za učešće pri osvajanju Jedrena 1913, ordenom Belog orla sa mačevima, ordenima Belog orla III, IV i V reda, ordenima svetog Save I, II, IV i V

reda, medaljom Crvenog krsta, Jugoslovenskom krunom II reda, Krstom milosrđa za negu ranjenika i obolelih u ratovima 1912–1913, ordenom Zasluge za narod I reda, ordenom Rada I reda i Jubilarnom spomenicom Gradskog odbora Narodnog fronta SR Srbije za zasluge na izgradnji Beograda 1944–1945. godine[1–3].

Zaključak

Akademik Đorđe P. Nešić smatra se jednim od začetnika oftalmologije u Srbiji i Jugoslaviji. Svojim ukupnim delom, dao je veliki doprinos afirmaciji srpske oftalmologije u zemlji i svetu.

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Radove (tekst i grafičke priloge) treba slati na disketi (CD) i štampane u tri primerka (original i dve kopije). Autori konačnu verziju rukopisa i priloga prihvaćenih za publikovanje predaju u jednom štampanom primerku i na disketi od 3,5" (očišćenoj od „virusa“) ili na kompakt disku. Za obradu teksta koristiti program **Word for Windows** verzije 97, 2000, XP ili 2003, a samo izuzetno i neki drugi. Za izradu grafičkih priloga koristiti standardne grafičke programe za **Windows**, poželjno iz programskog paketa **Microsoft Office** (**Excel, Word Graph**). Kod kompjuterske izrade grafika izbegavati upotrebu boja i senčenja pozadine.

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Priprema rada

Delovi rada su: **naslovna strana, apstrakt sa ključnim rečima, tekst** i **literatura.**

1. ***Naslovna strana***

a) Naslov treba da bude kratak, jasan i informativan i da odgovara sadržaju rada. Podnaslove treba izbegavati.

b) Ispisuju se puna imena i prezimena autora.

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2. ***Apstrakt i ključne reči***

Na drugoj stranici nalazi se strukturisani apstrakt sa naslovom rada. Kratkim rečenicama na srpskom i engleskom jeziku iznosi se **uvod i cilj** rada, osnovne procedure - **metode** (izbor ispitanika ili laboratorijskih životinja; metode posmatranja i analize), glavni nalazi - **rezultati** (konkretni podaci i njihova statistička značajnost) i glavni **zaključak**. Naglasiti nove i značajne aspekte studije ili zapažanja. Strukturisani apstrakt (**250** reči) ima podnaslove: *uvod/cilj, metode, rezultati* i *zaključak*. Za apstrakte na engleskom dozvoljeno je i do **450** reči. Strukturisani apstrakt je obavezan za metaanalize (istog obima kao i za originalne članke) i kazuistiku (do 150 reči, sa podnaslovima *uvod, prikaz slučaja i zaključak*). Ispod apstrakta, pod podnaslovom „Ključne reči“ predložiti 3–10 ključnih reči ili kratkih izraza koji oslikavaju sadržinu članka.

3. ***Tekst članka***

Tekst sadrži sledeća poglavlja: **uvod**, **metode**, **rezultate** i **diskusiju**. **Zaključak** može da bude posebno poglavlje ili se iznosi u poslednjem pasusu diskusije. U **uvodu** ponovo napisati naslov rada, bez navođenja autora. Navesti hipotezu (ukoliko je ima) i ciljeve rada. Ukratko izneti razloge za studiju ili posmatranje. Navesti samo strogo relevantne podatke iz literature i ne iznositi opširna razmatranja o predmetu rada, kao ni podatke ili zaključke iz rada o kome se izveštava.

Metode. Jasno opisati izbor metoda posmatranja ili eksperimentnih metoda (ispitanici ili eksperimentne životinje, uključujući kontrolne). Identifikovati metode, aparaturu (ime i adresa proizvođača u zagradi) i proceduru, dovoljno detaljno da se drugim autorima omogući reprodukcija rezultata. Navesti podatke iz literature za uhodane metode, uključujući i statističke. Tačno identifikovati sve primenjene lekove i hemikalije, uključujući generičko ime, doze i načine davanja. Za ispitivanja na ljudima i životinjama navesti saglasnost etičkog komiteta.

Rezultate prikazati logičkim redosledom u tekstu, tabelama i ilustracijama. U tekstu naglasiti ili sumirati samo značajna zapažanja.

U **diskusiji** naglasiti nove i značajne aspekte studije i izvedene zaključke. Posmatranja dovesti u vezu sa drugim relevantnim studijama, u načelu iz poslednje tri godine, a samo izuzetno i starijim. Povezati zaključke sa ciljevima rada, ali izbegavati nesumnjive tvrdnje i one zaključke koje podaci iz rada ne podržavaju u potpunosti.

