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SADRŽAJ / CONTENTS

Ovogodišnje Olimpijske i Paraolimpijske igre još jednom su potvrdile da je za postizanje vrhunskih rezultata u sportu, kao i u životu uopšte, neophodno očuvanje i fizičkog i mentalnog zdravlja. U oktobru, u sklopu obeležavanja Svetskog dana protiv osteoporoze (20. oktobar) i Svetskog dana protiv moždanog udara (29. oktobar), eksperti Svetske zdravstvene organizacije poseban akcent staviće na značaj prevencije za ostavrenje tog cilja (vidi Uvodnik, str. 831–2).

The London 2012 Olympic and Paralympic Games confirmed once again the necessity to maintain both physical and mental health for achieving top results not only in sport but in life generally. On October 20 and 29, within marking World Osteoporosis Day and World Stroke Day, respectively, the World Health Organisation experts will specially emphasize the significance of prevention in realizing this goal (see Editorial, p. 831–2).

E D I T O R I A L

Myths about stroke – on the road to change

Mitovi o moždanom udaru – na putu ka promenama

Tihomir V. Ilić

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Editorials that are written at the time when the world marks the fight against certain diseases always aim to attract the attention of general public to the importance of certain medical problems. Stroke is certainly one of such issues, since unlike myocardial infarction, it has long lagged behind in the shadow of therapeutic nihilism. Starting with the 2006, World Stroke Organization, with the help of national organizations around the world, through promotional events, on 29 October each year tries to raise awareness and educational level on this difficult but treatable and preventable disease.

As every year, the campaign will have its slogan, this time "Because I care ...", refering to the understanding of personal risk factors, the need for physical activity, healthy nutrition and to recognize the warning signs of stroke and how to take action against it.

So, what has changed in recent years about this disease that particularly drew attention to the entire population?

Stroke is a very important area that is growing rapidly. Considering the fact that this disease affects about 15 million people worldwide annually, along with a high mortality rate of about 6 million deaths every year, stroke creates a huge economic burden on society [1]. Interestingly, at the same time, the economic aspect of this burden relates more to developing countries, where the incidence of stroke in the last 4 decades has increased by about 2 times, as opposed to the reducing incidence in developed countries which is about 40%. These changes in the economically well-off societies are believed to be the consequence of improved medical education of the entire population and raising awareness of the importance of risk factors strict control [2].

For year, the essential role of medicine in this area was reflected in the claim "that the stroke does not happen" and if it still happens, what remained were almost exclusively supportive measures. However, over the past two decades, the picture is gradually changing. Several innovative procedures substantially changed the landscape of the disease, as well as the future of its victims.

The first major breakthrough occurred in the mid-nineties after FDA approval of the first thrombolytic therapy for acute ischemic stroke, recombinant intravenous tissue plasminogen activator (rTPA) [3]. This treatment approach has begun very cautiously, due to the concern about high rate intracranial bleeding, as already seen in some previous attempts to use thrombolysis in acute stroke. However, with numerous success stories and the dramatic beneficial changes that rTPA brings to stroke victims, the effect was named – the Lazarus Effect (after the biblical story, Jesus is said to have raised Lazarus from the dead). A new approach to the treatment is accomplished on health effects and cost savings to the society of enormous proportions, so that the USA achieved a total savings in the amount of 363 mill. $ per the year 2010, although it is estimated that rTPA applies in only 1%–8% of people with acute stroke [4].

However, along with this change in the form of effective therapeutic interventions, in the same decade in the wider world begans the organization of specific units for the treatment of this category of patients – so-called stroke units. Doubt about the contribution of the specific organization of health care and treatment through stroke units, was completely overcome by analyzing more than 7,000 patients, treated in this way, by the Cohrane Collaboration group. According to this analysis the specific organization of health care and patient care fundamentally has changed the outcome, both in terms of survival and by the functional improvement and independence [5]. Yet, stroke units are still more often located in academic institutions even in developed countries, assuming that the application of rTPA or certain neuroradiological interventional procedures (thrombectomy, angioplasty and stenting of the carotid and other cerebral arteries) need experience and expertise.

Therefore, in some countries, an attempt was made to organize regional telemedical networks with the so-called virtual stroke units, located in university hospitals. Neurologists with special expertise in the treatment of stroke in these

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departments *via* videoconferencing perform the evaluation of neurologic status in patients in smaller district hospitals and rural areas, such as the Telemedi Pilot Project for Integrative Stroke Care (TEMPiS) Network, the program which is particularly successfully organized in Germany, Bavaria [6].

In addition to these highlights, many other procedures and approaches contributing to a greater or lesser extent, to the prevention and treatment of this disease, lead the transformation of this area of modern neurology orphan, to the growing wave of optimism and enthusiasm, which requires increased levels of public awareness of what stroke is and how it can be successfully treated.

So, let us continue to keep an eye on the news to cover this area and…tell everyone "Stroke is no longer – the Stroke of God's Hand."

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Prevalencija prekomerne telesne mase i gojaznosti kod odrasle seoske populacije Bačke i Banata

Prevalence of overweight and obesity in adult rural population of the northern part of Bačka and Banat

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Apstrakt

Uvod/Cilj. Gojaznost danas predstavlja čest hronični zdravstveni problem razvijenih zemalja. Povezana je sa kardiovaskularnim bolestima, dijabetesom i mnogim oblicima malignih bolesti. Cilj rada bio je da se utvrdi prevalencija prekomerne telesne mase i gojaznosti kod odrasle populacije Bačke i Banata. **Metode.** Na osnovu višeetapnog stratifikovanog uzorka, metodom slučajnog uzorka odabrane su 4 504 odrasle osobe prosečne starosti 40,61 ± 11,29 godina. Ispitivanje je urađeno u 46 ruralnih naselja. Prevalencija prekomerne telesne mase i gojaznosti izračunata je na osnovu antropometrijskih pokazatelja: indeksa telesne mase (*body mass index* – BMI), obima struka (*waist circumference* – WC) i odnosa između obima struka i obima kukova (*waist to hip ratio* – WHR). Korelacija između BMI, WC i WHR utvrđena je Pirsonovim koeficijentom korelacije, a multiplom regresionom analizom utvrđena je povezanost sociodemografskih parametara i pokazatelja gojaznosti. **Rezultati.** Utvrđena je statistički značajna pozitivna korelacija za sve antropometrijske parametre kod oba pola. Podaci pokazuju da 66,32% muškaraca i 49,68% žena ima problem povećane uhranjenosti. U proseku, kod oba pola, 38,52% ima prekomernu telesnu masu dok je gojaznih 19,48%. Faktori koji su najviše uticali na povećane vrednosti BMI, WC i WHR bili su kod muškaraca starost, a kod žena starost, obrazovanje i poreklo. Obrazovanje žena bilo je u negativnoj korelaciji sa stepenom uhranjenosti. **Zaključak.** Prevalencije prekomerno uhranjenih i gojaznih osoba koje su dobijene na osnovu antropometrijskih parametara razlikuju se. Međutim, bez obzira na primenjenu metodu prevalencija osoba povećane uhranjenosti veoma je visoka i jedna je od najviših u Evropi. Rezultati ukazuju na potrebu za obukom stanovništva i redovnom kontrolom njihovog zdravstvenog stanja.

Ključne reči:
gojaznost; prevalenca; srbija; demografija; socijalni faktori; pol, faktor.

Abstract

Background/Aim. Obesity represents one of the frequent health problems in developed countries today. It is related to cardiovascular diseases, diabetes and various cancer forms. The aim of the study was to determine the prevalence of overweight and obesity in adult population of the northern Bačka and Banat. **Methods.** On the basis of a multistage stratified random sampling, 4,505 individuals of the age 40.61 ± 11.29 years took part in the study. The study included 46 rural settlements. The overweight and obesity prevalence was obtained using the anthropometric indicators of body mass index (BMI), waist circumference (WC) and the waist to hip ratio (WHR). The correlations among BMI, WC and WHR were determined by the Pearson's correlation coefficient while the multiple regression analysis was used for correlating sociodemographic parameters and the obesity index. **Results.** A significant positive correlation was found in relation to all anthropometric parameters in both sexes. The data indicated that 66.32% of males and 49.68% of females had an overweight problem. On average, approximately 38.52% of subjects of both sexes were overweight, while 19.48% were obese. The factors that largely contributed to higher values of the obesity index were the age of male subjects and the age, education and origin in females. Ragarding the female subjects, the level of education negatively correlated with the level of nutritional condition. **Conclusion.** The prevalence values of the overweight and obese subjects, obtained on the basis of the anthropometric parameters, vary. However, regardless methods applied, the percentage of the overweight and obese persons is very high, being among the highest recorded in European populations. The obtained results indicate the necessity of introducing better education programmes and conducting regular health controls among citizens in these regions.

Key words:
obesity; prevalence; serbia; demography; social conditions; gender.

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Uvod

Gojaznost danas predstavlja čest hronični zdravstveni problem koji snižava kvalitet života i značajno utiče na morbiditet i ukupni mortalitet. Prema podacima Svetske zdravstvene organizacije (SZO) [1], prevalencija prekomerne telesne mase i gojaznosti u stalnom je porastu u razvijenim zemljama od 1980-te godine. Procenjuje se da je danas u svetu oko milijardu ljudi prekomerno uhranjeno, dok je gojaznih oko 300 miliona [2]. Prekomerna uhranjenost i gojaznost ranije su bili problem razvijenih zemalja, međutim, novija istraživanja zemalja u razvoju pokazuju da je u nekim zemljama prevalencija gojaznosti visoka, ili čak i veća od one u razvijenim zemljama [3]. Nedavna istraživanja kod odraslih u Šri Lanki [4] ustanovila su visoku učestalost prekomerne telesne mase i gojaznosti, posebno abdominalne gojaznosti. Istraživanja koja su rađena pre 1989. godine pokazuju da je u zemljama u razvoju gojaznost povezana sa višim socioekonomskim statusom i da predstavlja bolest bogatijih slojeva, dok je u razvijenim zemljama trend obrnut [5]. Novija istraživanja u zemaljama u razvoju pokazuju drugačiju povezanost socioekonomskog statusa i gojaznosti. Značajne socioekonomske promene kroz koje prolaze zemlje u razvoju doprinose promenama u načinu i stilu života. To je uslovilo manju zastupljenost gojaznosti kod osoba koje pripadaju višim društvenim slojevima, što je karakteristika razvijenih zemalja [6, 7]. Prevalencija gojaznosti može se značajno razlikovati između regiona iste države [8]. Istraživanja u nekim zemljama Evrope [9] i u Americi [10] utvrdila su veću prevalenciju gojaznosti kod stanovništva seoskih krajeva u odnosu na stanovništvo iz gradskih sredina. Ove razlike naročito su izražene u zemljama sa niskim bruto društvenim proizvodom [8].

Prema podacima Instituta za javno zdravlje Srbije [11] više od polovine odraslog stanovništva Srbije (54%) ima povećanu telesnu masu, pri čemu je 36,7% sa prekomernom telesnom masom, dok je 17,3% gojazno [12]. Gojaznost je povezana sa kardiovaskularnim bolestima, dijabetesom i mnogim formama malignih bolesti [2]. Prema zvaničnim podacima Ministarstva zdravlja Republike Srbije [12], više od 46% odrasle populacije u Srbiji ima hipertenziju, a 56,8% smrtnih ishoda je prouzrokovano bolestima srca i krvnih sudova. U populaciji Beograda starosti od 30 do 69 godina, od 1990. do 2002. godine, skoro svaka druga osoba umrla je od neke kardiovaskularne bolesti [13]. Poznavanje telesnog sastava zbog toga je veoma značajno i često se istražuje u epidemiološkim, kliničkim i populacionim studijama [14]. Količina i distribucija masnog tkiva danas se najčešće određuju pomoću antropoloških indeksa. Prednost antropometrijskih metoda je što su one neinvazivne, jednostavne za korišćenje, ne iziskuju velika materijalna ulaganja i vrlo su pogodne za terenska istraživanja. Indeks telesne mase (*Body mass index* – BMI kg/m^2) prema preporuci SZO veoma je korisna mera za procenu uhranjenosti i indikator rizika od bolesti uslovljenih telesnom masom. Pokazatelji distribucije masnog tkiva su obim struka i kukova, kao i (*weist hip ratio* – WHR) indeks koji se dobija iz njihovog međusobnog odnosa. Istraživanja [15, 16] su ukazala na važnost distribucije masnog tkiva u proceni gojaznosti i pojavi zdravstvenog rizika. Utvrđeno je da gomilanje masnog tkiva u abdominalnom regionu (androidna gojaznost) ima veći zdravstveni rizik od bolesti od akumulacije masti u predelu kukova. Androidna gojaznost povezana je sa hipertenzijom, povećanim nivoom triglicerida i dijabetesom [17, 18]. Kako bi se potencijalni zdravstveni rizik otkrio u ranom stadijumu, značajno je poznavati distribuciju masnog tkiva, čak i kod osoba sa normalnom telesnom masom.

Vojvodina je region Srbije koja je po broju gojaznih, obolelih i umrlih od raznih kardiovaskularnih bolesti bila na samom vrhu još u bivšoj Jugoslaviji, a situacija nije manje alarmantna ni danas. Stoga, cilj ovog rada bio je da se pomoću antropometrijskih indeksa utvrdi zastupljenost prekomerne telesne mase i gojaznosti kod odrasle ruralne populacije Bačke i Banata.

Metode

Transverzalno antropološko istraživanje izvršeno je u periodu od 2001. do 2007. godine u skladu sa preporukama Internacionalnog biološkog programa (IBP) [18] i SZO [2].

Na osnovu višeetapnog stratifikovanog uzorka metodom slučajnog uzorka odabrane su 4 504 odrasle osobe (1 965 muškaraca, 2 539 žena) prosečne starosti 40,61 ± 11,29 godina iz 46 seoskih naselja koja su ravnomerno raspoređena na celokupnoj teritoriji Bačke i Banata i obuhvataju većinu ovih oblasti. Prema humano-biološkoj klasifikaciji stanovništvo je bilo podeljeno na starosedeoce, doseljenike i stanovništvo mešanog porekla. Starosedeoci su oni čiji su praroditelji (babe i dede) rođeni na teritoriji Vojvodine. Tu spadaju etničke grupe Srba, Mađara, Slovaka, Rumuna, Rusina, Roma i drugih manje brojnih etničkih grupa. Doseljeno stanovništvo obuhvata one čiji su praroditelji sa obe strane rođeni van teritorije Vojvodine, a doseljeni su iz Crne Gore, Bosne, Hercegovine, Hrvatske, Like i Srbije. Mešanom stanovništvu pripadaju oni čiji su praroditelji sa jedne strane rođeni u Vojvodini, a sa druge strane van Vojvodine. Za svakog ispitanika izračunate su decimalne godine na osnovu datuma ispitivanja i datuma rođenja, a na osnovu decimalne starosti stanovništvo je bilo podeljeno na pet uzrasnih kategorija. Prema stepenu obrazovanja ispitanici su bili podeljeni na tri grupe: sa osnovnim (do 8 godina školovanja), srednjim (12 godina školovanja) i višim i visokim obrazovanjem (14 i 16 godina školovanja).

Korišćenjem standardnih antropometrijskih instrumenata (Sieber Hegner, Switzerland) izmerene su visina tela, masa tela, obim struka i obim kukova. Sva merenja vršena su u prepodnevnim časovima, a ispitanici su bili lako obučeni i bez obuće. Visina tela merena je pomoću antropometra sa tačnošću 0,1 cm. Masa tela merena je na digitalnoj vagi sa tačnošću od 100 g. Obim struka meren je pomoću merne trake na središnjoj liniji između najniže tačke rebarnog luka i najviše tačke bedrenog grebena karlične kosti, na kraju normalne ekspiracije. Obim kukova meren je u nivou velikog trohantera butne kosti.

Uhranjenost je utvrđena pomoću formule za BMI [BMI = masa tela/visina^2 (kg/m^2); pothranjeni < 18,5 kg/m^2; normalno uhranjeni 18,5–24,9 kg/m^2; prekomerno uhranjeni 25,0–29,9 kg/m^2; gojazni ≥ 30 kg/m^2]. Abdominalna gojaz-

nost utvrđena je preko obima struka (WC) i indeksa distribucije masnog tkiva (*Waist circumference* – WHR). Usvojene granične vrednosti za obim struka kod muškaraca bile su WC ≥ 94 cm za prekomernu uhranjenost i WC ≥ 102 cm za gojaznost, a kod ženskog pola WC ≥ 80 cm za prekomernu uhranjenost i WC ≥ 88 cm za gojaznost. Kod muškog pola granična vrednost koja označava prekomernu uhranjenost bila je za WHR ≥ 0,95, a za gojaznost WHR ≥ 1,0; kod ženskog pola vrednosti su bile ≥ 0,80 za prekomernu uhranjenost, a ≥ 0,85 za gojaznost [2].

Podaci su obrađeni korišćenjem programa SPSS 10. Izračunate su prevalencije prekomerne uhranjenosti i gojaznosti na osnovu sva tri antropološka parametra, a razlike između grupa testirane su χ^2 testom. Korelacija između BMI, WC i WHR utvrđena je Pirsonovim koeficijentom korelacije na nivou značajnosti od $p < 0,01$. Multiplom regresionom analizom utvrđena je povezanost sociodemografskih parametara i indeksa gojaznosti.

Rezultati

U tabeli 1 predstavljeni su podaci o sociodemografskim karakteristikama ispitanika. Uočava se da je većina ispitanika bila mlađa od 60 godina, većinom su živeli u naseljima do 5000 stanovnika, najviše su starosedelačkog porekla i sa srednjim obrazovanjem.

Pirsonovim koeficijentom korelacije utvrđena je statistički značajna pozitivna korelacija za sve antropometrijske parametre kod oba pola. Kod muškaraca korelacija je iznosila: BMI i WHR R = 0,63, $p < 0,01$; BMI i WC = 0,87, $p < 0,01$; WHR i WC = 0,83, $p < 0,01$, a kod žena koeficijenti korelacije bile su: BMI i WHR R = 0,56, $p < 0,01$; BMI i WC = 0,89, $p < 0,01$; WHR i WC = 0,89, $p < 0,01$.

U tabeli 2 predstavljena je prevalencija muškaraca sa prekomernom telesnom masom i gojaznošću na osnovu BMI, obima struka i WHR. Kod muškaraca, na osnovu BMI, prevalencija prekomerne telesne mase bila je, 45,09% a gojaznosti 21,23%. Procenat prekomerno teških i gojaznih povećavao se sa uzrastom i uočena je značajna povezanost gojaznosti sa godinama života ($p < 0,001$). Muškarci su samo u najmlađoj grupi najčešće bili normalno uhranjeni, a u svim ostalim uzrasnim grupama preovlađivala je prekomerna uhranjenost. Muškarci različitog porekla imali su sličnu prevalenciju prekomerno teških i gojaznih osoba. Obrazovanje muškaraca nije bio značajan faktor koji utiče na BMI ($p > 0,05$), a prevalencija prekomerno teških i gojaznih osoba bila je slična u sve tri obrazovne grupe. Prema obimu struka znatan broj muškaraca (57,55%) imao je povećane vrednosti i centralnu gojaznost. Najmanju prevalenciju gojaznosti imali su muškarci u najmlađoj uzrasnoj kategoriji, a zatim se ona povećavala, te je u ostalim grupama gojaznost bila zastupljena kod više od polovine muškaraca. Nije utvrđena značajnija povezanost između povećanog obima struka i porekla ($p > 0,05$) i obrazovanja ($p > 0,05$). Nešto manji procenat centralne gojaznosti (45,59%) uočen je na osnovu WHR. Kao u slučaju prethodne dve karakteristike, uzrast ispitanika predstavljao je najznačajniji faktor koji je uticao na vrednosti WHR ($p < 0,001$).

Tabela 1

Sociodemografske karakteristike ispitanika

Karakteristike	Muškarci (n = 1 865, 43,91%)		Žene (n = 2 382; 56,09%)	
	n	%	n	%
Godine života				
20–29	448	24,02	423	17,76
30–39	446	23,91	577	24,22
40–49	511	27,40	799	33,54
50–59	386	20,70	529	22,21
> 60	74	3,97	54	2,27
Broj stanovnika				
do 5,000	1007	53,99	1205	50,59
5,000–10,000	491	26,33	668	28,04
10,000–20,000	367	19,68	509	21,37
Poreklo				
starosedeoci	1112	59,62	1437	60,33
doseljenici	675	36,19	863	36,23
mešano	78	4,18	82	3,44
Obrazovanje				
osnovno	264	14,15	532	22,33
srednje	1245	66,76	1283	53,86
više	356	19,09	567	23,80

Kod ženskog pola (tabela 3) na osnovu BMI utvrđen je značajno manji procenat ($p < 0,01$) prekomerno uhranjenih (31,95%) i gojaznih (17,73%) osoba. Značajan uticaj na vrednosti BMI imao je uzrast ispitanica ($p < 0,001$), a sa starenjem se povećavao procenat prekomerno teških i gojaznih žena. Na vrednosti BMI značajno su uticali poreklo ($p < 0,001$) i obrazovanje ($p < 0,001$). Žene različitog porekla međusobno se nisu razlikovale u frekvenciji prekomerno uhranjenih, međutim, kod žena starosedelaca utvrđen je značajno veći procenat gojaznih ($p < 0,01$). Obrazovanje je bio značajan faktor koji je uticao na vrednosti BMI. Sa povećanjem stepena obrazovanja opadao je procenat prekomerne uhranjenosti, a u grupi sa višim i visokim obrazovanjem nije

Tabela 2
Prekomerna uhranjenost i gojaznost u različitim grupama muškaraca prema indeksu telesne mase (*body mass index* – BMI), obimu struka (*waist circumference* – WC) i indeksu distribucije masnog tkiva (*waist to hip ratio* – WHR)

Sociodemografske karakteristike	BMI, n (%)			WC, n (%)			WHR, n (%)		
	prekomerna telesna masa	gojaznost	ukupno (%)	prekomerna telesna masa	gojaznost	ukupno (%)	prekomerna telesna masa	gojaznost	ukupno (%)
Ukupni uzorak (n)	886 (45,09)	417 (21,23)	66,32	499 (25,39)	632 (32,16)	57,55	477 (24,27)	419 (21,32)	45,59
Godine života									
20–29	179 (37,84)	44 (9,30)	47,14	90 (19,03)	65 (13,74)	32,77	53 (11,20)	21 (4,44)	15,64
30–39	203 (43,38)	102 (21,8)	65,18	120 (25,64)	134 (28,63)	54,27	114 (24,36)	68 (14,53)	38,89
40–49	243 (45,68)	145 (27,26)	72,94	143 (26,88)	208 (39,10)	65,98	156 (29,32)	138 (25,94)	55,26
50–59	218 (53,30)	104 (25,43)	78,73	114 (27,87)	189 (46,21)	74,08	127 (31,05)	151 (36,92)	67,97
> 60	43 (51,81)	22 (26,51)	78,32	32 (38,55)	36 (43,37)	81,92	27 (32,53)	41 (49,40)	81,93
Poreklo									
starosedeoci	504 (42,62)	234 (19,78)	62,4	286 (24,17)	355 (30,00)	54,17	274 (23,16)	255 (21,55)	44,71
doseljenici	335 (47,99)	164 (23,49)	71,48	187 (26,79)	252 (36,10)	62,89	174 (24,93)	152 (21,78)	46,71
mešano	42 (50,00)	14 (16,67)	66,67	26 (30,95)	25 (29,76)	60,71	29 (34,52)	12 (14,29)	48,81
Obrazovanje									
osnovno	115 (40,21)	48 (16,78)	56,99	58 (20,21)	83 (28,92)	49,13	57 (19,86)	69 (24,04)	43,9
srednje	542 (44,14)	282 (22,96)	67,10	304 (24,76)	410 (33,39)	58,15	311 (25,32)	258 (21,01)	46,33
više	194 (50,52)	65 (16,93)	67,45	121 (31,51)	115 (29,95)	61,46	88 (22,92)	79 (20,57)	43,49

Tabela 3
Prekomerna uhranjenost i gojaznost u različitim grupama žena prema indeksu telesne mase (*body mass index* – BMI), obimu struka (*waist circumference* – WC) i indeksu distribucije masnog tkiva (*waist to hip ratio* – WHR)

Sociodemografski parametri	BMI, n (%)			WS, n (%)			WHR, n (%)		
	prekomerna telesna masa	gojaznost	ukupno (%)	prekomerna telesna masa	gojaznost	ukupno (%)	prekomerna telesna masa	gojaznost	ukupno (%)
Ukupni uzorak	811 (31,95)	450 (17,73)	49,68	579 (22,80)	813 (32,02)	54,82	695 (27,37)	614 (24,18)	51,55
Godine									
20–29	58 (12,98)	24 (5,37)	18,35	57 (12,75)	42 (9,40)	22,15	68 (15,18)	37 (8,28)	23,46
30–39	151 (24,47)	63 (10,21)	34,68	145 (23,50)	116 (18,80)	42,3	153 (24,80)	103 (16,70)	41,5
40–49	320 (37,78)	173 (20,43)	58,21	240 (28,30)	295 (34,79)	63,09	277 (32,67)	211 (24,88)	57,55
50–59	260 (45,86)	166 (29,27)	75,13	126 (22,22)	315 (55,55)	77,77	186 (32,80)	225 (39,68)	72,48
> 60	25 (41,67)	29 (48,33)	90,00	11 (18,33)	45 (75,00)	93,33	11 (18,33)	38 (63,33)	81,66
Poreklo									
starosedeoc	484 (31,25)	306 (19,75)	51,00	341 (22,90)	495 (33,24)	55,50	449 (28,99)	386 (24,91)	53,90
doseljenik	302 (33,55)	134 (14,89)	48,44	190 (22,22)	268 (31,34)	53,78	226 (25,11)	213 (23,67)	48,78
mešano	25 (27,78)	10 (11,11)	38,89	19 (23,75)	19 (23,75)	47,50	20 (22,22)	15 (16,67)	38,89
Obrazovanje									
osnovno	211 (37,02)	161 (28,25)	65,27	120 (21,05)	274 (48,07)	69,12	250 (43,86)	140 (24,56)	68,42
srednje	399 (30,86)	210 (16,24)	47,10	298 (23,03)	372 (28,75)	51,78	485 (37,48)	146 (11,28)	4876
više	69 (11,42)	- (-)	11,42	142 (23,51)	150 (24,83)	48,34	202 (33,44)	56 (9,27)	42,71

uočena nijedna gojazna osoba. Značajan procenat žena se odlikovao povećanim vrednostima obima struka (54,82%). Prevalencija centralne gojaznosti bila je povezana sa uzrastom ($p < 0,001$), pa je u najstarijoj kategoriji više od 90% žena imala povećane vrednosti obima struka. Kod muškaraca do 40. godine uočena je veća ukupna prevalencija centralne gojaznosti. Od 40. do 59. godine oba pola imala su sličnu zastupljenost osoba sa povećanim vrednostima obima struka, a

u najstarijoj kategoriji prevalencija je bila veća kod žena. Obrazovanje je prepoznato kao značajan faktor koji utiče na povećane vrednosti obima struka ($p < 0,001$). Najviše žena sa značajno povećanim vrednostima obima struka (≥ 88 cm) bilo je u kategoriji sa osnovnim obrazovanjem, a sa povećanjem stepena obrazovanja prevalencija centralne gojaznosti se smanjivala. Sličan procenat centralne gojaznosti uočen je i na osnovu WHR. U ukupnom uzorku 51,55% ispitanica imala je povećane vrednosti WHR. Stariji uzrast ispitanica ($p < 0,001$), starosedelačko poreklo ($p < 0,001$) i niže obrazovanje ($p < 0,001$) uticali su na povećane vrednosti WHR.

Diskusija

Podaci istraživanja ukazuju na to da 66,32% muškaraca i 49,68% žena ima problem povećane uhranjenosti. U proseku, kod oba pola oko 38,52% ima prekomernu telesnu masu dok je gojaznih oko 19,48%. Ovi podaci slični su podacima Ministarstva zdravlja Republike Srbije [11], koji ukazuju da u Srbiji najveću prevalenciju prekomerne telesne mase (35,5%) i gojaznosti (23%) ima Vojvodina. Slična prevalencija prekomerne telesne mase (35,7%) i gojaznosti (21,7%) uočena je i u drugim ispitivanjima vojvođanskog stanovništva [19].

Veća frekvencija osoba sa prekomernom telesnom masom uočena je kod muškaraca (45,05%) nego žena (31,95%), što je uočeno i ranije u našoj zemlji [19] i svetu [14]. U odnosu na podatke SZO [20] o učestalosti osoba sa prekomernom telesnom masom i gojaznih u različitim delovima sveta, ispitani uzorak vojvođanskog stanovništva nalazi se u samom vrhu evropskih zemalja.

Faktori koji su najviše uticali na povećane vrednosti BMI, bili su starost kod muškaraca, a kod žena starost, obrazovanje i poreklo. Rezultati su pokazali progresivno povećanje mase tela sa godinama života, s posledičnim povećanim vrednostima BMI u starijim uzrastima. Razlog ovome je što sa starenjem dolazi do sniženja utroška energije, što je prouzrokovano opadanjem bazalnog metabolizma i smanjenom fizičkom aktivnošću. Kod muškaraca najveći porast mase tela i BMI je između dve najmlađe uzrasne kategorije, a od 40. godine vrednosti se ne menjaju značajnije, što se ogleda u sličnim frekvencijama prekomerne telesne mase i gojaznih u starijim uzrastima. Muškarci su samo u najmlađoj kategoriji (20–29 godina) većinom normalno uhranjeni, a u svim ostalim uzrastima preovlađuje prekomerna uhranjenost. Porast mase tela i BMI kod žena je linearan, te se procenat povećane uhranjenosti povećava u svakoj uzastopnoj dekadi. Do 50. godine najveći broj žena je normalno uhranjen, ali njihov procenat opada sa starenjem. Nakon 50. godine one su većinom sa prekomernom telesnom masom i gojazne. Obrazovanje žena je u negativnoj povezanosti sa stepenom uhranjenosti. Najveći procenat žena sa prekomernom telesnom masom i gojaznošću uočen je u grupi sa osnovnom školom, a sa povećanjem stepena obrazovanja njihov procenat opada, te u grupi sa višim i visokim obrazovanjem nije nađena nijedna gojazna žena. Negativna povezanost obrazovanja sa stepenom uhranjenosti uočena je i u drugim ispitivanjima u našoj zemlji [21, 19] i svetu [22–24]. Razlike između ovih grupa žena verovatno su uzrokovane kako finansijskom situacijom, tako i različitim stilom života, higijenskim i nutritivnim navikama. Han i sar. [22] navode da obrazovni nivo može uticati na nedostatak znanja ili interesa za zdravim načinom života, kao i na ishranu hranom lošijeg kvaliteta. Nešto veća frekvencija gojaznih žena uočena je kod starosedelaca. Ista tendencija zabeležena je i u ranijim istraživanjima u Vojvodini [25], kada su, takođe, uočene veće prosečne vrednosti BMI kod starosedelaca.

Iako je danas BMI preporučen od strane SZO i najčešće se koristi u antropološkim i epidemiološkim studijama kao pokazatelj uhranjenosti, on ima i nedostataka, s obzirom na to da se na osnovu njega ne može razdvojiti masna i mišićna komponenta. Stoga, njegovo korišćenje nije preporučljivo kod izrazito mišićavih osoba, male dece i starijih osoba kod kojih je mišićna masa zamenjena masnom [14]. Osobe koje imaju slične vrednosti BMI mogu se značajno razlikovati u količini abdominalnog masnog tkiva. Zbog toga se pored BMI danas često koriste i WHR i obim struka koji ukazuju kako na ukupnu, tako i na centralnu gojaznost. Distribucija masnog tkiva, tj, veličina intraabdominalnog masnog tkiva, značajan je faktor, koji može da ukaže na predispoziciju od nastanka kardiovaskularnih i metaboličkih oboljenja [26–29]. Kako bi se potencijalni zdravstveni rizik otkrio u ranom stadijumu značajno je poznavati distribuciju masnog tkiva, čak i kod osoba sa normalnom masom tela [17]. Iako su BMI, obim struka i WHR u značajno visokoj korelaciji, prevalencije prekomerne mase i gojaznosti dobijene na osnovu ovih parametara mogu značajno varirati. Najveći procenat prekomerno uhranjenih muškaraca i žena dobijen je na osnovu BMI (25,0–29,9 kg/m^2), a najmanji kod muškaraca sa WHR ≥ 0,95 i žena sa obimom struka ≥ 80 cm. Kod oba pola najveća zastupljenost gojaznih (32%) utvrđena je na osnovu obima struka (WC ≥ 102 cm muškarci; WC ≥ 88 cm žene). Indeksi BMI i WHR pokazuju isti procenat gojaznih muškaraca (21%), a najmanje gojaznih žena dobijeno je na osnovu BMI (17,73%). Istraživanja u drugim zemljama [14] pokazala su da prevalencija prekomerne uhranjenosti može značajno da varira među populacijama kada se određuje na osnovu obima struka (≥ 94 cm za muškarce, ≥ 80 cm za žene) ili BMI (25,0–29,9 kg/m^2). Autori ističu da razlike u prevalencijama koje su dobijene na osnovu ovh parametara kod muškaraca mogu biti i više od 20%, a kod žena oko 10%. Kod muškaraca, takođe, uočili su veću prevalenciju prekomerno uhranjenih, na osnovu BMI u odnosu na obim struka, što je slično rezultatima ovog istraživanja.

Na povećanje abdominalne gojaznosti pozitivno utiču godine života kod muškaraca, a kod žena godine života, nizak nivo obrazovanja i poreklo. Do 40. godine muškarci imaju veću učestalost centralne gojaznosti. Nakon 50. godine prevalencija raste kod žena, ali razlike u odnosu na muški pol nisu značajne. Porast abdominalne gojaznosti kod žena posledica je menopauze koja dovodi do promena u telesnoj kompoziciji i promena u adipoznom tkivu [30]. Kao u slučaju BMI kod ženskog pola uočena je značajna negativna povezanost pokazatelja abdominalne gojaznosti sa obrazovanjem, dok kod muškaraca ova povezanost nije utvrđena, slično drugim istraživanjima [31]. Najveću prevalenciju abdominalne gojaznosti, koja je

izražena preko obima struka i WHR, imale su žene sa osnovnim obrazovanjem, a najmanju žene sa višim obrazovanjem. Rezultati ovog istraživanja pokazuju da je stepen uhranjenosti i distribucija masnog tkiva kod žena u znatnoj meri uslovljena obrazovanjem. U mnogim istraživanjima [22, 32, 33] utvrđeno je da su osobe sa najnižim stepenom obrazovanja imale povećane vrednosti WHR i BMI. Manje obrazovane žene najčešće su prekomerno uhranjene. U većini zemalja bolje obrazovanje uslovljava određeni stil života, koji podrazumeva racionalniju ishranu, bolje higijenske uslove, manje konzumiranje alkohola i duvana, pravilnu fizičku aktivnost i više preventivnih zdravstvenih pregleda, što su elementi na koje obrazovanje može imati značajnog uticaja. Svi pokazatelji gojaznosti imali su veće vrednosti kod žena starosedelaca. Razlike između starosedelačkih i doseljeničkih žena danas su manje izražene nego u ranijim istraživanjima [25], što je verovatno posledica prilagođavanja, zajedničkog života i menjanja navika u ishrani. Međutim, razlike između ove dve grupe i žena mešanog porekla su veće. Ovi rezultati su možda posledica manjeg broja ispitanica u toj grupi. Drugi razlog je možda manja prosečna vrednost decimalnih godina, koja kod žena mešanog porekla iznosi 44,04 ± 9,16, a kod starosedelaca i doseljenica 44,96 ± 9,84 i 47,14 ± 8,37.

Zaključak

Prevalencije prekomerno uhranjenih i gojaznih osoba, dobijene na osnovu BMI, obima struka i WHR razlikuju se. Međutim, bez obzira na to, dobijena prevalencija povećane uhranjenosti veoma je visoka i jedna je od najviših u Evropi. Ovi rezultati su u skladu sa rezultatima drugih sličnih istraživanja vojvođanskog stanovništva, i ukazuju na potrebu edukacije stanovništva o zdravom načinu života i usvajanju zdravih životnih navika. Potrebna su stalna antropološka istraživanja, kako bi se na vreme otkrile osobe sa stvarnim i potencijalnim zdravstvenim problemima.

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Prevalence of renal dysfunction and its influence on functional capacity in elderly patients with stable chronic heart failure

Učestalost bubrežne disfunkcije i njen uticaj na funkcionalni kapacitet kod starijih bolesnika sa hroničnom stabilnom insuficijencijom srca

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Abstract

Bacground/Aim. Chronic heart failure (CHF) is highly prevalent and constitutes an important public health problem around the world. In spite of a large number of pharmacological agents that successfully decrease mortality in CHF, the effects on exercise tolerance and quality of life are modest. Renal dysfunction is extremely common in patients with CHF and it is strongly related not only to increased mortality and morbidity but to a significant decrease in exercise tolerance, as well. The aim of our study was to investigate the prevalence and influence of the renal dysfunction on functional capacity in the elderly CHF patients. **Methods.** We included 127 patients aged over 65 years in a stable phase of CHF. The diagnosis of heart failure was based on the latest diagnostic principles of the European Society of Cardiology. The estimated glomerular filtration rate (eGRF) was determined by the abbreviated Modification of Diet in Renal Disease (MDRD2) formula, and patients were categorized using the Kidney Disease Outcomes Quality Initiative (K/DOQI) classification system. Functional capacity was determined by the 6 minute walking test (6MWT). **Results.** Among 127 patients, 90 were men. The average age was 72.5 ± 4.99 years and left ventricular ejection fraction (LVEF) was 40.22 ± 9.89%. The average duration of CHF was 3.79 ± 4.84 years. Ninty three (73.2%) patients were in New York Heart Association (NYHA) class II and 34 (26.8%) in NYHA class III. Normal renal function (eGFR ≥ 90 mL/min) had 8.9% of participants, 57.8% had eGFR between 60–89 mL/min (stage 2 or mild reduction in GFR according to K/DOQI classification), 32.2% had eGFR between 30–59 mL/min (stage 3 or moderate reduction in GFR) and 1.1% had eGFR between 15–29 mL/min (stage 4 or severe reduction in GFR). We found statistically significant correlation between eGFR and 6 minute walking distance (6MWD) ($r = 0.390$, $p < 0.001$), LVEF ($r = 0.268$, $p < 0.05$), NYHA class ($\varrho = -0.269$, $p < 0.05$) and age ($r = -0.214$, $p < 0.05$). In multiple regression analysis only patients' age was a predictor of decreased 6MWD < 300 m (OR = 0.8736, CI = 0.7804 - 0.9781, $p < 0.05$). **Conclusion.** Renal dysfunction is highly prevalent in the elderly CHF patients. It is associated with decreased functional capacity and therefore with poor prognosis. This study corroborates the use of eGFR not only as a powerful predictor of mortality in CHF, but also as an indicator of the functional capacity of cardiopulmonary system. However, clinicians underestimate a serial measurement of eGFR while it should be the part of a routine evaluation performed in every patient with CHF, particularly in the elderly population.

Key words:
heart failure; aged; kidney failure; glomerular filtration rate; quality of life.

Apstrakt

Uvod/Cilj. Srčana insuficijencija (SI) je značajan zdravstveni problem koji ima epidemijske razmere. U terapiji SI koriste se mnogobrojni lekovi koji utiču na smanjenje mortaliteta. Međutim, oni ne popravljaju značajno funkcionalni kapacitet i kvalitet života. Bubrežna disfunkcija, često prisutna kod bolesnika sa SI, značajno je udružena sa povećanim morbiditetom i mortalitetom, ali i sa smanjenim funkcionalnim kapacitetom. Cilj istraživanja bio je da se utvrdi učestalost bubrežne disfunkcije i njen uticaj na funkcionalni kapacitet kod starijih bolesnika sa stabilnom SI. **Metode.** U istraživanje je bilo uključeno 127 bolesnika, starijih od 65 godina u stabilnoj fazi SI. Funkcionalni kapacitet određivan je pomoću 6-minutnog testa hodom, glomerularne filtracije (GFR) pomoću skraćene *Modification of Diet in Renal Disease* (MDRD) formule. **Rezultati.** Od ukupno 127 bolesnika u stabilnoj fazi SI (prosečnog trajanja 3,79 ± 4,84 godina), funkcionalne *New York Heart Association* (NYHA) klase II ili III, 90 je bilo muškog pola. Njihova prosečna starost iznosila je 72,5 ± 4,99 godina, a prosečna ejekciona frakcija (EF) 40,2 ± 9,9%. Normalnu bubrežnu funkciju imalo je 8,9%

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ispitanika, 57,8% bolesnika imalo je lako smanjenu GFR [stadijum 2 prema *Kidney Disease Outcomes Quality Initiative* (K/DOQI klasifikaciji), 32,2% imalo je umereno redukovanu GFR (stadijum 3) dok je 1,1% bolesnika imalo teško redukovanu GFR (stadijum 4)]. Nađena je značajna korelacija između GFR i rastojanja pređenog tokom 6-minutnog testa hodom ($r = 0,390$, $p < 0,01$), EF ($r = 0,268$, $p < 0,05$), NYHA klase ($\varrho = -0,269$, $p < 0,05$) i životnog doba ($r = -0,214$, $p < 0,05$). Jedini prognostički pokazatelj rastojanja pređenog tokom 6-minutnog testa hodom ispod 300 m bila je starost bolesnika (OR = 0,8736, CI = 0,7804 – 0,9781, $p < 0,05$). **Zaključak.** Najveći broj ispitanika imao je bubrežnu disfunkciju koja je bila udružena sa smanjenim funkcionalnim kapacitetom koji je u SI udružen sa lošom prognozom. Serijsko određivanje GFR trebalo bi da bude rutinski deo kliničkog pregleda svih bolesnika sa SI, posebno starijih.

Ključne reči:
srce, insuficijencija; stare osobe; bubreg, insuficijencija; glomerulska filtracija; kvalitet života.

Introduction

Chronic heart failure (CHF) is a disorder associated with high mortality and persistent and prolonged hospitalizations, and affects over 10 million people in the countries represented by the European Society of Cardiology. The prevalence of CHF increases markedly with age when the treatment is often complicated by the presence of multiple comorbidities [1]. A significant portion, up to 39% of patients with CHF, also has renal insufficiency, and the prevalence increases with the age. Renal insufficiency is directly associated with morbidity and mortality independent on established risk factors such as New York Heart Association (NYHA) class and left ventricle ejection fraction (LVEF) [2, 3]. Chronic heart failure is now seen not only as a cardiac disorder but rather a cardiorenal and neurohumoral syndrome which affects quality of life more profoundly than many other chronic diseases [4, 5].

Survival in heart failure is closely related to functional capacity and some studies suggest that quality of life is a predictor of CHF course [6, 7]. Patients' functional status and ultimately quality of life are impaired because the heart is unable to meet the demands of skeletal musculature, and symptoms manifest as signs of fatigue and dyspnea even in patients with guideline-based optimized therapy. Abnormalities in central hemodynamic function are not sufficient to fully explain exercise intolerance in CHF because indices of resting ventricular function such as LVEF are poorly correlated with peak exercise capacity [1, 8, 9].

However, not only heart failure, but advanced age and renal dysfunction both closely related, have influence on functional capacity [10]. The HF-ACTION trial showed that reduced renal filtration is associated with impaired cardiorespiratory fitness and a clustering of high-risk features in systolic heart failure patients which portend a more complicated course and higher all-cause mortality [11].

The 'gold standard' method for the assessment of functional capacity is the cardiopulmonary exercise test (CPET). However, CPET equipment is expensive and cumbersome, and availability of trained staff is limited. A simple, self-paced, and submaximal alternative is the 6 minute walk test (6MWT) [12]. It is commonly used, and is both reproducible and cheap to administer [1].

The aim of our study was to assess the prevalence of renal dysfunction and its influence on functional capacity in elderly patients with stable CHF.

Methods

In our study we included 127 consecutive patients aged over 65 years in a stable phase of CHF (2 weeks without worsening of cardiovascular symptoms and without changes in medical treatment or need for intravenous inotropic support) who were recruited during the scheduled visit to the cardiologist. The diagnosis of heart failure was based on the latest diagnostic principles of the European Society of Cardiology (ESC) [13]. We enrolled patients with systolic (LVEF ≤ 45%) and diastolic heart failure with NYHA function class II and III with at least of one episode of acute cardiac decompensation. Echocardiography measurements were performed on the Vivid 4, GE ultrasound system and LVEF was measured according to the Simpson's biplane method. Serum creatinine concentration was measured by the Jaffé method (alkaline picrate reaction) with laboratory referent values 53–115 μmol/L. It is often quoted as a barometer of renal impairment, but it is actually a poor indicator of renal function. Therefore, estimation of the glomerular filtration rate (eGFR) is preferred for the accurate assessment of renal function [4, 10]. The eGFR was determined by the abbreviated Modification of Diet in Renal Disease (MDRD) formula and patients were categorized using the Kidney Disease Outcomes Quality Initiative (K/DOQI) classification system [14]. The abbreviated MDRD formula provides valid estimation of glomerular filtration rate (GFR) and according to recent findings it is superior to the Cockcroft-Gault formula [4, 15–18]. According to the World Health Organization (WHO) anemia is defined as hemoglobin (Hb) concentration < 13.0 g/dL in men and < 12.0 g/dL in women [19]. The presence of chronic obstructive pulmonary disease (COPD) was assessed according to the definition of Global Initiative for COPD – „GOLD" criteria: spirometrically assessed ratio of a post-dilatory forced expiratory volume in the first second divided by forced vital capacity (FEV1/FVC), the so-called Tiffno index, less than 70% [20]. The functional capacity was determined by the 6MWT. 6MWT was performed on flat floor, being 25 meters on straight line. The patients were instructed to walk at their own pace while attempting to cover as much ground as possible in 6 minutes. After 6 minutes the distance walked was measured to the nearest meter. The study was performed in Clinic for Cardiovascular Disease, Clinical Center Niš. The study complied with the Declaration of Helsinki. The Medical Ethical Committee of the Faculty of Medicine, University of Niš, Niš, Serbia, approved the study protocol. All participants submitted written informed consent.

Data are presented as mean ± standard deviation (SD) for continuous measures and as a proportion for categorical variables. We used Pearson's correlation coefficient (r) for variables with normal distribution and Spearman's *rho* correlation coefficient (ρ) for ordinal variables. Multiple regression analysis was used to determine predictors of reduced 6MWD and therefore, decreased functional capacity. All the values of p were two-tailed and statistical significance was established as $p < 0.05$. Statistical analysis was completed using the SPSS software, version 17.0 for Windows.