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Literatura se u radu citira kao superskript, a popisuje rednim brojevima pod kojima se citat pojavljuje u tekstu. Navode se svi autori, ali ako broj prelazi šest, navodi se prvih šest i dodaje et al. Svi podaci o citiranoj literaturi moraju biti tačni. Literatura se u celini citira na engleskom jeziku, a iza naslova se navodi jezik članka u zagradi. Ne prihvata se citiranje apstrakata, sekundarnih publikacija, usmenih saopštenja, neobjavljenih radova, službenih i poverljivih dokumenata. Radovi koji su prihvaćeni za štampu, ali još nisu objavljeni, navode se uz dodatak „u štampi“. Rukopisi koji su predati, ali još nisu prihvaćeni za štampu, u tekstu se citiraju kao „neobjavljeni podaci“ (u zagradi). Podaci sa *Interneta* citiraju se uz navođenje datuma.

Primeri oblika referenci:

Đurović BM. Endothelial trauma in the surgery of cataract. Vojnosanit Pregl 2004; 61(5): 491–7. (Serbian)

Balint B. From the haemotherapy to the haemomodulation. Beograd: Zavod za udžbenike i nastavna sredstva; 2001. (Serbian)

Mladenović T, Kandolf L, Mijušković ŽP. Lasers in dermatology. In: *Karadaglić Đ*, editor. Dermatology. Beograd: Vojnoizdavački zavod & Verzal Press; 2000. p. 1437–49. (Serbian)

Christensen S, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: *Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG,* editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer; 2002. p. 182-91.

Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [serial on the Internet]. 2002 Jun [cited 2002 Aug 12]; 102(6): [about 3 p.]. Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htm

Tabele

Sve tabele štampaju se sa proredom 1,5 na posebnom listu hartije. Obeležavaju se arapskim brojevima, redosledom pojavljivanja, u desnom uglu (**Tabela 1**), a svakoj se daje kratak naslov. Objašnjenja se daju u fus-noti, ne u zaglavlju. Za fus-notu koristiti sledeće simbole ovim redosledom: ***, †, ‡, §, ||, ¶, **, ††, ...** Svaka tabela mora da se pomene u tekstu. Ako se koriste tuđi podaci, obavezno ih navesti kao i svaki drugi podatak iz literature.

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Slikama se zovu svi oblici grafičkih priloga i predaju se u tri primerka i na disketi (CD). Fotografije treba da budu oštre, na glatkom i sjajnom papiru, do formata dopisnice. Slova, brojevi i simboli treba da su jasni i ujednačeni, a dovoljne veličine da prilikom umanjivanja budu čitljivi. Na svakoj slici treba na poleđini, tankom grafitnom olovkom, označiti broj slike, ime prvog autora i gornji kraj slike. Slike treba obeležiti brojevima, onim redom kojim se navode u tekstu (**Sl. 1; Sl. 2** itd.). Ukoliko je slika već negde objavljena, obavezno citirati izvor.

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The second page should carry a structured abstract with the title for original articles, metanalyses and case reports. The abstract should state the purposes of the study or investigation, basic procedures (selection of study subjects or laboratory animals; observational and analytical methods), main findings (giving specific data and their statistical significance, if possible), and the principal conclusions. It should emphasize new and important aspects of the study or observations. S t r u c - t u r e d abstract should contain typical subtitles: *background/aim, methods, results* and *conclusion*. The abstract for metaanalyses and obrginal papers should have up to 450 words, and up to 150 words for case reports (with subtitles *background, case report, conclusion*). Below the abstract authors should provide, and identify as such, 3–10 key words or short phrases that will assist indexers in cross-indexing the article and will be published with the abstract.

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The text of original articles is divided into sections with the headings: **Introduction**, **Methods**, **Results**, and **Discussion**. Long articles may need subheadings within some sections to clarify their content.

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Examples of references:

Jurhar-Pavlova M, Petlichkovski A, TrajkovD, Efinska-Mladenovska O, Arsov T, Strezova A, et al. Influence of the elevated ambient temperature on immunoglobulin G and immunoglobulin G subclasses in sera of Wistar rats. Vojnosanit Pregl 2003; 60(6): 657–612.

DiMaio VJ. Forensic Pathology. 2nd ed. Boca Raton: CRC Press; 2001.

Blinder MA. Anemia and Transfusion Therapy. In: Ahya NS, Flood K, Paranjothi S, editors. The Washington Manual of Medical Therapeutics, 30th edition. Boston: Lippincot, Williams and Wilkins; 2001. p. 413-428.

Christensen S, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: *Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG,* editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer; 2002. p. 182-91.

Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [serial on the Internet]. 2002 Jun [cited 2002 Aug 12]; 102(6): [about 3 p.]. Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htm

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Type each table double-spaced on a separate sheet. Number tables consecutively in the order of their first citation in the text in the upper right corner **(Table 1)** and supply a brief title for each. Place explanatory matter in footnotes, using the following symbols, in this sequence: ***, †, ‡, §, ||, ¶, **, ††, ...** Each table has to be mentioned in the text. If you use data from another source, acknowledge fully.

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