Results

Among 127 patients, 90 (70.9%) were men. The baseline patients' characteristics are presented in Table 1. The average age was 72.5 ± 4.99 years and LVEF was 40.22 ± 9.89%. The average duration of CHF was 3.79 ± 4.84 years. Ninty three (73.2%) patients were in NYHA class II and 34 (26.8%) in NYHA class III. Only 17 (13.38%) patients had diastolic heart failure (heart failure with preserved LVEF). Comorbidities and previous medical procedures are presented in Table 2. The etiology of heart failure is presented in Table 3. Twenty four (18.9%) patients had anemia (the lowest value of hemoglobin was 98 g/L) and 17 (13.38%) patients had COPD (the average value of Tiffno index was 0.61). They were on stable medical therapy during at least 2 weeks before inclusion in the study (Table 4). Only 8.9% of the participants had eGFR ≥ 90 mL/min, 57.8% had eGFR between 60–89 mL/min (stage 2 or mild reduction in GFR according to K/DOQI classification), 32.2% had eGFR between 30–59 mL/min (stage 3 or moderate reduction in GFR) and 1.1% had eGFR between 15–29 mL/min (stage 4 or severe reduction in GFR) (Figure 1). Figure 2 shows a scattered diagram with creatinin values grouped in the adequate K/DOQI class. We correlated all the relevant factors with the 6MWD and eGFR including LVEF, NYHA class, age, gender, body mass index (BMI), heart rate (HR),

Table 3
Etiology of heart failure in the patients included in the study

Etiology of CHF	n (%) of patients
Ischemic heart disease	86 (67.6)
Arterial hypertension	30 (23.8)
Dilated cardiomyopathy	9 (7.4)
Valvular disease	2 (1.2)

Table 4
Cardiovascular medical treatment of the patients included in the study

Medication	n (%) of patients
ACE inhibitors	107 (84.5)
Beta blockers	127 (100)
Antiplatelet agents	105 (82.5)
Anticoagulants (vitamin K antagonist)	41 (32)
Digoxin	33 (25.8)
Diuretics	90 (71.1)
Spironolacton	60 (47.4)
Nitrates	63 (49.5)
Calcium antagonists	26 (20.6)
Statins	43 (34)
Amiodaron	14 (11.3)

Table 1
The baseline characteristics of the patients included in the study

Characteristics	Mean ± SD	Min– Max
Age (years)	72.5 ± 4.996	63–86
Duration of CHF (years)	3.79 ± 4.836	0–11
LVEF (%)	40.22 ± 9.887	20–75
6MWD (m)	307.31 ± 100.055	60–513
Serum creatinine (μmol/L)	102.26 ± 31.820	66–281
eGFR (mL/min)	66.17 ± 18.451	15–109
Haemoglobin (g/L)	137.41 ± 14.948	98–172
BMI (kg/m^2)	26.55 ± 3.720	19–38
HR (/min)	72.77 ± 12.190	53–129
FEV1/VC (Tiffno index)	0.74 ± 0.094	0.43–0.96

CHF – chronic heart failure, LVEF – left ventricle ejection fraction, 6MWD – six minute walk distance, eGFR – estimated glomerular filtration rate, BMI – body mass index, HR – heart rate

Table 2
Comorbidities and previous medical procedures in patients included in the study

Comorbidities and previous medical procedures	n (%) of patients
Diabetes mellitus	38 (30.1)
Arterial hypertension	92 (72.6)
Dyslipidemia	54 (42.5)
COPD	17 (13.38)
Coronary artery disease	96 (75.7)
Previous myocardial infarction	76 (60.2)
Previous percutaneus coronary intervention	10 (8)
Previous coronary artery bypass surgery	18 (14.2)

COPD – chronic obstructive pulmonary disease

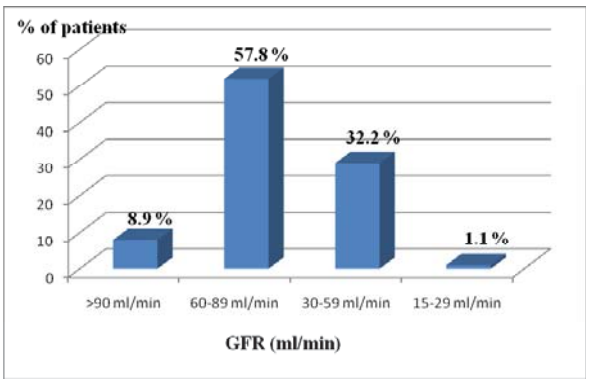

Fig. 1 – Percentage of patients with different stages of renal dysfunction

eGFR – estimated glomerular filtration rate

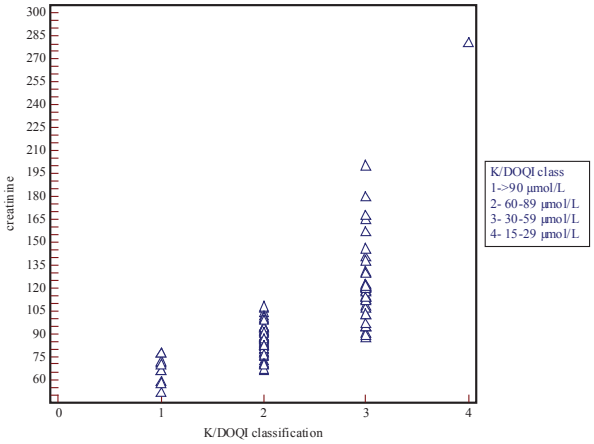

Fig. 2 – Scattered diagram with creatinine values grouped in the adequate Kidney Disease Outcomes Quality Initiative (K/DOQI) class

hemoglobin level, and the presence of COPD, systolic or diastolic heart failure. A statistically significant correlation was found between eGFR and 6MWD ($r = 0.390$, $p < 0.01$) (Figure 3), LVEF ($r = 0.268$, $p < 0.05$), NYHA class ($\rho = -0.269$, $p < 0.05$), age ($r = -0.214$, $p < 0.05$) and female gender ($\rho = -0.388$, $p < 0.01$). However, there was no significant correlation between 6MWD and creatinine ($r = -1.75$, $p = 0.1$; linear regression, $R^2 = 0.03$, $p = 0.1$) (Figure 4). Six-minute walk distance correlated with NYHA class ($\rho = -0.231$, $p < 0.05$), age ($r = -0.245$, $p < 0.01$) and female gender ($\rho = -0.446$, $p < 00.01$), as well. In multiple regression analysis (where we included age, gender, the presence of COPD, anaemia, eGFR, NYHA class, LVEF) only patients' age was a predictor of decreased 6MWD < 300 m (OR = 0.8736, 95%, CI = 0.7804 - 0.9781, $p < 0.05$). The probability of reducing the 6MWD < 300 m increased by 8.7% with every year of age.

Discussion

Heart failure plays an important role in public health, being one of the major complications of heart disease and a leading cause of death in developed countries. The natural history of this illness constitutes impairment of functional capacity, physical performance, and ability to perform daily activities, finally becoming detrimental to the quality of life [9].

Concomitant and significant renal dysfunction is common in patients with heart failure [21, 22]. In the study of Waldum et al., [23] 44.9% of the elderly outpatients with heart failure had eGFR lower than 60 mL/min. Accordingly, in our study 91.1% of patients had renal dysfunction and among them 33.3% had moderate or severe renal dysfunction (eGFR < 60 mL/min). For adequate interpretation of epidemiological studies it is essential to use the universal definitions of renal dysfunction (GFR = 60–89 mL/min), renal impairment and chronic kidney disease (GFR below 60 mL/min for at least 3 months, among other criteria) [14]. As patients with advanced heart failure are also likely to have an element of renal dysfunction, it is of interest to know how prognostically relevant this is. Renal impairment is often associated with CHF owing to renal hypoperfusion, diuretic treatment, disease-modifying heart failure therapy (angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, aldosterone antagonists), as well as other concomitant medication and comorbidities [4]. Scardovi et al. [24] showed that renal dysfunction in elderly CHF patients is a main independent prognostic predictor across the spectrum of ventricular impairment indices. Although the pathogenesis of reduced GFR may differ between patients and even over

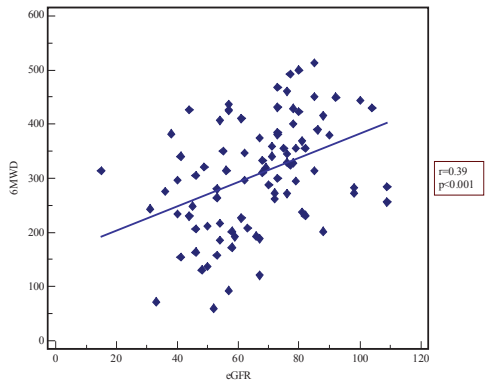

Fig. 3 – Correlation between eGFR and 6MWD

eGFR – estimated glomerular filtration rate

6MWD – 6-minute walk distance

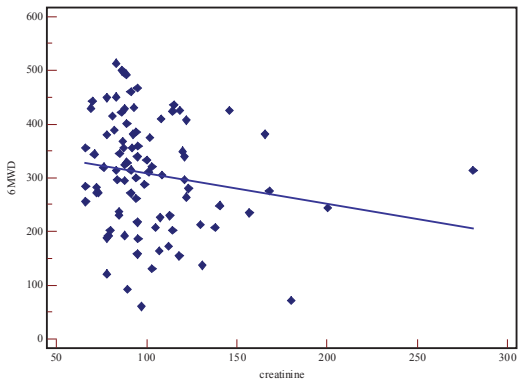

Fig. 4 – Linear regression line [influence of creatinine on 6-minute walk distance (6MWD)]

time within an individual, the result is the same: reduced GFR is strongly related to increased mortality and morbidity and impaired functional capacity in CHF.

In our study we found a significantly positive correlation between eGFR and 6MWD, while NYHA class, female gender and age inversely correlated with eGFR which is in accordance with previous reports [11, 25, 26]. A positive correlation was found between LVEF and eGFR. Although a greater proportion of patients with low eGFR have a worse NYHA class, no evidence of association between LVEF and eGFR can be consistently demonstrated. Thus, patients with systolic and diastolic CHF appear to have similar eGFR [27].

Functional capacity provides a strong independent insight into the prognosis of patients with heart failure. Information on peak oxygen consumption (PvO_2) during cardiopulmonary exercise testing is used extensively to evaluate cardiovascular performance. Several studies have supported PvO_2 as an independent prognostic index of survival in patients with heart failure [28].

The 6MWT has been proposed as a simple, inexpensive, reproducible alternative to CPET. The test showed a good reproducibility and a significant relation between the distance walked during the test and the PvO_2 and, respectively, survival has been demonstrated. The 6MWT reproduces the activity of daily life and this is particularly relevant in elderly patients who usually develop symptoms below their theoretical maximal exercise capacity [6]. We determined a significant inverse correlation between 6MWD, NYHA class, age, female gender and renal dysfunction (eGFR) which is in accordance with findings of Ingle et al. [12]. However, hemoglobin concentration, BMI, resting heart rate and the presence of COPD did not correlate with 6MWD which is not in line with previous reports [12, 29]. However, the lowest value of hemoglobin was 98 g/L, which means that our patients had very mild anemia. Furthermore, our patients with COPD had the average Tiffno index of 0.61 and therefore mild COPD, which could partially explain the effect of those comorbidities on functional capacity. In our study 6MWD significantly correlated with LVEF, and there was no significant difference between patients with systolic or diastolic heart failure, which is in line with published literature [27, 30]. It has been demonstrated that a walking distance less than 300 m during the 6MWT is an independent predictor of long-term mortality in patients with mild-to-moderate heart failure [28, 31]. In our study, multiple regression analysis showed that only patients' age was a predictor of reduced 6MWD < 300 m. However, only 47.8% of our patients had 6MWD below 300 m, so more than 50% of our patients were not included in this analysis. In the HF-ACTION study age was the strongest predictor of PvO_2 and a significant predictor of exercise capacity. Age-dependent comorbidities, such as renal dysfunction, do not explain changes in PvO_2. Age-related changes in cardiovascular physiology, potentially magnified by the CHF, should be considered as a contributor to the pathophysiology and a target for more effective therapy in older patients with CHF [32].

A number of biologically diverse chronic illnesses such as renal failure, COPD and congestive heart failure result in a significant decrease in exercise tolerance. In each of these disease states, treatments aimed at the primary pathology have provided powerful palliative effects. However, in general, improvements in exercise tolerance following such interventions are delayed and incomplete. This has led to an increasing awareness that secondary treatment strategies, such as prescribed exercise, designed to restore some level of physical performance and quality of life can be beneficial [33]. The American Heart Association has recently taken the position that exercise rehabilitation has an important place in the treatment of heart failure [34]. The potential mechanisms by which CHF and renal dysfunction may negatively impact skeletal muscle are complex, resulting from alterations in muscle perfusion, substrate delivery, and catabolic state mediated by various factors such as metabolic acidosis, corticosteroids, proinflammatory cytokines, and decreased physical activity, among others. In summary, numerous disorders promote skeletal myopathy developement, impaired exercise tolerance, and hence a sedentary lifestyle in CHF patients. Reduction in physical activity, in turn, leads to further decline in muscle mass, progressive disability, and various other untoward consequences. Regular exercise regimens can interrupt this vicious cycle and improve physical condition. Thus the inclusion of exercise as a standard component of care appears to be warranted in the overall management of these patients [33, 35]. Nevertheless, pharmacological management, focused on kidney protection to prevent or slow progression of renal impairment, may improve outcome in elderly HF patients [24].

Conclusion

Renal dysfunction is highly prevalent in elderly CHF patients. It is associated with decreased functional capacity and, therefore, poor prognosis. This study corroborates the use of eGFR not only as a powerful predictor of mortality in CHF, but also as an indicator of the functional capacity of cardiopulmonary system. Large, prospective studies remain to be performated for understanding the etiology of reduced eGFR in patients with CHF. Inclusion of patients with renal insufficiency in heart failure studies and the published guidelines for medication, device, and interventional therapies would likely improve therapeutic outcomes. This will lead to novel therapeutic strategies not only in reducing mortality but also in improving life quality in CHF. However, clinicians underestimate serial measurement of eGFR while it should be a part of routine evaluation initially performed in every patient with CHF, particularly in elderly population.

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Karakteristike čitanja gluvih i nagluvih učenika

Reading characteristics of deaf and hard-of-hearing pupils

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Apstrakt

Uvod/Cilj. Motorni mehanizmi artikulacije imaju presudnu ulogu u demutazicionom procesu, jer obuhvataju sve elemente sukcesivnog nastajanja govornih pokreta koji dovode do formiranja govora (tzv. govorna kinestezija). Cilj ovog rada bila je procena uticaja perceptivno motornog akta na saznajni proces čitanja kod 130 učenika redovnih škola i škola za gluvu i nagluvu decu na teritoriji Republike Srbije. **Metode.** Za procenu brzine čitanja korišćen je test Kostića i Vladisavljevićeve prema težini od deset nivoa. Za procenu razumevanja pročitanog teksta prema verbalnim odgovorima, korišćen je adaptirani trodimenzionalni test čitanja Helene Sax. **Rezultati.** Na trijažnom artikulacionom testu za procenu brzine čitanja Kostića i Vladisavljevićeve prema težini od deset nivoa, utvrđeno je da su učenici redovnih škola u statistički značajnoj meri brže čitali tekstove od gluvih i nagluvih učenika. Rezultati dobijeni na adaptiranom trodimenzionalnom testu čitanja Helene Sax pokazali su da naučene reči kod gluvog deteta egzistiraju izolovano u njegovoj svesti, tačnije ako kod gluvog ne postoji etalon akustičke predstave za grafičku sliku, svaka reč, štampana ili napisana samo je zbir slova bez značenja. **Zaključak.** Postoji značajna razlika u brzini čitanja teksta, kao i u razumevanju pročitanog teksta između dece koja čuju i gluve i nagluve dece. Neophodno je da se u surdopedagoškoj praksi, pored rada na razvoju govora, uporedo radi na semantičkoj obradi pojma kako bi svaka reč dobila punoću svog sadržaja i mogućnost širenja njenog značenja u raznim upotrebnim vrednostima.

Ključne reči:
gluvoća; sluh, parcijalni gubitak; artikulacija, poremećaji; deca; čitanje; upitnici; škole.

Abstract

Background/Aim. Speech motor mechanisms play a crucial role in the process of demutization, due to the fact that they cover all the elements of the successive development of spech production movements leading to speech formation (so-called kinesthesia in speach). The aim of this study was to estimate the impact of perceptual motor actions on the cognitive process of reading in 130 students in regular schools and schools for the deaf and hard-of-hearing children in the Republic of Serbia. **Methods.** Kostić and Vladisavljević test consisted of the ten levels weight was used for the assessment of reading speed. To assess understanding of text read by verbal responses, we used three-dimensional adapted reading test of Helene Sax. **Results.** The triage-articulation test for assessing reading speed (Kostić and Vladisavljević's test according to the weight of ten levels, revealed that students in regular schools statistically significantly faster read texts as compared to the deaf students. The results of the three-dimensional adapted reading test of Helena Sax, show that the words learned by deaf children exist in isolation in their mind, *ie*, if there is no standard of acoustic performance for graphic image, in deaf child every word, printed or written, is just the sum of letters without meaning. **Conclusion.** There is a significant difference in text reading speed and its understanding among the children who hear and the deaf and hard-of-hearing children. It is essential that in deaf and heard-of-hearing children education, apart from the development of speech, parallelly use the concept of semantic processing in order to get each word by the fullness of its content and the possibility of expanding its meaning in a variety of assets.

Key words:
deafness; hearing loss, functional; articulation disorders; child; reading; questionnaires; schools.

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Uvod

Čitanje je kompleksna aktivnost koja podrazumeva više raznih aspekata kao što su vizuelna percepcija grafeme, transformacija grafeme u fonemu, razumevanje pročitane reči, razumevanje suštine neuroloških procesa aktivnosti korteksa u procesu saznavanja, funkcionisanje kognitivnih polja, itd [1–5].

Do savremenih psiholingvističkih proučavanja procesa čitanja, čitanje je smatrano i vezivano, uglavnom, za nastavu jezika, [4] a u fiziološkom pogledu za vidnu percepciju grafema. Ova istraživanja pokazala su da proces čitanja krije u sebi mnogo složenije procese koji uključuju aktivnost nekoliko područja mozga, pa je u neurobiološkom smislu teško objasniti kako određenu kombinaciju slova na papiru povezujemo u smislenu poruku koju mozak dešifruje [1]. Teškoće i greške koje se javljaju u procesu čitanja, u prepoznavanju grafičkih znakova, a posebno u shvatanju značenja pročitanih grafema u reči, potiču iz znatno dubljih i složenijih neuropsiholoških izvora od onih na koje nastavnici obraćaju pažnju [4]. Akt čitanja možemo podeliti na tri dela: upoznavanje grafema i njihovo međusobno diferenciranje; transformacija grafema u fonemu i njihova međusobna katenizacija u reči, razumevanje pročitanog – ideacija pojma [1–3, 6, 7].

Razumevanje bioloških osnova čitanja gotovo da nije bilo moguće sve do upotrebe savremenih tehnologija u istraživanju kao što je funkcionalno neurosnimanje, koje obuhvata pozitronsku emisijsku tomografiju (PET), funkcionalnu magnetnu rezonancu (fMRI) i transkranijalnu magnetnu stimulaciju (TMS). Primenom funkcionalnog snimanja upotpunjena su brojna ranija istraživanja funkcije čitanja, elektrofiziološke i neuropsihološke studije, kao i studije deficita funkcionalnih oštećenja mozga nakon hirurškog odstranjenja ili traume određenog njegovog dela. Na ovaj način, moderna istraživanja funkcije čitanja ujedinjuju saznanja iz molekularne biologije, neuronauka, kognitivnih nauka i bioinformatike [6, 8].

Mnogi istraživači došli su do zaključaka da greške u čitanju nisu rezultat poremećaja relativno jednostavnog mehanizma koji upravlja fonetsko-grafemskom analizom, već posledice poremećaja u semantičkim poljima i gramatičkim kategorijama [1, 5, 9, 10, 11]. Čitanje naglas nije prosto dekodiranje jednog grafičkog sklopa u odgovarajuće glasove, već je to prenošenje i primanje značenja iz teksta. Pre nego što dođe do oralnog glasovnog izgovaranja fonema u sklopu grafeme, reč se kao celina bira iz jednoopšteg kognitivno-semantičkog depozita koji se nalazi u svesti i saznanju čitaoca [1, 6, 10].

Motorni mehanizmi artikulacije imaju presudnu ulogu u demutizacionom procesu, jer obuhvataju sve elemente sukcesivnog nastajanja govornih pokreta, koji dovode do formiranja govora (tzv. govorna kinestezija) [11, 12]. Učenje govora gluvog deteta ne odvija se prirodnim putem i nije bazirano na istim neuropsihološkim dispozicijama *feed-backa* koji postoji kod deteta koje čuje, niti se stvara u periodu u kome još nije došlo do pre-mijelinizacije nervnih puteva. Govor deteta urednog sluha stvara se automatski, dok se kod gluvog deteta automatizam stvara praksom i velikom aktivnošću različitih segmenata centralnog nervnog sistema (CNS) [7, 11, 12]. Pri tome se svaki artikulacioni pokret pamti u formi engrama koji se u datim uslovima reprodukuju, što daje njihove posebnosti [4, 10, 13–16].

Cilj ovog istraživanja bio je da proverimo uticaj perceptivno-motornog akta na saznajni proces čitanja, kao i da ustanovimo da li brzina čitanja utiče na razumevanje pročitanog kod gluvih i nagluvih učenika, te tako objasnimo i potvrdimo neke surdopedagoške postavke u praksi u cilju njenog unapređenja.

Metode

Uzorak za istraživanje činilo je 130 učenika redovnih i škola za gluvu i nagluvu decu, od 4. do 8. razreda, sa teritorije Republike Srbije (63 učenika škola za gluvu i nagluvu decu i 67 učenika redovnih škola). Kako bi se mogli porediti rezultati dobijeni na testu brzine čitanja, učenici redovnih i škola za gluvu i nagluvu decu ujednačeni su prema sledećim faktorima: školskom uzrastu, polu, oceni iz srpskog jezika kao i intelektualnim sposobnostima. Za procenu brzine čitanja korišćen je test Kostića i Vladisavljevićeve prema težini od deset nivoa (I – pojedine reči; II – proste rečenice; III – proširene rečenice; IV – složene rečenice; V – tekst putopisa; VI – tekst studije; VII – filozofski tekst; VIII – tekst iz pravopisa; IX – tekst iz fiziologije i X – tekst iz Hegelove dijalektike) [9, 10].

Za procenu razumevanja pročitanog teksta prema verbalnim odgovorima, korišćen je adaptirani trodimenzionalni test čitanja Helene Sax. [9, 10]. Trodimenzionalni test čitanja primenjen je za ispitivanje razumevanja pročitanog samo na delu uzorka gluvih i nagluvih učenika. Ovaj test meri stepen razumljivosti čitanja jer zahteva da ispitanik pobroji određeni broj činjenica iz teksta koji je pročitao. Na osnovu našeg iskustva u radu sa gluvom i nagluvom decom i njihovih ograničenih sposobnosti verbalnog izražavanja, zahteve testa prilagodili smo na taj način što smo pružili mogućnost gluvim ispitanicima da, ako ne mogu verbalno da se izraze (pobroje određeni broj činjenica), iste sem verbalnog načina izraze gestom, slikom, ili da sadržaj prepoznaju među prikazanim slikama sličnog sadržaja. Tekst za čitanje bio je kratka priča iz čitanke za osnovnu školu sa rečima koje su deci poznate iz svakodnevnog života. Zadatak se sastojao u tome da deca prepričaju priču rečima, da kažu pet bitnih činjenica, da priču prepričaju gestom, da je nacrtaju kao i da prepoznaju odgovarajuću sliku koja se odnosi na sadržaj teksta.

Pri statističkoj analizi podataka korišćeni su χ^2 i *t*-test.

Rezultati

Karakteristike ispitanika ujednačenih prema školskom uzrastu, polu i oceni iz srpskog jezika dati su u tabeli 1.

Brzina čitanja teksta prema težini sadržaja

Rezultati dobijeni na ovom testu poslužili su nam da sagledamo kako sadržaj reči utiče na brzinu čitanja jer se ovim testom ne meri samo brzina čitanja, već i semantički aspekt u brzini čitanja [9, 10].

Nakon merenja vremena potrebnog za čitanje teksta, izračunate su prosečne vrrednosti izražene u sekundama, a rezultati su prikazani u tabeli 2. Testiranjem dobijenih rezultata *t*-testom utvrđeno je da su učenici redovnih škola statistički značajno brže čitali tekstove od gluvih i nagluvih učenika. Rezultati su prikazani u tabeli 3.

Trodimenzionalni test čitanja Helene Sax

Trodimenzionalni test čitanja primenjen je za ispitivanje razumevanja pročitanog samo na delu uzorka gluvih i nagluvih učenika. Zahteve testa prilagodili smo na taj način što smo pružili mogućnost gluvim ispitanicima, ako ne mogu

Tabela 1

Karakteristike ispitanika ujednačenih prema školskom uzrastu, polu i oceni iz srpskog jezika

Parametri	Učenici škola za gluvu i nagluvu decu		Učenici redovnih škola		Ukupno	
	n	%	n	%	n	%
Razred	$\chi^2 = 1{,}381$; $df = 4$, $p = 0{,}847$					
IV	13	50,0	13	50,0	26	100
V	13	46,4	15	53,6	28	100
VI	11	44,0	14	56,0	25	100
VII	12	44,4	15	55,6	27	100
VIII	14	58,3	10	41,7	24	100
Ukupno	63	48,5	67	51,5	130	100
Pol	$\chi^2 = 0{,}889$; $df = 1$, $p = 0{,}346$					
muški	39	52,0	38	48,0	75	100
ženski	24	43,6	31	56,4	55	100
Ukupno	63	48,5	67	51,5	130	100
Ocena iz srpskog jezika	$\chi^2 = 2{,}058$; $df = 3$; $p = 0{,}560$					
dovoljan (2)	7	43,8	9	56,3	16	100
dobar (3)	17	53,1	15	46,9	32	100
vrlo dobar (4)	20	41,7	28	58,3	48	100
odličan (5)	19	55,9	15	44,1	34	100
Ukupno	63	48,5	67	61,5	130	100

Tabela 2

Prosečna brzina čitanja teksta različite težine sadržaja kod učenika oštećenog sluha (OS) i učenika sa urednim sluhom (US) izražena u sekundama

Težina sadržaja teksta*	Učenici	Brzina čitanja (sek) Razred					$\bar{x} \pm SD$ (sek)	*p* (*t*-test)
		IV	V	VI	VII	VIII		
I	OS	87,0	47,15	44,64	47,92	45,21	54,65 ± 18,02	
	US	30,0	31,4	21,86	26,53	24,0	26,94 ± 5,26	0,001
II	OS	64,46	38,69	35,64	35,92	33,79	41,86 ± 13,52	
	US	22,69	20,0	15,57	16,73	17,0	18,42 ± 4,48	0,001
III	OS	69,38	37,92	35,64	36,50	32,36	42,51 ± 15,67	
	US	18,15	16,80	14,36	16,73	15,20	16,30 ± 3,78	0,001
IV	OS	78,46	43,46	42,91	42,58	36,43	48,86 ± 17,48	
	US	21,31	18,0	16,71	16,87	14,50	17,60 ± 3,99	0,001
V	OS	72,08	47,62	47,27	38,00	36,29	48,25 ± 15,65	
	US	26,46	20,27	20,64	17,47	15,50	20,21 ± 5,07	0,001
VI	OS	72,46	47,46	52,45	44,67	39,07	51,10 ± 14,47	
	US	31,0	23,80	24,21	20,53	20,80	24,10 ± 5,08	0,001
VII	OS	75,77	45,23	44,45	42,67	37,36	49,16 ± 16,35	
	US	26,77	20,47	20,71	18,40	16,70	20,72 ± 4,94	0,001
VIII	OS	86,85	53,23	52,91	47,00	43,36	56,73 ± 18,79	
	US	33,69	23,67	24,50	20,53	19,30	24,43 ± 6,02	0,001
IX	OS	103,31	77,62	78,36	64,17	66,64	77,60 ± 19,40	
	US	50,31	37,60	41,64	36,40	33,60	40,04 ± 8,16	0,001
X	OS	83,54	52,08	54,36	46,58	41,36	55,54 ± 17,95	
	US	31,62	24,73	23,14	22,93	19,50	24,55 ± 5,08	0,001

***Test Kostića i Vladisavljevićeve: I – pojedine reči; II – proste rečenice; III – proširene rečenice; IV – složene rečenice; V – tekst putopisa; VI – tekst studije; VII – filozofski tekst; VIII – tekst iz pravopisa; IX – tekst iz fiziologije i X – tekst iz Hegelove dijalektike [9, 10]**

Tabela 3

Rezultati trodimenzionalnog testa čitanja kod gluve i nagluve dece (test Helene Sax)

Način izlaganja pročitanog teksta	Razred					
	IV n (%)	V n (%)	VI n (%)	VII n (%)	VIII n (%)	Ukupno n (%)
Prepričavanje rečima	χ^2= 9,452; *df* = 2; *p* = 0,306					
- dobro		3 (23,1)	1 (9,1)	1 (8,3)	2 (14,3)	7 (11,1)
- delimično dobro	3 (23,1)	4 (30,8)	3 (27,3)	4 (33,3)	8 (57,1)	22 (34,9)
- loše	10 (76,9)	6 (46,2)	7 (63,6)	7 (58,3)	4 (28,6)	34 (54,0)
Ukupno	13 (100)	13 (100)	11 (100)	12 (100)	14 (100)	63 (100)
Izdvajanje bitnih činjenica	χ^2= 11,549; *df* = 2; *p* = 0,172					
- dobro		3 (23,1)	2 (18,2)	5 (41,7)	6 (42,9)	16 (25,4)
- delimično dobro	4 (30,8)	3 (23,1)	1 (9,1)	2 (16,7)	4 (28,6)	14 (22,2)
- loše	9 (69,2)	7 (53,8)	8 (72,7)	5 (41,7)	4 (28,6)	33 (52,4)
Ukupno	13 (100)	13 (100)	11 (100)	12 (100)	14 (100)	63 (100)
Gestovno izlaganje	χ^2= 6,792; *df* = 2; *p* = 0,559					
- dobro	2 (15,4)	4 (30,8)	3 (27,3)	6 (50,0)	3 (21,4)	18 (28,6)
- delimično dobro	5 (38,5)	4 (30,8)	6 (54,5)	3 (25,0)	7 (50,0)	25 (39,7)
- loše	6 (46,2)	5 (38,5)	2 (18,2)	3 (25,0)	4 (28,6)	20 (31,7)
Ukupno	13 (100)	13 (100)	11 (100)	12 (100)	14 (100)	63 (100)
Ilustrovanje priče	χ^2= 18,769; *df* = 2; *p* = 0,016					
- dobro	3 (23,1)	4 (30,8)	3 (27,3)	8 (66,7)	8 (57,1)	26 (41,3)
- delimično dobro	3 (23,1)	7 (53,8)	7 (63,6)	2 (16,7)	5 (35,7)	24 (38,1)
- loše	7 (53,8)	2 (15,4)	1 (16,7)	2 (16,7)	1 (7,1)	13 (20,6)
Ukupno	13 (100)	13 (100)	11 (100)	12 (100)	14 (100)	63 (100)
Prepoznavanje sadržaja priče na slici	χ^2 = 3,925; *df* = 1; *p* = 0,416					
- dobro	2 (15,4)	4 (30,8)	2 (18,2)	5 (41,7)	6 (42,9)	19 (30,2)
- loše	11 (84,6)	9 (69,2)	9 (81,8)	7 (58,3)	8 (57,1)	44 (69,8)
Ukupno	13 (100)	13 (100)	11 (100)	12 (100)	14 (100)	63 (100)

verbalno da se izraze (pobroje određeni broj činjenica), iste, sem verbalnog načina, izraze gestom, slikom, ili da sadržaj prepoznaju među prezentiranim slikama sličnog sadržaja. Tekst za čitanje bio je kratka priča iz čitanke za osnovnu školu sa rečima koje su deci poznate iz svakodnevnog života.

Diskusija

Rezultati koje smo dobili ispitivanjem brzine čitanja na osnovu testa Kostića i Vladisavljevićeve [9, 10] prema težini od deset nivoa [6, 7] pokazuju da brzina čitanja nije bila srazmerna težini teksta, kao ni da se brzina čitanja sukcesivno ne smanjuje, već stvara određene skokove, bilo prema školskom uzrastu, bilo prema težini teksta. Brzina čitanja povećava se sa porastom školskog uzrasta. Ovakva distribucija brzine čitanja prema težini ukazuje da gluvi učenici ne razmišljaju o sadržaju teksta koji čitaju.

Prosečne brzine čitanja učenika redovnih škola pokazuju da oni brže čitaju od gluvih i nagluvih učenika; da je distribucija vremena ravnomernija u odnosu na težinu teksta i da kod učenika svih školskih uzrasta težina teksta usporava čitanje; da je tekst iz Gajtonove Fiziologije znatno teži za sve uzraste od Hegelove Logike, zbog specifičnosti medicinskih izraza; da su najlakši tekst kod svih uzrasta najsporije čitali (pojedinačne izolovane reči svrstane u I stepen teškoća u čitanju), što pokazuje da deca nisu naučila da čitaju izolovane reči bez logičkog smisla, već da su čitala sa razumevanjem, što je već drugi nivo čitanja; da se brzina čitanja svih nivoa težine teksta povećava sa školskim uzrastom.

Slični rezultati dobijeni su i u drugim studijama [13–16].

Na osnovu rezultata brzine čitanja u našem istraživanju, možemo zaključiti da misaona komponenta nema nikakvog udela u brzini čitanja. Za gluvo dete slova su samo grafički znaci iza kojih ne stoji sadržaj [4, 12]. Tu je suština problema koji za sobom povlači delimično ili potpuno oštećenje sluha, posebno ukoliko je nastalo u prelingvalnom uzrastu. Kako gluvo dete samo ne može da nauči govor, već mora da bude govoru naučeno od strane drugog lica to je dominantno pitanje – koje reči treba dati gluvom detetu da bi one bile elemenat misli pomoću kojih se uslovljava mišljenje. Dakle, koje reči u pogledu frekventne upotrebne vrednosti treba dati gluvom detetu i što je još važnije, na koji će način ono biti njima naučeno?

Na testu razumevanja pročitanog teksta Helene Sax [9, 10], dobijeni rezultati pokazali su da je samostalno verbalno prepričavanje – razumevanje pročitanog teksta, bilo veoma loše. Deca mnoge pojmove ne znaju (ne razumeju), a reč je o pojmovima za koje smatramo da su laki i deci pristupačni. Prilikom ispitivanja zapaženo je da je prepričavanje bilo praćeno gestovnim načinom izražavanja. Većina učenika nije bila u stanju da prepriča priču svojim rečima, već su ponavljali reči iz priče. Priču su uspeli da prepričaju tri učenika V razreda sa kohlearnim implantom i po jedan učenik iz starijih razreda sa umernim ili težim oštećenjem sluha.

Dobijeni rezultati ukazuju, prvo, na način učenja čitanja u školama za gluvu i nagluvu decu, koji se svodi na verbalno memorisanje reči, bez pravog razumevanja njihove semantike, i drugo, da učenici veoma slabo aktiviraju svoj verbalni depozit i da isti ne umeju funkcionalno da koriste. Rezultati ukazuju i na neke od specifičnosti u radu sa

gluvom i nagluvom decom, pre svega, da svaku reč koju dete pročita, treba proveriti kako ju je ono razumelo, kakvo značanje ima i da li je shvata u kontekstu ili izolovano – reč po reč. Jedna od specifičnosti u razvoju mišljenja gluve i nagluve dece, a koja se javlja kao uzrok slabijeg školskog uspeha, jeste teškoća u izdvajanju bitnog od nebitnog. Čak i prilikom posmatranja slike, deca će izdvajati manje važne karakteristike od onih suštinskih. Dobijeni rezultati u ovom istraživanju potkrepljuju izneto mišljenje. Iako u starijim razredima raste i broj tačnih odgovora, ne postoji statistički značajna razlika između odgovora učenika u odnosu na razred. Najviše netačnih odgovora dali su učenici IV i V razreda, među kojima su bile i reči koje nemaju nikakve veze sa pročitanim tekstom.

Ni kod prepričavanja priče uz gestovno izražavanje nisu dobijeni očekivani rezultati. Iako su koristili veći broj pojmova, učenici nisu bili u stanju da samostalno prepričaju priču, već su, kao i kod verbalnog izražavanja, te reči koristili izolovano.

Učenici IV razreda gestom su izražavali nekoliko pojmova kao što su: drvo, ptica, kuća. Učenici V razreda su, pored ovih pojmova, koristili još i pojmove: gusenica, opasno, šteta, krov. Učenici VI razreda dodavali su: gusenica štetočina (odraz znanja iz poznavanja prirode i biologije), plače, upomoć i slično. Učenici VII razreda već su mogli da izraze više detalja: leto, sunce, vrućina, pala kiša, gusenica, lepo drvo, ružno. Slične odgovore dali su i učenici VIII razreda, ali su samo tri učenika mogla da sastave priču.

Ovakvi rezultati govore da su gluvi učenici, razumevajući pojedine reči, njih prevodili na gestovni izraz, a da pri tome nisu shvatili pravo značenje reči.

Četvrti oblik provere shvatanja pročitanog je ilustrovanje priče. Kao parametre za ocenjivanje uspešnosti, korišćeno je istih pet elemenata na crtežu (drvo, ptica, gusenica, sunce, kiša). Za razliku od ostalih rezultata, koji su ispod očekivanih za uzrast, na ovom zadatku učenici su bili najuspešniji. Na osnovu prikazanih frekvencija i procenata može se zaključiti da deca iz viših razreda bolje ilustruju tekst priče, što je znak da su ga i bolje shvatili, a čak je bilo odgovora i u formi strip ilustracije. Treba napomenuti da je bilo odgovora, posebno u IV razredu koji nisu imali nikakve veze sa sadržajem priče.

Kako su na ovom zadatku učenici bili najuspešniji, može se zaključiti i da im ovakav način provere najviše odgovara, a ujedno je ovo i najbolji način za prijem novih informacija u toku obrade novog gradiva.

Kao poslednju mogućnost razumevanja pročitane priče, pripremili smo pet slika, od kojih su tri bile vezane za tekst i koje je trebalo sukcesivno poređati, dok su druge dve bile bez ikakve sadržajne povezanosti sa pričom. Odgovori učenika svrstavani su u dve kategorije.

Rezultati dobijeni ovakvim načinom provere razumevanja priče bili su ponovo niži od očekivanih. Većina učenika IV i V razreda davala je loše odgovore, dok su stariji učenici bili uspešniji, ali ne i u dovoljnoj meri. Prilikom ispitivanja je uočeno da su deca postupala po istom obrascu, naime, iako su individualno ispitivani, svi su pravili iste greške prilikom raspoređivanja slika i pri tome su koristili sve slike. Pokušavajući da razumemo prirodu ove greške, tražili smo objašnjenje od učenika i kao odgovor dobili da se i na drugim slikama nalazi neki od elemenata koje su pročitali u tekstu.

Dobijeni rezultati na testu razumevanja pročitanog teksta pokazuju da reči koje nauči gluvo dete egzistiraju izolovano u njegovoj svesti ili u kontekstu u kojem su naučene, dok se međusobno same ne povezuju u istu kategoriju. Fonološka predstava reči ne postaje leksička memorija koja se prepoznaje u čitanju, niti se širi pobuđenost radijalno na susedne memorije (teorija lingvističkih polja). To znači da grafemska predstava reči nije podržana odgovarajućom fonemskom predstavom (posebno akustičkom, jer je dete nije prethodno čulo), te i ne dovodi do pobuđenja engrama u svesti, a samim tim ni do povratne veze preko semantike natrag u memoriju. Zato, ako kod gluvog ne postoji etalon (engram, memorija, adresa) akustičke predstave za grafičku sliku, svaka reč, štampana ili napisana, samo je zbir slova bez značenja [12].

Zaključak

Dobijeni rezultati pokazuju da perceptivno-motorni aspekt nije dominantan u saznajnom procesu iako ima vrlo veliku funkciju. Kod učenika oštećenog sluha primarni akt u čitanju je čist perceptivno-motoričan postupak bez komponente saznavanja. Deca su jednakom brzinom čitala i reči koje su razumela, kao i one koje nisu. To znači da je dominantan bio isključivo mehanički momenat. Gluva deca uče reči izolovano, a ne u kontekstu misaone celine, pa one takve ostaju i u svesti – izolovane jedna od druge. Dakle, problem formiranja pojma i njegova sadržajna strana dominantne su u surdopedagoškoj nastavi, a da njima nije bilo posvećeno dovoljno pažnje može se zaključiti na osnovu dobijenih rezultata. Stoga, pored rada na razvoju govora, treba uporedo raditi i na semantičkoj obradi pojma kako bi svaka reč dobila punoću svog sadržaja koji će joj omogućiti dalji razvoj po principu radijalnog asocijativnog efekta i stalnog širenja njenog značenja u raznim upotrebnim vrednostima.

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Fotorefraktivna keratektomija u korekciji miopije – naše jednogodišnje iskustvo

Photorefractive keratectomy for correction of myopia – our one-year experience

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Apstrakt

Uvod/Cilj. Fotorefraktivna keratektomija (PRK) posle laser *in situ* keratomileuze (LASIK) po učestalosti izvođenja druga je refraktivna hirurška metoda u svetu. Cilj studije bio je da se ispita uspešnost i bezbednost metode PRK u korekciji različitih dioptrijskih jačina miopije, kao i da se proceni koliko se tkiva rožnjače uklanja pri korekciji 1 dioptrije sfere (Dsph) korišćenjem različitih optičkih zona (OZ). **Metode.** Izvedena je prospektivna studija sa periodom praćenja od šest meseci u koju je bilo uključeno 55 bolesnika kod kojih je metodom PRK operisano 100 miopnih očiju (kod 10 bolesnika u studiju je bilo uključeno jedno oko). Analizirane su miopne oči s preoperativno najbolje korigovanom vidnom oštrinom (NKVO) = 1.0 (20/20). U cilju procene uspešnosti PRK metode operisane miopne oči podelili smo u četiri grupe zavisno od dioptrijske jačine: 1) ≤ -1,75 Dsph (n = 26); 2) od - 2 do - 3,75 Dsph (n = 44); 3) od -4 do - 6,75 Dsph (n = 23); i 4) ≥ - 7 Dsph (n = 7). Iz analize su isključene miopne oči s preoperativnom NKVO ≤ 0,9 (ambliopne oči), kao i oči s astigmatizmom > - 1,5 Dcyl. Uspešnost smo procenjivali na osnovu procenta očiju u okviru gore navedenih grupa, kod kojih je šest meseci nakon izvedene intervencije nekorigovana vidna oštrina (NVO) bila: a) NVO = 1,0 (20/20) i b) NVO ≥ 0,5 (20/40). U cilju procene bezbednosti PRK metode ispitali smo učestalost intraoperativnih i postoperativnih komplikacija, dok smo za procenu koliko se tkiva rožnjače uklanja pri korekciji 1 Dsph korišćenjem različitih OZ koristili preoperativne i postoperativne (nakon šest meseci) vrednosti centralne pahimetrije izražene u μm i volumena rožnjače (centralnih 7 mm) izraženog u mm³. U ovoj analizi koristili smo samo miopne oči sa preoperativno čistom sfernom refrakcijom. Ukupan broj takvih očiju bio je 27, i od toga broja 16 očiju je tretirano korišćenjem OZ 6,5 mm, a 11 očiju korišćenjem OZ 7 mm. **Rezultati.** Refraktivni sferni ekvivalent (RSE) svih očiju bio je u rasponu od - 0,75 do -8,75 Dsph, a preoperativna srednja vrednost RSE sa standardnom devijacijom (srednja RSE ± SD) bila je -3,32 ± 1,83 Dsph. Šest meseci nakon PRK 91% očiju imalo je NVO = 20/20, a 99% očiju NVO ≥ 20/40. U okviru prve grupe (≤ -1,75 Dsph) preoperativna srednja RSE ± SD bila je -1,34 ± 0,32 Dsph, šest meseci nakon PRK 96% očiju imalo je NVO = 20/20, a 100% očiju NVO ≥ 20/40. U okviru druge grupe (od -2 do -3,75 Dsph) preoperativna srednja RSE ± SD bila je -2,95 ± 0,57 Dsph, šest meseci nakon PRK 89% očiju imalo je NVO = 20/20, a 100% očiju NVO ≥ 20/40. U okviru treće grupe (od -4 do -6,75 Dsph) preoperativna srednja RSE ± SD bila je -4,93 ± 0,70 Dsph, šest meseci nakon PRK 100% očiju imalo je NVO = 20/20. U okviru četvrte grupe (≥ -7 Dsph) preoperativna srednja RSE ± SD bila je -7,71 ± 0,67 Dsph, šest meseci nakon PRK 57% očiju imalo je NVO = 20/20, a 86% očiju NVO ≥ 20/40. Intraoperativnih komplikacija nije bilo, dok su se postoperativne komplikacije javile kod dva bolesnika, i to kod oba bolesnika na jednom oku (2%). Radilo se o defektima epitela rožnjače. U grupi očiju koje su tretirane korišćenjem OZ 6,5 mm srednja RSE ± SD bila je -2,45 ± 0,99 Dsph, dubina ablacije po 1 Dsph bila je 17,54 ± 5,58 μm i ablatirani volumen centralnih 7 mm rožnjače po 1 Dsph bio je 0,43 ± 0,18 mm³. U grupi očiju koje su tretirane korišćenjem OZ 7 mm srednja RSE ± SD bila je -3,32 ± 2,26 Dsph, dubina ablacije po 1 Dsph bila je 23,73 ± 6,91 μm i ablatirani volumen centralnih 7 mm rožnjače po 1 Dsph bio je 0,61 ± 0,31 mm³. **Zaključak.** Metoda PRK je uspešna i bezbedna refraktivna hirurška metoda za korekciju miopije do -8,75 Dsph. Veličina OZ je glavni faktor koji određuje dubinu *excimer* laser ablacije i volumen utrošenog tkiva rožnjače po 1 Dsph. Što je OZ veća, to je i utrošak tkiva rožnjače veći.

Ključne reči:
fotorefraktivna keratektomija; miopija; postoperativne komplikacije; lečenje, ishod.

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Abstract

Background/Aim. Photorefractive keratectomy (PRK), after laser *in situ* keratomileusis (LASIK), is commonly performed refractive surgical method worldwide. The aim of this study was to examine the effectiveness and safety of PRK in correction of various strengths of myopia and to assess how much corneal tissue is being removed with one diopter sphere (Dsph) correction by using different optical zones (OZ). **Methods.** A prospective study with a follow-up period of 6 months included 55 patients of which 100 myopic eyes were treated by PRK method (one eye was included in 10 patients). Myopic eyes with a preoperative best corrected visual acuity (BCVA) = 1.0 (20/20) were analysed. In order to assess the effectiveness of PRK operated myopic eyes were divided into four groups according to the dioptric power: 1) ≤ -1.75 Dsph (n = 26); 2) from -2 to -3.75 Dsph (n = 44); 3) from -4 to -6.75 Dsph (n = 23), and 4) ≥ -7 Dsph (n = 7). Myopic eyes with preoperative BCVA ≤ 0.9 (amblyopic eyes) were excluded from the study, as well as eyes with astigmatism > -1.5 Dcyl. To assess the effectiveness of PRK we examined the percentage of eyes in the mentioned groups, which derived uncorrected visual acuity (UCVA) 6 months after the intervention to the following: a) UCVA = 1.0 (20/20) and b) UCVA ≥ 0.5 (20/40). To assess the safety of PRK we examined the frequency of intraoperative and postoperative complications. To estimate how much corneal tissue was removed with one Dsph correction by using different OZ, we used preoperative and postoperative (after 6 months) central pachymetry values expressed in μm and volume of cornea (central 7 mm) expressed in mm^3. In that sense, we used only the myopic eyes with clear preoperative spherical refraction. The total number of these eyes was 27, of which 16 eyes were treated using a 6.5 mm OZ and 11 eyes using a 7 mm OZ. **Results.** Refractive spherical equivalent (RSE) for all eyes was in the range from -0.75 to -8.75 Dsph, and preoperative mean value of RSE with standard deviation (mean RSE ± SD) was -3.32 ± 1.83 Dsph. Six months after PRK, 91% of eyes had UCVA = 20/20, and 99% of eyes had UCVA ≥ 20/40. In the first group (≤ -1.75 Dsph) preoperative mean RSE ± SD was -1.34 ± 0.32 Dsph, six months after PRK, 96% of eyes had UCVA = 20/20, and 100% of eyes had UCVA ≥ 20/40. In the second group (from -2 to -3.75 Dsph) preoperative mean RSE ± SD was - 2.95 ± 0.57 Dsph, six months after PRK, 89% of eyes had UCVA = 20/20, and 100% of eyes had UCVA ≥ 20/40. In the third group (from -4 to -6.75 Dsph) preoperative mean RSE ± SD was - 4.93 ± 0.70 Dsph, six months after PRK, 100% of eyes had UCVA = 20/20. In the fourth group (≥ - 7 Dsph) preoperative mean RSE ± SD was -7.71 ± 0.67 Dsph, six months after PRK, 57% of eyes had UCVA = 20/20, and 86% of eyes had UCVA ≥ 20/40. There were no intraoperative complications while postoperative complications occurred in 2 patients – in both cases in one eye (2%). In that cases, epithelial defects were detected. In the group of eyes that were treated by 6.5 mm OZ mean RSE ± SD was -2.45 ± 0.99 Dsph, the ablation depth per 1 Dsph was 17.54 ± 5.58 μm and ablated volume of central 7 mm cornea by 1 Dsph was 0.43 ± 0.18 mm^3. In the group of eyes that were treated by 7 mm OZ mean RSE ± SD was -3.32 ± 2.26 Dsph, the ablation depth per 1 Dsph was 23.73 ± 6.91 μm and ablated volume of central 7 mm cornea by 1 Dsph was 0.61 ± 0.31 mm^3. **Conclusion.** PRK is effective and safe refractive surgical method for correcting myopia up to -8 .75 Dsph. OZ size is the main factor determining the depth of the excimer laser ablation of the corneal tissue volume consumed by 1 Dsph. Higher OZ value determines higher consumption of cornea tissue.

Key words:
photorefractive keratectomy; myopia; postoperative complications; treatment, outcome.

Uvod

Tokom poslednje tri decenije refraktivna hirurgija je brzo evoluirala od radijalne keratotomije do femtosekundne laser *in situ* keratomileuze (LASIK). Metoda fotorefraktivne keratektomije (PRK) je posle LASIK-a po učestalosti izvođenja druga refraktivna hirurška metoda u svetu. Ona predstavlja uspešnu metodu u određenim indikacijama i danas se širom sveta primenjuje kao PRK ili u obliku svojih modifikacija – LASEK i EpiLASIK [1]. Sve metode za svoje izvođenje zahtevaju korišćenje *excimer* lasera. *Excimer* (skraćenica od *excited dimer*) laser je ultraljubičasti gasni laser (argon-fluorid, ArF) talasne dužine 193 nm kojim se ostvaruje fotoablativni efekat na tkivo strome rožnjače [2].

Metoda PRK je površinska ablativna metoda jer se *excimer* laserom tanji i remodelira prednji deo strome rožnjače neposredno ispod Bowman-ove membrane. Ovim se obezbeđuje veća rezidualna debljina strome i time jača biomehanička snaga rožnjače. Međutim, ablacija prednjeg dela strome, a posebno ablacija kroz sloj Bowman-ove membrane, dovodi do izraženijeg odgovora pri zarastanju rane, što može rezultirati češćom pojavom subepitelnog zamagljenja (haze) i ožiljaka u poređenju sa LASIK metodom. Oporavak nakon PRK metode je sporiji i bolniji u odnosu na LASIK metodu. Većina bolesnika 1–4 dana nakon intervencije ima prolazne pojave bola manjeg intenziteta. Postoperativna rehabilitacija vida je nešto duža i traje nekoliko nedelja [2, 3].

Metoda PRK je pogodna kod osoba sa rizikom od povrede oka, distrofijom epitelne bazalne membrane, tanjom rožnjačom (kod kojih bi debljina strome nakon ablacije bila manja od 300 μm), duboko usađenim očima, manjim palpebralnim otvorom, umereno suvim okom, ravnijom (< 41D) ili strmijom rožnjačom (> 48D), ili stanjima koja su rizična za jatrogeno povećanje intraokularnog pritiska tokom LASIK-a, kao što su glaukom ili degenerativne promene na očnom dnu tipa *farinate*, *palissadice* i *microcystoides* [3].

Metoda PRK izvodi se tako što se prvo ukloni epitel rožnjače (mehanički sljušti nožićem-hokejom, hemijskom abrazijom 20% rastvorom etanola, ili abrazijom rotacionom četkicom), potom se stroma rožnjače izloži dejstvu *excimer*

lasera čime se ona tanji i remodelira shodno vrsti ametropije i njenoj vrednosti, a nakon toga se u cilju reepitelizacije postavi terapeutsko meko kontaktno sočivo koje se nosi pet dana.

Prema preporuci Američke oftalmološke akademije [*American Academy of Ophthalmology* (AAO)] indikacije za PRK metodu su: miopija do -8,0 dioptrija (Dsph), hipermetropija do +4,0 Dsph i astigmatizam do 4 Dcyl [4].

Cilj studije bio je da se ispita uspešnost i bezbednost metode PRK u korekciji različitih dioptrijskih jačina miopije, kao i da se proceni koliko se tkiva rožnjače uklanja pri korekciji 1 Dsph korišćenjem različitih OZ na Wavelight Allegretto (400 Hz) *excimer* laseru.

Metode

U ovu prospektivnu studiju, koja je izvedena u periodu od septembra 2008. do septembra 2009. godine sa periodom praćenja od šest meseci, bilo je uključeno 55 bolesnika kod kojih je PRK metodom operisano 100 miopnih očiju (kod 10 pacijenta operisano je jedno oko). Operisano je 35 muškaraca i 20 žena. U analizu su bile uključene miopne oči s preoperativnom najbolje korigovanom vidnom oštrinom (NKVO) = 1.0 (20/20). Iz analize su bile isključene miopne oči s preoperativnom NKVO ≤ 0.9 (ambliopne oči), kao i oči s astigmatizmom > -1,5 Dcyl.

U cilju procene uspešnosti PRK metode u korigovanju miopije operisane oči smo podelili u 4 grupe zavisno od dioptrijske jačine: 1) ≤ -1,75 Dsph (n = 26); 2) od -2 do -3,75 Dsph (n = 44); 3) od -4 do -6,75 Dsph (n = 23); 4) ≥ -7 Dsph (n = 7).

Uspešnost smo procenili na osnovu procenta očiju u okviru gorenavedenih grupa, kod kojih je šest meseci nakon izvedene intervencije nekorigovana vidna oštrina (NVO) bila: a) NVO = 1.0 (20/20) i b) NVO ≥ 0.5 (20/40) (vidna oštrina dovoljna za upravljanje motornim vozilom).

Za manifestni refraktivni sferni ekvivalent (MRSE), koji predstavlja postoperativnu sfernu refrakciju merenu automatskom refraktometrijom (ARK), a koja odstupa od ciljne refrakcije = 0 Dsph uzeli smo ± 1.0 Dsph.

U cilju procene bezbednosti metode PRK ispitali smo učestalost intraoperativnih i postoperativnih komplikacija.

U cilju procene koliko se tkiva rožnjače uklanja pri korekciji 1 Dsph korišćenjem različitih OZ na Wavelight Allegretto (400Hz) *excimer* laseru koristili smo podatke sa Allegro Oculyzera i to preoperativnu i postoperativnu (nakon šest meseci) centralnu pahimetriju izraženu u μm i volumen rožnjače (centralnih 7 mm) izražen u mm³. U tu svrhu analizirane su samo miopne oči sa preoperativnom čistom sfernom refrakcijom. Ukupan broj takvih očiju bio je 27, i od toga broja 16 očiju je tretirano korišćenjem OZ 6,5 mm, a 11 očiju korišćenjem OZ 7 mm.

Svaki kandidat za izvođenje PRK metode morao je biti stariji od 21 godine i morao je imati stabilnu dioptriju u periodu od godinu dana. Bolesnici koji su nosili meka kontaktna sočiva pravili su pauzu u nošenju od 7 dana, a oni koji su nosili tvrda ili tvrda gas propustljiva kontaktna sočiva, 30 dana pre pregleda i 30 dana pre PRK intervencije. Preoperativna procena svakog kandidata podrazumevala je opštu i oftalmološku anamnezu, ARK (KR 8100 P, Topcon, Japan), NVO i NKVO, Schirmer-ov test; pregled prednjeg segmenta oka na slit lampi (SL-D8Z, Topcon, Japan), aplanacionu tonometriju (AT 900 Haag Streit, Swiss), pregled očnog dna na široku zenicu, pregled prednjeg segmenta oka na Allegro Oculyzer-u i Allegro Analyzer-u (Wavelight, Germany). Na dobijenim snimcima, između ostalog, sagledavali smo: kornealnu topografiju (prednje i zadnje površine rožnjače) sa vrednostima keratometrije (K1 i K2) i postojećih elevacija; kornealnu pahimetriju (od limbusa do limbusa) sa centralnom pahimetrijom (*central corneal thickness*, CCT); krivu progresije kornealnog istanjenja (krivu keratokonusa); volumen rožnjače (centralnih 7 mm).

Kao graničnu vrednost rezidualne debljine strome rožnjače (*residual stromal bed*), nakon uklanjanja epitela i dejstva *excimer* lasera, uzimali smo 300 μm i kao kritične vrednosti strmijeg meridijana rožnjače (*steep* K) uzimali smo < 39 D ili > 47 D. Prilikom korigovanja miopije za izračunavanje vrednosti dioptrije koju treba ukloniti *excimer* laser ablacijom pridržavali smo se nomograma Wellington.

U sklopu preoperativne pripreme i postoperativne terapije, kao i pri izvođenju same PRK intervencije pridržavali smo se protokola „bezbolne" PRK procedure. Za uklanjanje (abraziju) epitela rožnjače tokom izvođenja PRK intervencije koristili smo rotacionu četkicu (marke Amoils). *Excimer* laser ablaciju izvodili smo na Wavelight Allegretto (400Hz) *excimer* laseru.

Protokol „bezbolne" PRK procedure izvodi se u cilju kontrole bola, brže epitelizacije rožnjače, kao i kontrole nastanka subepitelnog zamagljenja (haze), a podrazumeva:

1. Preoperativnu pripremu – uzimanje *per os* vitamina C i omega-3-masnih kiselina 1 nedelju preoperativno, ibuprofena 2 dana preoperativno, prednizolona i anksiolitika 30 min pre intervencije; i ukapavanje kapi sa kombinacijom deksametason/tobramicin neposredno pre intervencije.
2. Intraoperativnu primenu smrznutog *balanced salt solution* (BSS) radi usporenja metabolizma rožnjače i uklanjanja citokina; 0,02% rastvora mitomicin-C samo ako ablaciona debljina prelazi 100 μm; i kapi deksametason/tobramicina i diklofenaka, uz postavljanje mekog terapeutskog kontakntog sočiva koje se nosi 5–7 dana.
3. Postoperativnu primenu: kapi deksametason/tobramicin prvih mesec dana, a potom kapi prednizolona drugi i treći mesec; diklofenak kapi, na dan intervencije i dva dana posle intervencije; rashlađenih kapi veštačkih suza (kombinacija hijaluronske kiseline sa dekspantenolom) za lubrikaciju i ispiranje svakih 10 min tokom ostatka dana nakon intervencije, a posle toga po potrebi; *per os* vitamina C i omega-3-masnih kiselina 2 nedelje, i ibuprofena i anksiolitika 3 dana nakon intervencije.

Bolesnici su redovno kontrolisani 1, 5, 15. i 30. postoperativnog dana, kao i 2, 3 i 6 meseci nakon PRK intervencije. Kontrolni pregledi na Oculyzer-u vršeni su 3. i 6. meseca nakon intervencije.

U obradi rezultata korišćene su deskriptivne statističke metode.

Rezultati

U prikazanoj studiji RSE svih očiju bio je u rasponu od -0,75 do -8,75 Dsph, a preoperativna srednja vrednost RSE sa standardnom devijacijom (srednja RSE ± SD) bila je -3,32 ± 1,83 Dsph. Šest meseci nakon PRK 91% očiju imalo je NVO = 20/20, a 99% očiju NVO ≥ 20/40 (slika 1 i 2).

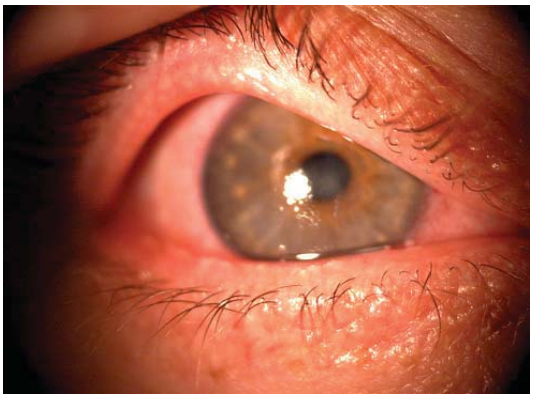
U okviru prve grupe (≤ -1,75 Dsph) preoperativna srednja RSE ± SD bila je -1,34 ± 0,32 Dsph, šest meseci nakon PRK 96% očiju imalo je NVO = 20/20, a 100% očiju NVO ≥ 20/40 (slika 1 i 2).

U okviru druge grupe (od -2 do -3,75 Dsph) preoperativna srednja RSE ± SD bila je -2,95 ± 0,57 Dsph, šest meseci nakon PRK 89% očiju imalo je NVO = 20/20, a 100% očiju NVO ≥ 20/40 (slika 1 i 2).

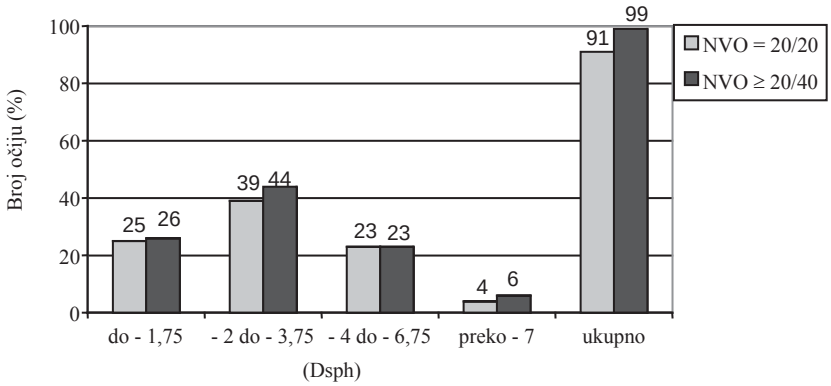
U okviru treće grupe (od -4 do -6,75 Dsph) preoperativna srednja RSE ± SD bila je -4,93 ± 0,70 Dsph, šest meseci nakon PRK 100% očiju imalo je NVO = 20/20 (slika 1 i 2).

U okviru četvrte grupe (≥ -7 Dsph) preoperativna srednja RSE ± SD bila je -7,71 ± 0,67 Dsph, šest meseci nakon PRK 57% očiju imalo je NVO = 20/20, a 86% očiju NVO ≥ 20/40 (slika 1 i 2).

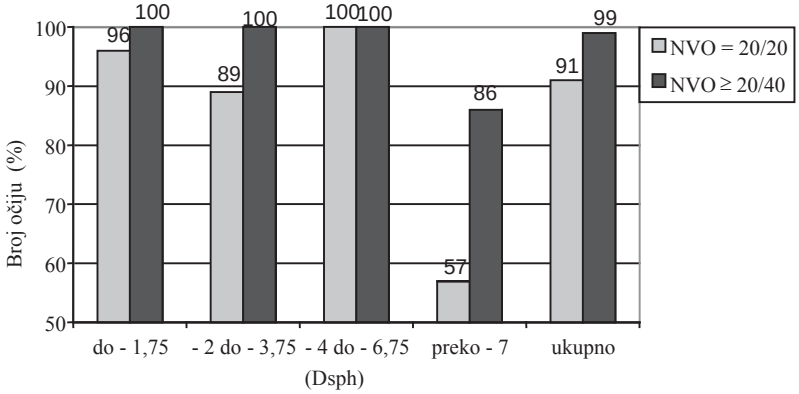
Kod prvog bolesnika, muškarac star 51 godinu, preoperativna NKVO bila je VOD = sa -3,75/-0,5 ax 107º = 1,0 i VOS = sa -3,75/0,25 ax 72º = 1,0. Na oba oka uspešno je izvedena PRK nakon koje je uvedena terapija u skladu sa protokolom „bezbolne“ PRK procedure. Mesec i po dana nakon izvedene intervencije došlo je do pojave defekata epitela rožnjače (slika 3) i pada vida na desnom oku: VOD = 0,5 s.c.



Sl. 3 – Defekti epitela rožnjače lokalizovani centralno (foto špalt desnog oka)



Sl. 1 – Broj očiju prema dioptrijskim grupama i ukupno kod kojih je šest meseci nakon izvedene fotorefraktivne keratektomije (PRK) nekorigovana vidna oštrina (NVO) = 20/20, odnosno NVO ≥ 20/40.



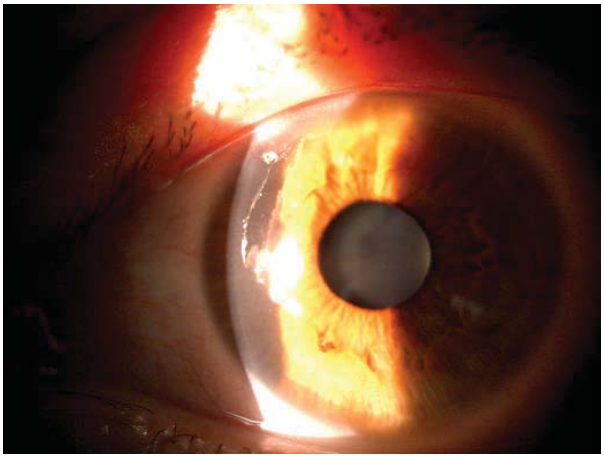
Sl. 2 – Procenat očiju prema dioptrijskim grupama i ukupno kod kojih je šest meseci nakon izvedene fotorefraktivne keratektomije (PRK) nekorigovana vidna oštrina (NVO) = 20/20, odnosno NVO ≥ 20/40.

Intraoperativnih komplikacija nije bilo, dok su se postoperativne komplikacije javile kod dva bolesnika, i to kod oba samo na jednom oku (učestalost 2%). Radilo se o defektima epitela rožnjače.

i VOS = 1,0 s.c. Isključena je lokalna kortikosteroidna terapija za oba oka i u terapiju su uvedene samo kapi sa veštačkim suzama na bazi Na-hijaluronata i dekspantenola, bez konzervansa (preparat Hylocare®) 6 x dnevno. Par dana na-

kon toga rožnjača desnog oka je epitelizovala i uspostavila svoju transparentnost i glatkoću. Na kontroli nakon šest meseci dobijene su vrednosti: ARK o.dex. +0,25/-0,5 ax 175º i ARK o. sin. -0,5 Dsph, a VOD = 0,9–1,0 s.c. i VOS = 1,0 s.c.

Kod drugog bolesnika, muškarca starog 30 godina, preoperativna NKVO bila je VOD = sa -2,25 Dsph = 1.0 i VOS = sa -2,25/-0,50 ax 88 º = 1,0. Na oba oka uspešno je izvedena PRK nakon koje je uvedena terapija u skladu sa protokolom „bezbolne" PRK procedure. Šest dana nakon izvedene intervencije, a jedan dan nakon uklanjanja terapeutskog sočiva, bolesnik se zbog osećaja suvoće i blagog pada vida na oba oka javio na pregled na kome je konstatovano da se radi o punktatnim defektima epitela rožnjače oba oka, te je korigovana terapija i smanjena učestalost ukapavanja deksametazon/tobramicin (Tobradex®) kapi sa 4 puta na 2 puta dnevno i u terapiju su uključene kapi sa hijaluronskom kiselinom i dekspantenolom, (Hylocare®), 8 puta dnevno. Sutradan je došlo do nestanka gore navedenih tegoba i uspostavljanja dobre vidne oštrine na oba oka, VOD = 1,0 s.c i VOS = 1,0 s.c, te je nastavljeno sa korigovanom terapijom. Nakon mesec dana, zbog iznenadnog bola u levom oku bolesnik se javio na pregled na kome je nađen veći defekt epitela rožnjače (slika 4), sa dobrom vidnom oštrinom na oba oka, VOD = 1,0 s.c i VOS = 1,0 s.c. Isključena je lokalna kortikosteroidna terapija za oba oka, za desno oko je data terapija – samo kapi Hylocare® 4 puta dnevno, a levo oko je uz mast sa hloramfenikolom 1%, zatvoreno pogačicom dva dana. Nakon dva dana rožnjača levog oka se epitelizovala i uspostavila svoju transparentnost i glatkoću, te je u terapiju uvedena mast Hloramfenikol 1% pre spavanja, kapi NaCl 5% 4 puta dnevno, dve nedelje, i kapi Hylocare®, 4 puta dnevno. Na kontroli nakon šest meseci dobijene su vrednosti: ARK o.dex. -0,50/-0,50 ax 113º i ARK o.sin. -0,25/-0,25 ax 110º, a VOD = 1,0 s.c. i VOS = 1,0 s.c.



Sl. 4 – Veći defekt epitela rožnjače lokalizovan periferno (foto špalt levog oka)

U grupi očiju koje su tretirane OZ 6,5 mm srednja RSE ± SD bila je -2,45 ± 0,99 Dsph, dubina ablacije po 1 Dsph bila je 17,54 ± 5,58 μm i ablatirana zapremina centralnih 7 mm rožnjače po 1 Dsph bila je 0,43 ± 0,18 mm³ (tabela 1). U grupi očiju koje su tretirane OZ 7 mm srednja RSE ± SD iznosila je -3,32 ± 2,26 Dsph, dubina ablacije po 1 Dsph bila je 23,73 ± 6,91 μm, a ablatirana zapremina centralnih 7 mm rožnjače po 1 Dsph 0,61 ± 0,31 mm³ (tabela 1).

Tabela 1

Uticaj veličine optičke zone (OZ) na dubinu ablacije i volumen ablatiranog tkiva rožnjače po 1 Dsph

Parametri	OZ 6,5 mm (n = 16)	OZ 7 mm (n = 11)
Srednja RSE (Dsph), $\bar{x}$ ± SD	-2,45 ± 0,99	-3,32 ± 2,26
Dubina ablacije po 1 Dsph, (μm), $\bar{x}$ ± SD	17,54 ± 5,58	23,73 ± 6,91
Ablatirana zapremina po 1 Dsph (mm³), $\bar{x}$ ± SD	0,43 ± 0,18	0,61 ± 0,31

RSE – refraktivni sferni ekvivalent

Diskusija

Analizirajući raspon RSE u našoj studiji (od -0,75 do -8,75 Dsph) možemo reći da se uklapa u preporuku koju je dala AAO za indikacije za PRK metodu [4]. U našoj studiji šest meseci nakon PRK 91% očiju imalo je NVO = 20/20, a 99% očiju NVO ≥ 20/40. Sakimoto i sar. [2] u svome revijalnom radu iznose kumulativnu analizu velikog broja studija koje ispituju uspešnost PRK u korekciji miopije (raspon RSE od -1 do -13 Dsph) i navode da je 61,1% očiju imalo NVO = 20/20, dok je 94,3% očiju imalo NVO ≥ 20/40. Pop i Payette [5] u svojoj studiji u kojoj porede uspešnost metoda PRK i LASIK u korekciji miopije (raspon RSE od -1 do -9,5 Dsph) dobijaju da je godinu dana nakon PRK 86% očiju imalo NVO = 20/20. U studiji u kojoj porede uspešnost metoda LASIK i PRK u korekciji miopije do -6,5 Dsph (srednja RSE ± SD = -3,44 ± 1,13 Dsph) Hashemi i sar. [6] navode da je 3 meseca nakon PRK 82% očiju imalo NVO ≥ 20/20, a 97% NVO ≥ 20/40. Lee i sar. [7] u svojoj studiji, u kojoj porede uspešnost metoda LASIK i PRK u korekciji miopije do -6 Dsph (srednja RSE ± SD = -4,54 ± 0,80 Dsph), nasli su da je šest meseci nakon PRK 77,8% očiju imalo NVO ≥ 20/20.

U cilju poređenja uspešnosti metode PRK u odnosu na metodu LASIK u korekciji različitih dioptrijskih jačina miopije možemo navesti studiju u kojoj Vukosavljević i sar. [8] daju svoje iskustvo sa metodom LASIK u korekciji miopije i hipermetropije. Oni navode da je preoperativni RSE miopnih očiju bio u rasponu od - 0,75 do - 12 Dsph, i dobijaju da je u grupi očiju sa preoperativnom refrakcijom ≤ -1,75 Dsph srednja RSE ± SD bila -1,39 ± 0,36 Dsph i šest meseci nakon LASIK-a 100% očiju imalo je NVO = 20/20. U grupi očiju sa preoperativnom refrakcijom od -2 do -3,75 Dsph srednja RSE ± SD bila je -2,85 ± 0,5 Dsph i šest meseci nakon LASIK-a 93% očiju imalo je NVO = 20/20, a 100% očiju NVO ≥ 20/40. U grupi očiju sa preoperativnom refrakcijom od -4 do -6,75 Dsph mean RSE ± SD bila je -5,03 ± 0,75 Dsph i

šest meseci nakon LASIK-a 90% očiju imalo je NVO = 20/20, a 100% očiju NVO ≥ 20/40. U grupi očiju sa preoperativnom refrakcijom ≥ -7 Dsph srednja RSE ± SD bila je -7,68 ± 1,03 Dsph i šest meseci nakon LASIK-a 96% očiju imalo je NVO = 20/20, a 100% očiju NVO ≥ 20/40.

Postoperativne komplikacije u našoj studiji javile su se kod dva oka (učestalost 2%) u vidu defekata epitela rožnjače, tj. erozije rožnjače. Edmison [9] u svome revijalnom radu o PRK komplikacijama navodi da je učestalost rekurentnih erozija rožnjače nakon PRK 0,5% i ističe da se one mogu javiti nakon bilo koje tehnike uklanjanja epitela (mehanički, alkoholom ili rotacionom četkicom), osim tehnike uklanjanja epitela laserom.

U našoj studiji u grupi očiju koje su tretirane OZ 6,5 mm dubina ablacije po 1 Dsph bila je 17,54 ± 5,58 μm, dok je u grupi očiju koje su tretirane OZ 7 mm dubina ablacije po 1 Dsph bila je 23,73 ± 6,91 μm. Wirbelauer i sar. [10], u svojoj studiji u kojoj su merili centralnu pahimetriju kornealnom optičkom koherentnom tomografijom pre intervencije i posle *excimer* laser ablacije metodom PRK, korišćenjem ablativne zone od 6 do 6,5 mm dobili su da je srednja RSE ± SD tretiranih očiju bila -6,7 ± 3,6 Dsph pri čemu je planirana srednja vrednost ablatiranog tkiva strome rožnjače bila 91 ± 38 μm. Wirbelauer i sar.[11], u studiji u kojoj su tokom LASIK intervencije merili centralnu pahimetriju primenom *online optical coherence pachymetry* (OCP) posle kreiranja flapa i posle *excimer* laser ablacije dobili su da je u grupi miopnih očiju dubina ablacije po 1 Dsph bila 24,63 ± 7,81 μm, što je za 29,2% više od vrednosti dobijenih kalkulacijom na *excimer* laseru (srednja RSE ± SD tretiranih očiju bila je -5,52 ± 2,29 Dsph).

U našoj studiji u grupi očiju koje su tretirane primenom OZ 6,5 mm ablatirana zapremina centralnih 7 mm rožnjače po 1 Dsph bila je 0,43 ± 0,18 mm³, dok je u grupi očiju koje su tretirane primenom OZ 7 mm ablatirani volumen centralnih 7 mm rožnjače po 1 Dsph iznosio 0,61 ± 0,31 mm³. Gatinel i sar. [12] u studiji u kojoj procenjuju volumen tkiva ablatiranog *excimer* laserom po 1 Dsph dobijaju da se pri korišćenju OZ 6,5 mm ablatira 0,2794 mm³, a pri korišćenju OZ 7 mm 0,3883 mm³ tkiva rožnjače miopnih očiju.

Zaključak

Naši rezultati pokazuju da je metoda PRK uspešna i bezbedna refraktivna hirurška metoda u korekciji miopije do -8,75 Dsph. Intraoperativnih komplikacija nije bilo, dok je učestalost postoperativnih komplikacija niska (u našem ispitivanju defekti epitela rožnjače javili su se kod dva bolesnika, kod svakog na jednom oku). Veličina OZ je glavni faktor koji određuje dubinu *excimer* laser ablacije i zapreminu utrošenog tkiva rožnjače po 1 Dsph. Što je OZ veća to je i utrošak tkiva rožnjače veći.

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Kvalitet života obolelih od dijabetesa melitusa tipa 2

The quality of life in patients with diabetes mellitus type 2

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Apstrakt

Uvod/Cilj. Svetska zdravstvena organizacija (SZO) svojom delatnošću doprinela je porastu razumevanja koncepta kvaliteta života. Kvalitet života je bolesnikova percepcija uticaja bolesti i odgovarajuće terapije na njegovu fizičku i radnu sposobnost, psihološko stanje, socijalnu komunikaciju i somatsko zdravlje. Osobe sa dijabetesom imaju lošiji kvalitet života od ljudi bez hroničnih bolesti. Cilj istraživanja bio je da se ispitaju razlike u kvalitetu života povezanog sa zdravljem kod obolelih od dijabetesa melitusa (DM) tipa 2 prema starosnim grupama, polu i vrsti primenjene terapije. **Metode.** Sprovedena je studija preseka u Dijabetološkoj dnevnoj bolnici Kliničkog centra Vojvodine u Novom Sadu i Domu Zdravlja Ruma – Služba opšte medicine. Bilo je uključeno 90 bolesnika sa DM tipa 2. Ispitanici su bili starosti od 40 do 80 godina, podeljeni u četiri grupe prema desetogodišnjim starosnim intervalima. Korišćen je upitnik za procenu kvaliteta života SZO (WHOQOL – BREF), koji se sastoji od četiri domena: fizičko zdravlje, psihološko zdravlje, socijalne relacije i životno okruženje. Opšti upitnik je sadržao pitanja o socijalnodemografskim podacima, dužini trajanja DM, poslednjoj vrednosti glikemije našte i glikoziliranog (HbA_{1C}) hemoglobina, obučenost i za samokontrolu glikemije i njeno sprovođenje, informisanosti bolesnika o svojoj bolesti, terapiji i njenom uticaju na svakodnevne aktivnosti, kao i o prisustvu komorbiditeta. **Rezultati.** Prosečna dužina trajanja DM tip 2 bila je 11,2 ± 9,2 godine. Većina bolesnika (76%) bili su obučeni za samokontrolu, a 91% dobilo je dovoljno informacija o svojoj bolesti. Oralne hipoglikemijske preparate koristilo je 49%, insulin 21%, oralnu terapiju i insulin 29%, a 1% ispitanika bilo je na terapiji dijetetskim režimom ishrane. Bez teškoće svakodnevne aktivnosti obavljalo je njih 29%, nešto teže 41%, a 30% nije moglo da obavlja svakodnevne aktivnosti. Naši ispitanici dali su nižu ocenu kvaliteta života, a najniži nivo bio je u oblasti fizičkog zdravlja (51,31). Najniži nivo kvaliteta života bio je kod osoba sa nižom stručnom spremom u oblasti mentalnog zdravlja, socijalnih relacija i životnih uslova ($p < 0,01$; $p < 0,05$; $p < 0,05$) redom. Komorbiditet je imalo 83% ispitanika i oni su imali niži kvalitet života u odnosu na grupu bez komorbiditeta. Najčešći komorbiditeti bili su: arterijska hipertenzija kod 63%, hronične kardiovaskularne bolesti kod 46%, neuropatija kod 23%, oštećenje vida kod 24%, povišene masnoće u krvi kod 39% i amputacije prstiju ili stopala kod 2,2% obolelih od DM. Prosečna vrednost HbA_{1C} u grupi sa komorbiditetom bila je 8,47%, a u grupi bez komorbiditeta 6,46% i ova razlika bila je statistički značajna ($t = 12,37$; $p < 0,01$). Nije bilo statistički značajne razlike u oceni kvaliteta života prema starosti, polu obolelih, kao ni prema vrsti primenjene terapije. **Zaključak.** DM tipa 2 ima negativan uticaj na kvalitet života. Lošija ocena kvaliteta života bila je u grupi bolesnika sa komorbiditetima. Kod bolesnika sa DM uočen je pad radne sposobnosti i sposobnosti za obavljanje svakodnevnih aktivnosti.

Ključne reči: dijabetes melitus tip 2; kvalitet života; upitnici; komorbiditet.

Abstract

Background/Aim. Through its vrious activities, World Health Organization (WHO) contributed to increasing the understanding of the concept of quality of life. People with diabetes have a lower quality of life than people without chronic illnesses. The aim of this study was to examine the differences in the quality of life, related to health, in patients with diabetes mellitus (DM) type 2 by age, gender and type of therapy. **Methods.** We performed a cross-sectional study at the outpatient department of the Clinical Center in Novi Sad and the Health Center Ruma – General Practice. The group consisted of 90 patients with DM type 2, 41 men and 49 women. The age of respondents was from 40 to 80 years and they were classifed into four groups according to the ten-year age intervals. We applied WHO Quality of life questinnaire – BREF 100 composed of four domains: physical health, psychological health, social relationships and environment. The general questionnaire asks questions about socio-demographic data, duration of diabetes, the last value of blood glucose and glycosylated hemoglobin, training for self-control and its implementation, informing pa-

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tients about their disease, therapy and its impact on daily activities and the presence of comorbidity. In statistical analysis the following tests were used: Student's t-test, F-test, ANOVA (one way). **Results.** The average duration of DM type 2 was 11.2 ± 9.2 years. Most of the patients (76%) were trained to self-control and 91% received enough information about their disease. Oral hypoglycemic preparations were used by 49%, insulin by 21%, and oral drugs and insulin by 29% patients while 1% were on a special regime of a diet therapy. Daily activities were performed without difficulties by over 29%, with some difficulties by 41% and 30% of patients who could not perform daily activities. The patients with DM type 2 had significantly lower scors in all 4 domains of quality of life (physical health, psychological health, social relations, environment). The biggest influence was on physical domains (51.31). Education level had an imact on physical and psychological domains. Comorbidity was found in 83% of the respondents. The most common were: arterial hypertension (63%), chronic cardiovascular disease (46%), neuropathy (23%), impaired vision 24%, elevated blood lipids (39%) and amputation of toes or feet (2.2%). The average value HbA_{1C} in the group with comorbidity was 8.47% and in the group without comorbidity 6.46%. The subjects with comorbidity had low quality of life assessment in relation to the group without comorbidity: the domain of physical health (45.64 *vs* 79.66), psychological health (50.3 *vs* 76.86), social relations (52.97 *vs* 75.46) and environment (52.7 *vs* 75.06). **Conclusion.** Diabetes mellitus type 2 has negative influence on the quality of life. It contributes to the presence of comorbidity. The occurrence of comorbidity was associated with higher glucosylated HbA_{1C} values. There was no difference in the assessment of quality of life regarding gender, age, or the type of therapy used. The quality of life was assessed as low in patients with comorbidity. However, certain personality characteristics play a decisive role in self-evaluation.

Key words:
diabetes mellitus type 2; quality of life; questionaires; comorbidity.

Uvod

Svetska zdravstvena organizacija (SZO) svojom delatnošću doprinela je porastu razumevanja koncepta kvaliteta života. Pod njenim okriljem početkom devedesetih godina prošlog veka formirana je grupa koja je sprovela multinacionalnu studiju o kvalitetu života. Prema SZO [1] kvalitet života definiše se kao percepcija pojedinca sopstvenog položaja u kontekstu kulture i sistema vrednosti u kojima živе, kao i prema svojim ciljevima, očekivanjima, standardima i interesovanjima. To je širok koncept koji čine fizičko zdravlje pojedinaca, psihološki status, materijalna nezavisnost, socijalni odnosi i njihovi odnosi prema značajnim karakteristikama spoljašnje sredine. Koncept kvaliteta života predstavlja subjektivni doživljaj individue, što znači da odslikava psihološko doživljavanje sebe i sveta oko sebe u različitim domenima. Iz perspektive zdravlja (ili bolesti) kvalitet života se odnosi na socijalno, emocionalno i fizičko blagostanje bolesnika nakon lečenja, odražavajući definiciju SZO, kao i na uticaj bolesti i lečenja na nesposobnost i svakodnevno funkcionisanje [1]. Sve je manje teoretičara koji smatraju da je kvalitet života isto što i zdravlje, jer ako bi se prihvatio takav stav onda se o kvalitetu života ne bi moglo govoriti kod osoba koje su zbog bolesti ili povrede izgubile manji ili veći deo svoje sposobnosti. Jedan od najtežih zadataka kod merenja kvaliteta života jeste prevođenje svake komponente i domena zdravlja u kvantitativne vrednosti. Najveći broj istraživača meri svako područje kvaliteta života posebno, postavljajući specifična pitanja koja se odnose na najznačajnije komponente. Interesovanje za kvalitet života stimulisano je uspehom u produžavanju života, ali i činjenicom da ljudi žele ne samo da prežive kritični momenat u svom životu, nego i da nastave da žive određenim kvalitetom.

Hronične bolesti znatno utiču na sniženje kvaliteta života, što pokazuju i rezultati studije u Japanu [2] koja je obuhvatila 2 762 starije osobe podeljene u devet grupa prema vrsti bolesti: cerebrovaskularne bolesti, hipertenzija, koronarna bolest, dijabetes melitus (DM), karcinom, fraktura kosti, hronične digestivne i respiratorne bolesti, koštano-mišićne bolesti. Zastupljenost dijabetesa dostiže epidemijske razmere u mnogim delovima sveta. Osobe sa dijabetesom imaju lošiji kvalitet života od ljudi bez hroničnih bolesti [3].

Skorovi na skalama kvaliteta života postaju niži usled istovremenog delovanja osnovne bolesti i nekog drugog obolenja (somatskog ili psihičkog), nastalo kao njena komplikacija ili kao njen komorbiditet [4]. Dijabetes je povezan sa visokim rizikom od ozbiljnih komplikacija koje utiču na smanjenje kvaliteta života. Međutim, pojedine karakteristike ličnosti igraju odlučujuću ulogu u samoproceni kvaliteta života. Glavni cilj u lečenju obolelih od dijabetesa je održavanje glukoze u krvi što bliže normali, postizanje odgovarajuće metaboličke kontrole i obezbeđivanje relativno uobičajenog kvaliteta života. Ovi ciljevi su pod uticajem mnoštva psiholoških i somatskih faktora koje treba shvatiti kao jednu složenu mrežu.

Cilj istraživanja bio je da se ispitaju razlike u kvalitetu života povezanog sa zdravljem obolelih od DM tipa 2 prema starosnim grupama, polu i vrsti primenjene terapije.

Metode

Sprovedena je studija preseka u Dijabetološkoj dnevnoj bolnici Specijalističke poliklinike Kliničkog centra Vojvodine, Novi Sad i Domu zdravlja Ruma – Služba opšte medicine. Istraživanje je trajalo od 01.03.2010. do 15.03.2010. Bilo je uključeno 90 osoba sa tipom 2 šećerne bolesti: 41 muškarac (46%) i 49 žena (54%), koje su se u tom periodu javile na pregled. Ispitanici su bili stari od 40 do 80 godina i prema tome podeljeni u četiri grupe prema desetogodišnjim starosnim intervalima. Kao instrument za prikupljanje podataka korišćen je upitnik za procenu kvaliteta života SZO – kratka verzija: *The World Health Organisation quality of life instrument* (WHOQOL- BREF) [5] . Radi se o upitniku za samopopunjavanje koji sadrži 26 pitanja na osnovu kojih se procenjuje kvali-

tet života iz četiri domena: fizičko zdravlje (dnevne aktivnosti, zavisnost o lekovima, energija i umaranje, pokretljivost, bol i uznemirenost, spavanje i odmor, radni kapacitet); psihološko zdravlje (doživljaj sopstvenog tela i izgled, negativna osećanja, pozitivna osećanja, samopoštovanje, religioznost, mišljenje, učenje, koncentracija); socijalne relacije (lični odnosi, socijalna podrška, seksualna aktivnost); životni uslovi (izvori finansiranja, sloboda, telesna sigurnost i zaštićenost, zdravstvena i socijalna zaštita, tj. dostupnost i kvalitet, kućna okolina, dostupnost informacijama i uslugama, mogućnost rekreacije). Odgovor na svako pitanje boduje se cifrom od 1 do 5, gde 1 označava najmanje slaganje, a 5 najveće slaganje. Svaki domen određuje se tako što se saberu vrednosti relevantnih odgovora, a taj zbir se zatim prevodi u nove vrednosti u rasponu od 1–100 pomoću specijalnih tabela.

Maksimalni skor za svaki domen je 100. Istražujući stepen validnosti i pouzdanosti ovog upitnika u našoj zemlji [6] utvrđena je visoka pouzdanost i validnost za sva četiri domena, a rezultati procene kvaliteta života su uporedivi sa rezultatima dobijenim u drugim zemljama gde je korišćena odgovarajuća verzija upitnika WHOQOL-BREF.

Upotrebljen je i Opšti upitnik koji sadrži pitanja o socijalno-demografskim podacima, kao i deo koji se odnosi na dužinu trajanja šećerne bolesti, poslednja vrednost glikemije našte i glikoziliranog hemoglobina (HbA_{1C}), obučenost za samokontrolu kao i njeno sprovođenje, informisanost bolesnika o svojoj bolesti od izabranog lekara, terapija i njen uticaj na svakodnevne aktivnosti, prisustvo komorbiditeta. U statističkoj analizi korišćeni su Studentov *t*-test, F-test i analiza varijanse – ANOVA (*one way*).

Rezultati

Dijabetes tipa 2 kod 24,4% ispitanika trajao je manje od 5 godina, kod 28% od 5–9 godina, kod 22% od 10–15 godina, kod 7,8% od 15–19 godina, a kod 17,8% duže od 20 godina. Prosečna dužina trajanja bolesti iznosila je 11,2 ± 9,2 godina.

Većina bolesnika (76%) dali su podatak da su obučeni za samokontrolu, njih 64,4% vršili su samokontrolu, a 91% smatrali su da su dobili dovoljno informacija o šećernoj bolesti od svog lekara.

U pogledu terapije 49% koristilo je oralne hipoglikemijske preparate, insulin 21%, oralnu terapiju i insulin 29%, a 1% bilo je na terapiji dijetetskim režimom ishrane i fizičkoj aktivnosti, bez upotrebe medikamentne terapije. Njih 76% izjasnili su se da im propisana terapija ne remeti svakodnevne aktivnosti.

Da bez teškoća obavljaju svakodnevne aktivnosti izjasnilo se 29% ispitanika, 41% da obavljaju nešto teže, a 30% da ne može da obavlja svakodnevne aktivnosti. O radnoj sposobnosti izjasnili su se na sledeći način: radna sposobnost kao i pre 29% ispitanika, manja nego pre 34% ispitanika, dok je radno nesposobnih bilo 37%. Naši ispitanici oboleli od DM 2 bili su zadovoljni zdravljem (47%), dok je njih 53% bilo nezadovoljno. Ukupno, 36% ispitanika ocenili su kvalitet života kao loš, a njih 64% kao dobar.

Komorbiditet je imalo 83% ispitanika, i to većina dva ili više udruženih. Najčešći komorbiditeti bili su arterijska hipertenzija (63% ispitanika), hronične bolesti kardiovaskularnog sistema (KVS) (46%), polineuropatija (23%), oštećen vid (24%), povišene masnoće u krvi (39%), amputacija prstiju ili noge (2,2%), hronična opstruktivna bolest pluća (7,7%), hronična bubrežna slabost (3,3%), hronična bolest jetre (3,3%), malignitet (6,6%) i druge bolesti – (7,7%).

Prosečna vrednost glikemije našte u grupi sa komorbiditetom bila je 10,2 mmol/L, a u grupi bez komorbidita 6,9 mmol/L. Prosečna vrednost HbA_{1C} bila je 8,47% u grupi sa komorbiditetom, što znači da su komorbiditeti udruženi sa lošijom metaboličkom kontrolom bolesti. U grupi obolelih od dijabetesa bez komorbiditeta prosečna vrednost HbA_{1C} bila je 6,46%.

Postojala je statistički značajna korelacija između visine HbA_{1C} i pojave komorbiditeta ($p < 0,01$). Ispitanici sa komorbiditetom imali su lošiju ocenu kvaliteta života u odnosu na grupu bez komorbiditeta u domenu fizičkog zdravlja (45,64 *vs* 79,66), psihološkog zdravlja (50,93 *vs* 76,86), socijalnih relacija (52,97 *vs* 75,46) i životnih uslova [(52,70 *vs* 75,06), ($p < 0,01$)] (tabela 1).

Oboleli od DM tipa 2 imali su statistički značajan pad u sva četiri domena kvaliteta života ($p < 0,01$). Najniži nivo kvaliteta života bio je u oblasti fizičkog zdravlja – skor 51,31 (tabela 2).

Tabela 1

Kvalitet života obolelih od dijabetesa melitusa tipa 2 sa i bez komorbiditeta

Oblast	Komorbiditet (n = 75)	Bez komorbiditeta (n = 15)	*t*-test	*p*
	$\bar{x} \pm SD$	$\bar{x} \pm SD$		
Fizičko zdravlje	45,64 ± 16,598	79,66 ± 13,524	8,547	0,000*
Psihološko zdravlje	50,93 ± 19,011	76,86 ± 11,225	7,143	0,000*
Socijalne relacije	52,97 ± 17,021	75,46 ± 12,411	5,983	0,000*
Životni uslovi	52,70 ± 15,452	75,06 ± 10,989	6,673	0,000*

*$p < 0,01$

Tabela 2

Kvalitet života bolesnika sa dijabetesom melitusom tipa 2

Oblast	DM 2 (n = 90)
	$\bar{x} \pm SD$
Fizičko zdravlje	51,31 ± 19,087
Psihološko zdravlje	55,26 ± 19,204
Socijalne relacije	56,73 ± 17,803
Životni uslovi	56,43 ± 15,583

U pogledu stručne spreme uočeno je da je najniži kvalitet života bio kod osoba sa nižom stručnom spremom u oblasti psihološkog zdravlja, socijalnih relacija i životnih uslova ($p < 0,01$; $p < 0,05$; $p < 0,05$). Međutim, nije bilo statistički značajne razlike u fizičkom zdravlju kod osoba različitog nivoa obrazovanja ($p > 0,05$) (tabela 3).

Tabela 3

Odnos kvaliteta života obolelih od dijabetesa melitusa tipa 2 i njihove stručne spreme

Oblast	Stručna sprema				F-test	*p*
	niska (n = 29)	srednja (n = 50)	viša (n = 6)	visoka (n = 5)		
	x̄ ± SD	x̄ ± SD	x̄ ± SD	x̄ ± SD		
Fizičko zdravlje	44,48 ± 14,093	54,62 ± 20,387	49,17 ± 26,438	60,40 ± 12,876	2,230	0,090
Psihološko zdravlje	44,90 ± 17,253	58,88 ± 19,027	61,67 ± 11,518	71,40 ± 13,831	5,544	0,002
Socijalne relacije	48,69 ± 16,327	61,04 ± 17,990	64,50 ± 14,543	51,00 ± 11,180	3,837	0,012
Životni uslovi	49,69 ± 14,023	59,00 ± 16,015	60,50 ± 10,291	65,00 ±14,950	3,109	0,031

Nije zabeležena statistički značajna razlika u kvalitetu života ispitanika obolelih od dijabetesa u odnosu na pol ($p > 0,05$) (tabela 4).

Istraživanje je pokazalo niže skorove kod svih ispitanika bez obzira na životno doba, ali bez statistički značajne razlike između starosnih grupa ispitanika ($p > 0,05$) (tabela 5).

Posmatrajući kvalitet života u odnosu na vrstu terapije kod obolelih od dijabetesa nije postojala statistički značajna razlika u oceni kvaliteta života ($p > 0,05$), bez obzira na vrstu primenjene terapije (tabela 6).

Diskusija

Ispitivanje kvaliteta života i mogućnosti za njegovo unapređenje posebno su važni ne samo u javnozdravstvenim, već i u kliničkim disciplinama, imajući u vidu povećanje očekivanog trajanja života i porasta učestalosti oboljenja sa kojim su mnogi ljudi prinuđeni da žive. Istražujući kvalitet života bolesnika obolelih od DM tipa 2, uočili smo da bolest doprinosi padu kvaliteta života u svim domenima, što odgovara i rezultatima drugih studija [7]. Na sniženje kvaliteta života svakako da utiču i komorbiditeti, a u našem istraživanju čak 83% ispitanika bilo je sa komorbiditetom i to: arterijskom hipertenzijom 63%, komplikacijama na očima, retinopatijom i kataraktom 24 %, polineuropatijom 23%, što odgovara i rezultatima drugih studija [8–10]. U studiji koja je sprovedena u Indiji [8] polineuropatiju je imalo 26,2% ispi-

Tabela 4

Povezanost pola i kvaliteta života obolelih od dijabetesa melitusa tipa 2

Oblast	Muškarci (n = 40)	Žene (n = 50)	*t*	*p*
	x̄ ± SD	x̄ ± SD		
Fizičko zdravlje	53,90 ± 20,875	49,24 ± 17,465	1,153	0,252
Psihološko zdravlje	59,68 ± 17,391	51,72 ± 20,010	1,985	0,050
Socijalne relacije	59,55 ± 19,757	54,48 ± 15,917	1,349	0,181
Životni uslovi	57,25 ± 17,925	55,78 ± 13,577	0,443	0,659

Tabela 5

Kvalitet života obolelih od dijabetesa melitusa tipa 2 u zavisnosti od godina života

Godine života (raspon)	Kvalitet života (x̄ ± SD)			
	Fizičko zdravlje	Psihološko zdravlje	Socijalne relacije	Životni uslovi
41–50	44,0 ± 24,8	59,5 ± 25,7	53,9 ± 14,2	55,6 ± 16,2
51–60	59,5 ± 16,5	63,1 ± 17,8	59,4 ± 18,3	58,5 ± 17,5
61–70	53,8 ± 19,9	55,6 ± 18,5	60,3 ± 19,4	58,7 ± 14,8
71–80	46,3 ± 16,2	50,1 ± 18,2	51,7 ± 15,7	52,8 ± 15,6
F	2,228	1,663	1,533	0,900
p	0,091	0,181	0,212	0,445

Tabela 6

Povezanost primenjene terapije sa kvalitetom života bolesnika sa dijabetesom melitusom tipa 2

Oblast	Terapija			F	*p*
	ORD (n = 44)	I (n = 20)	I + ORD (n = 25)		
	x̄ ± SD	x̄ ± SD	x̄ ± SD		
Fizičko zdravlje	50,00 ± 18.911	55,45 ± 22,758	50,12 ± 16,746	0,610	0,546*
Psihološko zdravlje	54,80 ± 18,250	61,15 ± 19,540	50,80 ± 20,265	1,639	0,200*
Socijalne relacije	56,36 ± 15,314	61,25 ± 21,701	53,04 ± 18,359	1,191	0,309*
Životno okruženje	55,66 ± 14,198	61,05 ± 17,554	54,36 ± 16,442	1,145	0,323*

ORD – oralni antidijabetici; I – insulin; I + ORD – insulin + oralni antidijabetici; *$p > 0,05$

tanika, što je u skladu sa nalazima drugih autora. Na primer, u studiji Jacobsona i sar [9] 48,8% ispitanika imalo je neuropatiju, dok su Mayou i sar. [10] našli da 20% ispitanika boluje od neuropatije. Naši ispitanici imali su duplo veću učestalost hipertenzije nego ispitanici u Indiji [8] (30,8%).

U grupi sa komorbiditetetom prosečna vrednost HbA_{1C} bila je veća (8,47%) u odnosu na grupu bez komorbiditeta (6,49%). To znači da je lošija metabolička kontrola bolesti povezana sa češćom pojavom komplikacija bolesti, a samim tim i lošijim kvalitetom života [11]. U prospektivnoj studiji DM tipa 2 u Velikoj Britaniji (UK *Prospective Diabetes Study* – UKPDS) [12] dokazano je da smanjenje srednjih godišnjih vrednosti HbA_{1C} za samo 1% smanjuje rizik od nastanka mikrovaskularnih komplikacija za 37%, periferne vaskularne bolesti za 43%, infarkta miokarda za 14% i ishemijskog moždanog udara za 12%. Ovi nalazi afirmisali su primenu HbA_{1C} kao izuzetno važnog parametra praćenja metaboličke kontrole dijabetesa u svakodnevnom radu. Snižavanjem HbA_{1C} ispod ili oko 7% smanjuje se rizik od mikrovaskularnih i neuropatskih komplikacija i kod DM tip 1 i kod onih sa tipom 2 bolesti. Stoga, za prevenciju komplikacija HbA_{1C} kod odraslih osoba treba da bude < 7% [13].

Rezultati naše studije pokazali su da 29% ispitanika bez teškoća obavlja fizičku aktivnost, 41% nešto teže, a 30% je nesposobno, dok je studija u Indiji [8] pokazala da 46,5% obolelih od dijabetesa obavlja redovnu fizičku aktivnost. Ista studija ukazala je na bolje trenutno stanje zdravlja kod muškaraca nego kod žena, a najviše je bio pogođen domen zdravlja, uopšte, i vitalnosti. Muškarci su višom ocenom ocenili kvalitet života nego žene. U našoj studiji ne postoji razlika u oceni kvaliteta života između polova.

Studija u Nemačkoj [14] pokazala je da oboleli od dijabetesa i hipertenzije imaju sličnu ocenu kvaliteta života kao i dijabetičari bez komorbiditeta, s obzirom na to da je arterijska hipertenzija u velikom procentu asimptomatska. Osobe sa dijabetesom i osteoartrozom dostigle su značajno niže skorove zbog bola i fizičkog oštećenja. Studija sprovedena u Kini [15] na 1 524 ispitanika pokazala je da je najmanje jedan komorbiditet imalo 52%, mikrovaskularne komplikacije 33,4%, a makrovaskularne 34,7% ispitanika. Prosečna vrednost HbA_{1C} kod bolesnika sa komorbiditetima bila je 8,2%, a 63% imalo je lošu metaboličku kontrolu bolesti.

Poznato je da je za uspeh terapije za dijabetes od velikog značaja učenje o bolesti i samokontrola. Naši ispitanici su u visokom procentu (91%) bili zadovoljni informacijom koju su dobili od izabranog lekara o svojoj bolesti, 76% bilo je obučeno za samokontrolu, a 64% sprovodilo je samokontrolu.

Metaanaliza koja je obuhvatala 20 radova i oko 1 892 osobe imala je za cilj da utvrdi efekte povećane fizičke aktivnosti na kvalitet života [16]. Uključivala je osobe starije od 21 godine, sa DM tipa 1 ili 2, kod kojih je procenjivan kvalitet života. U većini slučajeva ispitanici su bili sredovečni i stariji, a samo u četiri studije prosek godina bio je ispod 57. Žene su bile zastupljene u većini slučajeva, a samo dve studije isključile su žene. Poređenjem grupa pre i nakon intervencije, utvrđeno je poboljšanje ne samo dijabetesa nego i kvaliteta života ispitanika. Ispitanici kontrolne grupe nisu poboljšali kvalitet života nakon učešća u studijiama.

U randomizovanoj studiji koja je obuhvatila obolele od dijabetesa i vaskularnih bolesti (*Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation* – ADVANCE) [17], sprovedenoj u Australiji na 978 ispitanika, može se uočiti da su osobe bez dijabetesa bolje ocenile kvalitet života nego bolesnici sa dijabetesom. Ukupni skorovi bili su niži u grupi bolesnika koji su imali nepoželjne događaje kao što su moždani udar ili infarkt miokarda.

U našoj studiji 87% ispitanika redovno je išlo na kontrole, a svega 13% neredovno. Većina (76%) je smatrala da im propisana terapija ne remeti svakodnevne aktivnosti. Oralne hipoglikemike koristilo je 49% ispitanika, insulin 21%, oralnu terapiu i insulin 29%, a 1% samo higijensko-dijetetski režim.

Oboleli su se u visokom procentu izjasnili da se pridržavaju propisane terapije. Rezultati drugih studija pokazuju da se od 36% do 93% bolesnika pridržava propisane terapije [18].

Autori randomonizovane studije preseka koja je sprovedena u Meksiku [19] na 238 bolesnika sa DM tipa 2, želeli su da utvrde koliko se bolesnici zaista pridržavaju propisane medikamentne terapije brojanjem lekova pri dve kućne posete. Utvrdili su da ne postoji povezanost između kvaliteta života i poštovanja uzimanja terapije. Međutim, kombinacija znanja i jak pozitivan stav bio je povezan sa pet od šest domena u upitniku. Samo 17,2% bolesnika pokazalo je da se pridržava propisane terapije, a 20,6% posedovalo je dobro znanje o terapiji i pozitivan stav prema njoj. Kvalitet života bio je značajno bolji kod muškaraca nego kod žena, u domenu telesnog i psihičkog zdravlja, kao i životne sredine ($p < 0,05$), ali nije bio statistički značajno različit u domenu životne nezavisnosti, socijalnih odnosa i duhovnosti. Međutim, nije postojala značajna razlika u oceni kvaliteta života u bilo kom od šest domena između bolesnika koji su koristili samo jedan oralni hipoglikemik i onih koji su koristili više. U našoj studiji, takođe, nije postojala razlika u domenima kvaliteta života među bolesnicima koji su koristili različitu terapiju. U studiji u Meksiku [19] postojala je statistički značajna razlika između domena nezavisnosti i starosti, kao i trajanja dijabetesa. Viši nivo obrazovanja i pozitivni stav imaju uticaja na veće rezultate u fizičkom domenu. Muškarci sa višim nivoom obrazovanja i jakim pozitivnim stavom imali su veću verovatnoću postizanja boljih rezultata u psihološkom domenu. Oboleli sa višim nivoom obrazovanja, bez hipertenzije, sa kombinacijom znanja i jakim pozitivnim stavom imali su više rezultate u domenu nezavisnosti. Veća ocena u domenu socijalnih odnosa bila je kod osoba sa visokim obrazovanjem, a u domenu životne sredine kod muškaraca sa višim nivoom obrazovanja. Rezultati naše studije takođe su pokazali da na kvalitet života utiče i nivo obrazovanja. Postoji statistički značajna razlika u kvalitetu života kod osoba niskog nivoa obrazovanja. Moramo priznati da je u mnogim situacijama veliki deo samoprocene kvaliteta života fundamentalno određen faktorima koji se nalaze u razvoju ličnosti, i to mnogo više nego u bolesti ili njenom lečenju.

Rose i saradnici [20] sproveli su istraživanje u Nemačkoj na obolelima od DM tipa 1 ili 2. Oboleli sa više optimizma

pokazuju jače verovanje u samoefikasnost i imaju veće vrednosti kvaliteta života, a oni sa težim oboljenjem imaju niži kvalitet života. Takođe, komunikacija lekara i bolesnika ima važnu ulogu u vrednosti kvaliteta života. Bolesnici koji su bili bolje informisani, imali su viši kvalitet života. Njihovi ispitanici imali su polineuropatiju (37,6%), retinopatiju (11%), koronarnu bolest (34,6%), nefropatiju (6,7%), amputaciju (0,8%).

U oceni kvaliteta života od velikog značaja je i lični stav bolesnika, njegov pogled na život. Ako on ima optimistički pogled i jako verovanje u samoefikasnost, veća je verovatnoća da će prijaviti viši kvalitet života i u prisustvu sekundarnih bolesti. Tako, 47% naših ispitanika bili su zadovoljni zdravljem, a 53% nezadovoljni. Kvalitet života 36% bolesnika ocenili su kao loš, a 64% kao dobar, što se može objasniti optimističkim pogledom na život i jakim verovanjem u samoefikasnost.

Zaključak

Iako lekari i drugi zdravstveni radnici mogu dati sveukupnu kliničku procenu težine oboljenja bolesnika ili stepen pogoršanja bolesti, neprikladno je da lekari procenjuju kvalitet života bolesnika. Informacija o kvalitetu života može se dobiti samo od strane bolesnika, jer samo bolesnici imaju direktan uvid u svoja osećanja i misli. Ljudi imaju različita očekivanja od toka bolesti, a i sama očekivanja vremenom se menjaju. Sve je podložno promenama, što i jeste suština dinamičkog modela kvaliteta života. Cilj u lečenju bolesnika sa dijabetesom je regulacija nivoa glikoze, postizanje zadovoljavajuće metaboličke kontrole i obezbeđivanje što boljeg kvaliteta života. Naši rezultati pokazali su da oboleli od DM tip 2 imaju pad kvaliteta života u sva četiri domena. U visokom procentu postojali su komorbiditeti kod obolelih od dijabetesa, koji statistički značajno utiču na pad kvalitet života. Pojava komorbiditeta bila je udružena sa višim vrednostima glikoziliranog HbA_{1C}. Uočen je pad radne sposobnosti, kao i sposobnosti za obavljanje svakodnevnih aktivnosti. Nije postojala razlika u oceni kvaliteta života između polova, starosnih grupa, kao ni između bolesnika lečenih različitim lekovima. Na kvalitet života utiče i dostignuti stepen obrazovanja. Međutim, pri oceni kvaliteta žvota moramo se voditi činjenicom da je reč o samoproceni kvaliteta života i da na to utiče psihološka struktura ličnosti.

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Uloga zadnjeg tibijalnog nagiba u rupturi prednje ukrštene veze

The role-share-influence of the posterior tibial slope on rupture of the anterior cruciate ligament

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Apstrakt

Uvod/Cilj. Povećan zadnji tibijalni nagib predstavlja jedan od najčešće navođenih faktora rizika koji doprinose rupturi prednje ukrštene veze (*ligamentum cruciatum anterius* – LCA). Cilj ove studije bio je da se utvrdi da li je povećan tibijalni nagib na spoljašnjem kondilu, odnosno smanjen tibijalni nagib na unutrašnjem kondilu, udružen sa rupturom LCA. **Metode.** Ispitanici ove studije bili su podeljeni u dve grupe. Ispitivana grupa sastojala se od bolesnika koji su imali hroničnu nestabilnost kolena zbog ranije rupture LCA. Kontrolnu grupu sačinjavali su pacijenti koji su u anamnezi imali povredu zgloba kolena, ali kod kojih nije dijagnostikovana ruptura LCA. Merenje zadnjeg tibijalnog nagiba vršeno je na sagitalnim MR presecima i uz pomoć sagitalnog rendgenskog snimka zgloba kolena. Meren je zadnji tibijalni nagib na spoljašnjem i unutrašnjem kondilu tibije i na osnovu dobijenih vrednosti računat je prosečan tibijalni nagib kao i razlika između nagiba na spoljašnjem i unutrašnjem kondilu. **Rezultati.** Pacijenti sa rupturom LCA imali su statistički značajno veći zadnji tibijalni nagib ($p < 0,01$) na spoljašnjem kondilu tibije (7,1° : 4,5°) kao i statistički značajno manji zadnji tibijalni nagib ($p < 0,05$) na unutrašnjem kondilu tibije (5,0° : 6,6°), nego pacijenti sa intaktnom LCA. **Zaključak.** Veliki zadnji tibijalni nagib na spoljašnjem kondilu tibije, udružen sa malim zadnjim tibijalnim nagibom na unutrašnjem kondilu, odnosno pozitivna razlika između spoljašnjeg i unutrašnjeg kondila, faktori su koji mogu uzrokovati rupturu LCA.

Ključne reči:
tibija; ligament, prednji, ukršen; koleni zglob; ruptura; faktori rizika; prognoza.

Abstract

Background/Aim. Posterior tibial slope is one of the most citated factors wich cause rupture of the anterior cruciate ligament (ACL). The aim of this study was to determine the association of a greather posterior tibial slope on the lateral condyle, that is a lesser posterior tibial slope on the medial condyle, with ACL rupture. **Methods.** The patients were divided into two groups. The study group included the patients with chronic instability of the knee besause of a previous rupture of ACL. The control group included the patients with knee lesion, but without ACL rupture. Posterior tibial slope measuring was performed by sagittal MR slices supported by lateral radiograph of the knee. We measured posterior tibial slope on lateral and medial condyles of the tibia. Using these values we calculated an average posterior tibial slope as well as the difference between slopes on lateral and medial condyles. **Results.** Patients with ACL rupture have highly statistically significantly greather posterior tibial slope ($p < 0.01$) on lateral tibial condyle (7.1° : 4.5°) as well as statistically significantly lesser posterior tibial slope ($p < 0.05$) on medial tibial condyle (5.0° : 6.6°) than patients with intact ACL. **Conclusion.** Great posterior tibial slope on lateral tibial condyle associated with the small posterior tibial slope on the medial tibial condyle, that is a positive differentce between lateral and medial tibial condyles are factors wich may cause ACL rupture.

Key words:
tibia; anterior cruciate ligament; knee joint; rupture; risk factors; prognosis.

Uvod

Pored međukondilarne jame, zadnji tibijalni nagib (*posterior tibial slope*) je jedna od najčešće navođenih anatomskih struktura koja doprinosi povređivanju prednje ukrštene veze (*ligamentum crciatum anterius* – LCA). Iako je u studijama ovaj faktor često potvrđivan kao značajan za povređivanje, još češće su dobijani rezultati koji ne dokazuju značajno učešće zadnjeg tibijalnog nagiba u povređivanju LCA.

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Zadnji tibijalni nagib se definiše kao ugao između linije okomite na tibijalnu osovinu i zadnje inklinacije tibijalnog platoa. Giffin i sar. [1] navode da mali tibijalni nagib nema uticaja na prednju tibijalnu translaciju i da kao takav može da predstavlja zaštitni faktor kod LCA – deficitarnih kolena. Dejour i sar. [2], u studiji na uzorku od 281 kolena, našli su značajnu korelaciju između nagiba zabnjeg tibijalnog platoa i prednje tibijalne translacije pri stajanju, kako kod normalnih tako kod LCA deficitarnih kolena. Veliki zadnji tibialni nagib može da dovede do veće prednje tibijalne translacije prilikom opterećenja zgloba kolena i do, sledstveno tome, prvo zatezanja, a zatim i pucanja LCA.

Jedan od najčešćih mehanizama nastanka nekontaktne rupture LCA je hiperekstenzija sa unutrašnjom rotacijom. Za razliku od unutrašnjeg tibijalnog platoa na kojem se unutrašnji kondil butne kosti oslanja tokom čitave fleksije u približno istoj tački, spoljašnji kondil butne kosti prilikom fleksije lagano se kreće nazad. Shodno tome, prilikom fleksije potkolenica pravi još jedan pokret unutrašnje rotacije. Povećan zadnji tibijalni nagib na spoljašnjem kondilu golenjače igra važnu ulogu tokom pokreta opružanja jer favorizuje unutrašnju rotaciju koja prilično pojačava naprezanje prethodno istegnute LCA.

Zbog različitih rezultata značajnosti zadnjeg tibijalnog nagiba dobijenih od pojedinih istraživača [1–6], sa jedne strane, i povećanog posteriornog kretanja spoljašnjeg kondila butne kosti prilikom fleksije potkolenice, sa druge, u ovoj studiji zadnji tibijalni nagib je podeljen na spoljašnji i unutrašnji odeljak. Samim tim, dobijene su dvostruke vrednosti, odnosno zadnji tibijalni nagib na spoljašnjem i unutrašnjem kondilu golenjače.

Kao referentna vrednost za merenje zadnjeg tibijalnog nagiba obično se uzima jedna od sledećih anatomskih osovina potkolenice: dijafizna tibijalna osovina (*tibial shaft anatomic axis* – TSAA), proksimalna tibijalna anatomska osovina (*proximal tibial anatomic axis* – PTAA), fibularna anatomska osovina (*fibular shaft axis* – FSA), proksimalna fibularna anatomska osovina (*fibular proximal anatomic axis* – FPAA), osovina zadnjeg tibijalnog korteksa (*posterior tibial cortex axis* – PTC), osovina prednjeg tibijalnog korteksa (*anterior tibial cortex* – ATC). U praksi mnogo češće se uzimaju u obzir proksimalne osovine nego dijafizne, pre svega zbog načina snimanja potkolenice i kolena, odnosno zbog nedostatka snimaka na kojima se vidi potkolenica, odnosno golenjača, čitavom dužinom.

Brazier i sar.[7] kao i Çullu i sar. [8] istraživali su povezanost različitih anatomskih osovina potkolenice sa tibijalnom dijafiznom anatomskom osovinom TSAA (stvarna tibijalna osovina) i utvrdili da najveću povezanost sa TSAA ima proksimalna tibijalna anatomska osovina PTAA.

Ova studija imala je za cilj da se utvrdi da li je povećan tibijalni nagib na spoljašnjem kondilu, odnosno smanjen tibijalni nagib na unutrašnjem kondilu, udružen sa rupturom LCA.

Metode

U ovoj retrospektivnoj studiji metodom slučajnog izbora formirane su bili dve grupe bolesnika sa hirurškom intervencijom na zglobu kolena. Pre formiranja grupa iz studije su isključeni pacijenti sa gonartrotičnim promenama i koštanim oštećenjima na zglobu kolena. Ispitivanu grupu sačinjavali su pacijenti koji su imali hroničnu nestabilnost kolena zbog ranije rupture LCA (57 pacijenata, 35 muškog i 22 ženskog pola). Kontrolnu grupu sačinjavali su pacijenti koji su u anamnezi imali povredu kolena, ali kod kojih nije dijagnostikovana ruptura LCA (42 pacijenta, 27 muškog i 15 ženskog pola). Kod svih pacijenata razlog hirurške intervencije bila je nekontaktna povreda zgloba kolena.

Prosečna starost pacijenata iznosila je u ispitivanoj grupi 30,4 ± 8,9 godina (od 15 do 48 godina), a u kontrolnoj 31,6 ± 11,4 godina (od 15 do 52 godine).

Merenje je vršeno na rendgenskim i snimcima magnetne rezonance (MR). Korišćeni su sagitalni rendgenski snimci kolena sa potkolenicom, kao i MR snimci u sagitalnoj ravni. Svi MR snimci napravljeni su upotrebom 1,5 T magnetne rezonance. Određivanje tibijalne PTAA na snimcima magnetne rezonance i način merenja zadnjeg tibijalnog nagiba na unutrašnjem i spoljašnjem kondilu prethodno je objavljen [9].

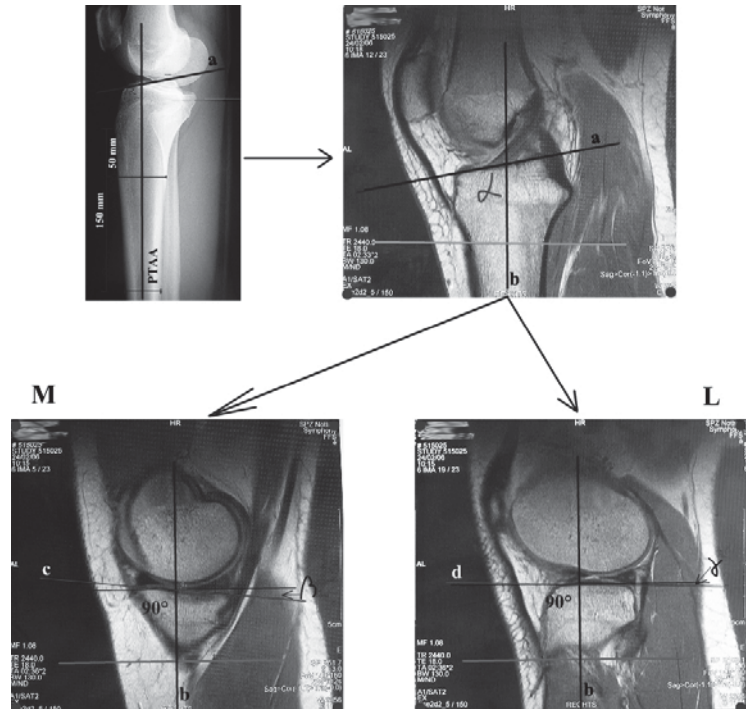
Na bočnom rendgenskom snimku određivana je PTAA uz pomoć dve tačke udaljene od golenjačnog ispupčenja 5 i 15 cm. Ove tačke su se nalazile na jednakom rastojanju od prednjeg i zadnjeg korteksa tibije. Zatim je ucrtavana linija koja je označavala pravac prednjeg tibijalnog platoa (korteks prednjeg međukondilarnog polja tibije). Ugao između ove dve linije predstavljao je ugao prednjeg tibijalnog platoa (alfa – α). Preostalo merenje vršeno je na MR snimcima a ugao alfa je služio kao referentna vrednost za određivanje PTAA na MR snimcima (slika 1).

Merenja su vršena na tri sagitalna preseka zgloba kolena. Prvi sagitalni presek je prolazio kroz sredinu prednjeg međukondilarnog polja, između dva međukondilarna ispupčenja. Sledeća dva, na kojima su mereni unutrašnji i spoljašnji tibijalni plato prolazili su mestima najmanjeg femorotibijalnog rastojanja na unutrašnjem i spoljašnjem platou.

Na sagitalnom MR snimku koji prolazi između dva međukondilarna ispupčenja ucrtavali smo liniju koja prati pravac prednjeg tibijalnog platoa. Na tu liniju dodavali smo vrednost ugla prednjeg tibijalnog platoa i dobijali smo liniju koja je paralelna sa PTAA. Uz pomoć birofolije, obeležene sa četiri ugaona markera radi preciznog prenošenja, linija paralelna sa pravcem PTAA prenošena je na MR presek unutrašnjeg i spoljašnjeg platoa. Između linije koja prati zadnji tibijalni nagib kondila i okomice na liniju paralelnu sa PTAA meren je ugao zadnjeg tibijalnog platoa na unutrašnjem, odnosno spoljašnjem tibijalnom kondilu.

Na osnovu vrednosti tibijalnog nagiba na unutrašnjem i spoljašnjem kondilu računata je srednja vrednost tibijalnog nagiba kao aritmetička sredina prethodne dve, kao i razlika između spoljašnjeg i unutrašnjeg kondila.

Svi podaci su obrađeni uz pomoć programa SPSS 11.0. Za ispitivanje razlika korišten je nezavisan Studentov *t*-test kao i Studentov test za povezane parove. Testirana je razlika između tibijalnog nagiba na spoljašnjem i unutrašnjem kondilu, kao i razlika između pomenutih nagiba. Nivo značajnosti je postavljen na 0,05.



Sl. 1 – Određivanje zadnjeg tibijalnog nagiba. Prvo je određivan ugao prednjeg tibijalnog platoa (α) na rendgenskom snimku uz pomoć proksimalne tibijalne anatomske osovine (PTAA) i linije koja je pratila prednji tibijalni plato (linija a). Prenošenjem „α" na liniju koja prati prednji tibijalni nagib (prednje tibijalno polje) na sagitalnom snimku magnetne rezonance (MR) (linija a), dobili smo liniju paralelnu PTAA (linija b). Dobijenu liniju smo prenosili na sagitalni MR snimak unutrašnjeg i spoljašnjeg tibijalnog kondila. Ugao zadnjeg tibijalnog nagiba (β i γ) unutrašnjeg i spoljašnjeg kondila dobili smo uz pomoć normale na PTAA i linije koja prati unutrašnji (linija c), odnosno spoljašnji (linija d) kondil.

Rezultati

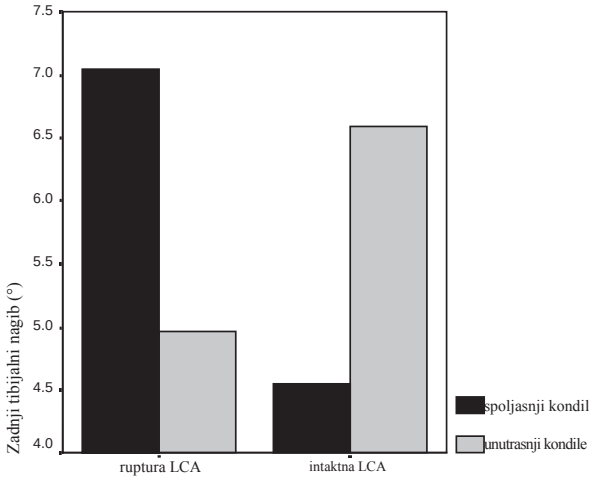
Prosečan zadnji tibijalni nagib na spoljašnjem kondilu pacijenta sa rupturom LCA iznosio je 7,1 ± 3,6°, dok je isti nagib kod pacijenta sa intaktnom vezom bio statistički značajno manji (p = 0,000), odnosno imao vrednost od 4,5 ± 2,3° (slika 2). Najveća vrednost zadnjeg tibijalnog nagiba od 13° izmerena je kod pacijenta sa rupturom LCA, dok je najmanja vrednost od -2° izmerena kod pacijenta sa intaktnom LCA.

Sa druge strane, prosečan zadnji tibijalni nagib na unutrašnjem kondilu pacijenta sa rupturom LCA iznosio je 5,0 ± 3,7°, dok je isti nagib kod pacijenta sa intaktnom vezom bio statistički značajno veći (p = 0,024) i imao je vrednost od 6,6 ± 3,1°. Zadnji tibijalni nagib na unutrašnjem kondilu imao je najveću (14°) i najmanju vrednost (-2°) kod pacijenta sa rupturom LCA.

Vrednosti prosečnog zadnjeg tibijalnog nagiba ispitivane (6,0 ± 3,5°) i kontrolne (5,6 ± 2,2°) grupe nisu imali statistički značajnu razliku (p = 0,449).

Upoređivanjem zadnjih tibijalnih nagiba na unutrašnjem i spoljašnjem kondilu unutar svake posmatrane grupe ponaosob, putem t-testa za povezane parove, nađena je statistički visokoznačajna razlika (p = 0,000) između navedenih vrednosti za obe, ispitivanu i kontrolnu grupu.

Ako upoređujemo razlike u nagibu spoljašnjeg i unutrašnjeg kondila naše dve grupe pacijenata, možemo reći da je ta razlike unutar ispitivane grupe pozitivna (2,1 ± 2,4°), dok je u kontrolnoj grupi negativna (-1,6 ± 3,4°). Testiranjem ove dve vrednosti dobili smo statistički visokoznačajnu razliku (p = 0,000).



Sl. 2 – Vrednosti zadnjeg tibijalnog nagiba na spoljašnjem i unutrašnjem kondilu tibije kod bolesnika sa i bez rupture prednje ukrštene veze (LCA)

Diskusija

Problematika merenja zadnjeg tibijalnog nagiba na kratkim sagitalnim MR presecima kolena ogleda se u nemogućnosti adekvatnog određivanja proksimalne tibijalne anatomske osovine. Da bi se odredila PTAA potreban je presek koji se prostire minimalno 150 mm ispod tibijalnog ispupčenja [7, 8]. Kuwano i sar. [10] su određivali zadnji tibijalni nagib na unutrašnjem i spoljašnjem kondilu pacijenata bez rupture LCA

uz pomoć trodimenzionalne kompjuterizovane tomografije (3D CT), sa slikom koja je zahvatala 150 mm proksimalnog kraja golenjače. Vrednosti dobijene u njihovoj studiji bile su nešto veće nego u našoj, ali su govorile u prilog činjenici da je kod pacijenata bez rupture LCA zadnji tibijalni nagib veći na unutrašnjem (9°) nego na spoljašnjem (8,1°) kondilu. Mi nismo imali na raspolaganju MR snimke sa adekvatnom dužinom proksimalnog dela golenjače. Ovaj nedostatak smo pokušali da kompenzujemo određivanjem PTAA i ugla prednjeg tibijalnog platoa na sagitalnim rendgenskim snimcima. Pomoću ugla prednjeg tibijalnog platoa dobijenog na rendgenskim snimcima i linije koja prati prednji tibijalni plato na sagitalnim MR snimcima definisana je linija paralelna PTAA.

U našoj studiji zadnji tibijalni nagib na spoljašnjem kondilu pokazao je statistički visokoznačajno veće vrednosti ($p < 0,01$) u ispitivanoj, nego u kontrolnoj grupi. Pošto je na spoljašnjem tibijalnom platou prednja tibijalna translacija tokom fleksije veća,[4, 11–14] dodatno povećanje nagiba tibijalnog platoa može više da opterećuje LCA i doprinese rupturi. Slične vrednosti dobili su Matsuda i sar. [13] mereći zadnji tibijalni nagib kod pacijenata bez rupture LCA. Ovi autori su dobili veće vrednosti zadnjeg tibijalnog nagiba na unutrašnjem (9,9º), nego na spoljašnjem kondilu (6,0º) tibije što se poklapa sa rezultatima naše kontrolne grupe. Drugi autori, takođe, utvrdili su veću vrednost tibijalnog nagiba na spoljašnjem kondilu pacijenata ispitivane grupe (7,5°), nego pacijenata kontrolne grupe (4,4°) [9]. Citirana studija sprovedena na 33 para ispitanika, takođe, rađena je na MR snimcima.

Veće vrednosti zadnjeg tibijalnog nagiba na unutrašnjem kondilu u kontrolnoj grupi govore u prilog tome da bi veći tibijalni nagib unutrašnjeg kondila trebalo da deluje protektivno. U prilog tome govori statistički značajna razlika između ispitivane i kontrolne grupe u vezi sa ovim parametrom. Chiu i sar. [15] su uz pomoć linije prednjeg tibijalnog korteksa određivali zadnji tibijalni nagib na prethodno fotografisanim tibijama i dobili vrednosti od 14,8º za unutrašnji i 11,8º za spoljašnji tibijalni kondil. Ova studija, kao i naša, govori u prilog većeg tibijalnog nagiba na unutrašnjem nego na spoljašnjem platou, kod pacijenta bez povrede LCA. Sa druge strane razlozi prilično veće vrednosti tibijalnog nagiba na oba, unutrašnjem i spoljašnjem platou su višestruki. Jedan od njih je korišćenje linije prednjeg tibijalnog korteksa kao polazne osovine u merenju (mi smo koristili PTAA). Isti autori navode da sa starošću dolazi do povećanja nagiba tibijalnog platoa. Naša populacija ispitanika je bila mlađa, prosečno 38 godina. Treći razlog mogu biti razlike između dve populacije, kineske i evropske. Slično prethodnoj studiji, radiografska studija izvedena na 100 pacijenata bez oštećenja na zglobu kolena, utvrdila je veći zadnji tibijalni nagib na unutrašnjem nego na spoljašnjem kondilu (9,2º : 4,8º) [16].

Dve različite indirektne metode za određivanje tibijalnog nagiba, na rendgenskim i snimcima MR, koristili su Hudek i sar. [14] i prikazali statistički značajnu korelaciju između ova dva merenja. Prosečne vrednosti zadnjeg tibijalnog nagiba izmerene na MR snimcima iznosile su 4,8º na unutrašnjem i 5,0º na spoljašnjem kondilu. Međutim, ispitanike ove studije činili su pacijenti sa i bez rupture LCA, pa shodno tome ne može se ni očekivati veći zadnji tibijalni nagib na unutrašnjem ili spoljašnjem kondilu.

U različitim studijama dobijeni su različiti podaci o povezanosti zadnjeg tibijalnog nagiba sa rupturom LCA [1–6, 9–15]. Naša studija je pokazala da se, kako u ispitivanoj, tako u kontrolnoj grupi, zadnji tibijalni nagib na spoljašnjem i unutrašnjem kondilu statistički visokoznačajno razlikuju ($p < 0,01$) i da se ne bi trebalo vršiti poređenje njihovih aritmetičkih sredina. Detaljnije, zadnji tibijalni nagib na spoljašnjem kondilu veći je od nagiba na unutrašnjem u ispitivanoj grupi (pozitivna razlika), dok je u kontrolnoj zadnji tibijalni nagib na spoljašnjem kondilu manji od nagiba na unutrašnjem (negativna razlika). Uzimanjem aritmetičkih sredina (prosečan tibijalni nagib) ove razlike se poništavaju, pa se dobijaju različiti podaci o njihovoj povezanosti sa LCA rupturom.

Zaključak

Veći zadnji tibijalni nagib na spoljašnjem kondilu, a manji na unutrašnjem, odnosno veća (pozitivna) razlika između zadnjeg tibijalnog nagiba na spoljašnjem i unutrašnjem kondilu su faktori koji mogu uticati na nastanak rupture prednje ukrštene veze zgloba kolena.

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Reliability and relationship of colposcopical, cytological and hystopathological findings in the diagnostic process

Pouzdanost i odnos kolposkopskih, citoloških i histopatoloških nalaza u dijagnostičkom procesu

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Abstract

Background/Aim. The question about the accuracy of cytology and colposcopy is more and more asked due to false positive and negative findings on the basis of which the decision on biopsy is made. The aim of this study was to examine reliability of biopsies based only on abnormal colposcopical findings, before receiving the results of Papanicolaou (PA) smear, by comparing findings of colposcopical, cytological and histopathological (HP) examinations as well as determining validity of these diagnostic methods. **Methods.** The study involved all patients who had their regular colposcopical and cytological examinations in the outpatient department during a two-year period (2009–2010) in the Clinic for Gynecology and Obstetrics, Clinical Center of Serbia, Belgrade. The material for HP examination was obtained by colposcopically directed biopsy, due to abnormal colposcopical findings and without waiting for PA smear results. The data obtained by these methods were statistically analyzed and compared. Furthermore, validity of colposcopical and cytological examinations was assessed. **Results.** Out of 127 patients highly significantly more patients had more malignant cervical changes on colposcopical exam compared to HP (p = 0.000), and cytological exam (p = 0.000). Highly significantly more patients had more malignant cervical changes on PA smear than HP exam (p = 0.000), unless when findings were assessed in the widest sense of benign and malignant changes when there were no significant differences in these findings (p = 0,450). Sensitivity of colposcopy as a diagnostic method was 87.5%, specificity 24.14%, positive predictive value (+PV) was 34.65% and negative predictive value (–PV) 80.77%. Sensitivity of PA smear as a diagnostic method was 62.5%, specificity 87.36%, +PV was 69.44%, and –PV 83.52%. **Conclusion.** Regarding the results of our study it is best to make a decision on treatment according to findings of all the three methods. Cytological analysis is more reliable than colposcopical examination. Therefore, it is advisable that following abnormal colposcopical findings, PA smear should always be taken and only after receiving the results further diagnostics can be planned (biopsy and HP). A final decision on the therapy has to be made based on HP findings which are the only method that can give the ultimate reliable diagnosis of cervical changes.

Key words:
uterine cervical neoplasms; uterine cervical displasia; diagnosis; diagnostic techniques and procedures; colposcopy; vaginal smears; histological techniques.

Apstrakt

Uvod/Cilj. Sve više se postavlja pitanje o tačnosti citologije i kolposkopije zbog slučajeva lažnih rezultata na osnovu kojih se planira biopsija. Cilj ove studije bio je da se ispita pouzdanost biopsija baziranih samo na abnormalnoj kolposkopskoj slici pre dobijanja rezultata Papanikolaou (PA) brisa, upoređivanjem nalaza kolposkopskog, citološkog i histopatološkog pregleda i određivanjem validnosti ovih dijagnostičkih metoda. **Metode.** Studija je obuhvatila sve bolesnike kojima su ambulantno rađeni kolposkopski i citološki pregled i ciljana biopsija promena sa histopatološkom analizom, tokom dvogodišnjeg perioda (2009 i 2010) na Ginekološko-akušerskoj klinici Kliničkog centra Srbije. Biopsija je rađena zbog patološke slike na kolposkopskom pregledu, bez čekanja rezultata PA. Nalazi sprovedenih analiza statistički su obrađeni i upoređeni. Procenjena je validnost kolposkopskog i citološkog pregleda. **Rezultati.** Od ukupno 127 bolesnica značajno više njih imalo je maligniju promenu na kolposkopskom pregledu u odnosu na histopatološki (p = 0,000) i citološki pregled (p = 0,000). Značajno više ispitanica imalo je maligniju promenu postavljenu PA nego histopatološkim pregledom (p = 0,000), osim kada se nalazi posmatraju u najširem smislu benignih i malignih promena kada nije nađena statistički značajna razlika (p = 0,450). Senzitivnost kolposkopije iznosila je 87,5%, specifičnost 24,14%, pozitivna prediktivna vrednost (+PV) je bila 34,65%, a negativna prediktivna vrednost (–PV) 80,77%. Senzitivnost

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citološke analize iznosila je 62,5%, specifičnost 87,36%, +PV 69,44%, a –PV 83,52%. **Zaključak.** Odluku o lečenju najbolje je bazirati na nalazima sva tri ispitivanja. Citološka analiza je pouzdaniji metod od kolposkopije. Zato savetujemo da se nakon abnormalne kolposkopske slike obavezno uzme PA bris i tek po dobijanju tog rezultata planira biopsija. Konačni stav o terapiji mora se bazirati na histopatološkom nalazu, kao jedinom metodu koji daje konačnu, pouzdanu dijagnozu stanja.

Ključne reči:
grlić materice, neoplazme; grlić materice, displazija; dijagnoza; dijagnostičke tehnike i procedure; kolposkopija; vaginalni brisevi; histološke tehnike.

Introduction

Cervical intraepithelial neoplasia (CIN) stands for pathological changes that represent developmental stages of invasive cervical carcinoma [1]. Diagnosing and treating of these asymptomatic lesions in due time is the most efficient way of preventing invasive cervical carcinoma development. CIN is diagnosed by colposcopy, cytology and histopathological (HP) examination of biopsy acquired tissue. There are numerous therapeutic methods and their application depends on cervical change stages determined by the level of malignant cells spreading in the epithelium. Changes of the low-grade squanous intraepithelial lesion (LSIL) (CIN I) type can merely be regularly monitored and only if they are present longer than two years some destructive therapeutic method may be applied. On the other hand, for adequate treating of high-grade squanous intraepithelial lesion (H-SIL) (CIN II and III) type changes one of the excision methods has to be applied. Excision has to be appropriately performed in order to remove a complete lesion. Final diagnosis is achieved by HP examination of the obtained tissue. Furthermore, the margins of the excised part are evaluated and according to those findings the decision on further treatment made [1–3].

The aim of this study was to examine reliability of biopsies based only on abnormal colposcopical findings, before receiving the results of Papanicolaou (PA) smear, by comparing findings of colposcopical, cytological and HP examinations, as well as to determine validity of these diagnostic methods.

Methods

The study involved all patients who had their regular colposcopical and cytological examinations in the outpatient department during a two-year period (2009–2010) in the Clinic for Gynecology and Obstetrics, Clinical Center of Serbia, Belgrade. The material for the HP examination was obtained by colposcopically directed biopsy, due to abnormal colposcopical findings and without waiting for PA smear results. Data obtained by these methods were statistically analyzed and compared. Descriptive [mean; median; standard deviation – (SD) coefficient of variation (CV%)] and analytical (Kolmogorov–Smirnov test – KSZ; Friedman test – FR χ^2; Wilcoxon test – Z) statistical methods were used. Furthermore, sensitivity, specificity, positive and negative predictive values (+PV and –PV respectively) of colposcopical and cytological examinations were assessed. For these calculations standard formulas were used: sensitivity = [(true positive / true positive + false negative) × 100], specificity = [(true negative / true negative + false positive) x 100], +PV = (true positive / true positive + false positive) x 100] and –PV = [(true negative / true negative + false negative) x 100)].

Results

The study involved 127 consecutive patients. Their age span was from 17 to 79 years (mean = 35.11; median = 32.00; SD = 11.131). These values were heterogeneous (CV = 31.703%) and they were not normally distributed (KSZ = 1.602; p = 0.012). The mayority of patients (n = 32) were from 30 to 34 years old and somewhat less patients (n = 26) were 25 to 29 years old. Still, 89.9% of the patients were younger than 50 years and therefore the distribution is asymmetrical to the left, *ie* towards the younger age.

There were 6 different colposcopical findings registered: 1 – ectopia and/or cervicitis; 2 – acetowhite (AW) epithelium and/or mosaic; 3 – leukoplakia; 4 – condylomas; 5 – suspicious neoplasm portio vaginalis uteri (NEO PVU); 6 – polypus. Cytological analysis diagnosed PA II, III, IV and V findings in investigated women. On HP examination 8 diagnoses were made: 1 – without atypia; 2 – ectopia and/or cervicits; 3 – polypus; 4 – para- or hyperkeratosis; 5 – condylomas; 6 – LSIL; 7 – HSIL; 8 – carcinoma potio vaginalis uteri (Ca PVU). In Table 1 frequencies of different diagnoses

Table 1
Frequencies of findings according to diagnostic methods

Findings	Number
Colposcopical findings	
– ectopia and/or cervicitis	22
– AW epithelium and/or mosaics	56
– leukoplakia	26
– condylomas	9
– suspicious neoplastic lesions	10
– polypus	4
PA smear findings	
– II	90
– III	29
– IV	2
– V	6
Histopathological findings	
– no atypia	21
– ectopia and/or cervicitis	32
– polypus	4
– para/hyperkeratosis	15
– condylomas	16
– LSIL	5
– HSIL	26
– Ca PVU	8

PA – Papanicolaou; LSIL – low grade squanous intraepithelial lesions; HSIL – high grade squanous intraepithelial lesions; Ca PVU – carcinoma of the portio vaginalis uteri; AW – acetowhite

attained by examined methods are presented. Ectopia and cervicitis as well as AW epithelium and mosaic were assessed and presented jointly in this analysis as there were numerous cases in which they were found together in one patient (17 mosaics, 20 AW epitheliums, 19 both).

On colposcopical examination the most frequent was the finding of AW epithelium and/or mosaic ($\chi^2 = 85.268$; df = 5; $p = 0.000$). By HP analysis the most frequently diagnosed were ectopia and/or cervicitis ($\chi^2 = 44.780$; df = 7; $p = 0.000$). Cytological evaluation showed that PA II and III were highly significantly more frequent while there were less PA IV and V findings ($\chi^2 = 155.866$; df = 3; $p = 0.000$).

Colposcopical findings were categorized as normal (ectopia, transformation zone, ovula Nabothi, atrophy), abnormal (AW epithelium, mosaic, punctuation, leukoplakia, condylomas), suspicious that meant suspicious invasion of cervical carcinoma (atypical blood vessels, ulcerations, necrosis) and other findings (polypus, infection and inflammation i.e. cervicitis, endometriosis etc). Cytological results were divided in standard groups (II, IIIa, IIIb, IV and V). HP findings were categorised as benign change (without atypia, ectropion, ectopia, cervicitis, polypus, para- and hyperkerathosis, condylomas), LSIL, HSIL and invasive cervical carcinoma. Tables 2 and 3 show relations of the examined methods according to the categories of their findings.

0.000). There were significantly more (n = 53) patients with more malignant changes on colposcopical examination. The diagnoses obtained by PA and HP were highly statistically different (Z = 4.706; $p = 0.000$). There were significantly more (n = 108) patients with more malignant changes on PA than on HP examination.

For sensitivity, specificity, positive and negative predictive values evaluation of colposcopy and cytology, normal and other colposcopical findings, PA II as well as histopathologically asserted benignant lesions were regarded as benignant cervical changes. On the other hand, abnormal and suspicious colposcopical findings, PA III, IV and V, LSIL, HSIL and invasive cervical carcinoma formed a group of malignant cervical changes. Colposcopical and cytological results were compared to HP findings, considering that histopathology is the only method able to give the precise diagnosis of the condition.

The diagnoses assessed only regarding the benign and malignant lesions were also highly statistically different regarding the diagnostic methods used in our study ($FR\chi^2 = 93.671$; df = 2; $p = 0.000$). There were significantly more (n = 66) patients with a more malignant changes on colposcopical than on HP examination (Z = 7.239; $p = 0.000$). There were also significantly more (n = 68) patients with more malignant changes on colposcopi-

Table 2

Relationship of colposcopical, cytological (Papanicolaou – PA) and histopathological (HP) findings according to diagnostic categories

Findings of diagnostic methods used	Diagnostic categories	HP findings			
		Benign changes	LSIL	HSIL	Carcinoma
Colposcopical findings	Normal	15	0	4	0
	Abnormal	64	6	20	1
	Suspicious	2	0	1	7
	Other	6	0	1	0
Cytological findings (PA)	II	74	3	12	1
	IIIa	8	2	2	1
	IIIb	5	1	10	0
	IV	0	0	2	0
	V	0	0	0	6

LSIL – low grade squanous intraepithelial lesions; HSIL – high grade squanous intraepithelial lesions

Table 3

Relationship of colposcopical and cytological (Papanicolaou – PA) findings according to the diagnostic categories in our study

Findings of diagnostic methods used	Diagnostic categories	Cytological findings (PA)				
		II	IIIa	IIIb	IV	V
Colposcopical findings	Normal	17	1	1	0	0
	Abnormal	63	11	15	2	0
	Suspicious	4	0	0	0	6
	Other	6	1	0	0	0

Categories of the diagnoses obtained by these three methods were highly statistically different ($FR\chi^2 = 88.487$; df = 2; $p = 0.000$). The diagnoses obtained by colposcopy and HP were highly statistically different (Z = 3.655; $p = 0.000$). There were significantly more (n = 73) patients with more malignant changes on the colposcopical than on the HP examination. The diagnoses obtained by colposcopy and cytology were also highly statistically different (Z = 8.212; $p =$ cal than on cytological examination (Z = 7.714; $p = 0.000$). Regarding this wider categorisation of findings diagnoses made by PA and HP do not differ significantly (Z = 0.756; $p = 0.450$).

Colposcopical examination registered 21 true negative *ie* benignant findings and 35 true positive *ie* malignant findings. There were 66 false positive and 5 false negative cases. According to these results sensitivity of colposcopy as a di-

agnostic method was 87.5%, specificity 24.14%, +PV was 34.65% and –PV was 80.77%.

Cytological examination registered 76 true negative *ie* benign findings, and 25 true positive *ie* malignant findings. There were 11 false positive and 15 false negative cases. According to these results sensitivity of PA smear as a diagnostic method was 62.5%, specificity 87.36%, +PV was 69.44% and –PV was 83.52%.

When all evaluated diagnostic methods were assessed together, 20 patients had benignant findings, while 22 had malignant findings on each of the three examinations. However, in 85 cases findings were of different categories on different examinations.

Discussion

Squamous cervical carcinoma develops from non-invasive forms and therefore the detection of abnormal pathological changes of the cervical epithelium and their removal is crucial for preventing a possibly fatal invasive carcinoma. Of major significance is the fact that early detected CIN is completely curable condition. The aim of successful treatment is not only a complete removal of the lesion but also sustaining the physiological cervical function as well as the reproductive female functioning [1, 2].

It is considered that CIN occurs mostly in early thirties with the prevalence of 2.6%, although lately it is more common in women in their twenties or even younger. After the age of 50 years the prevalence is decreasing to 0.9% [1, 3]. Patients in the examined population were also mostly in their thirties, while only 10% were older than 50 years. Unfortunately, in our patients HSIL was more frequent than LSIL.

Classification of the lesions used in our study was according to BETHESDA system and in concordance with categorisations used by other authors in the studies from the available literature [4].

Expholiative cytology is of great importance for diagnosing CIN as pathological findings can direct toward looking for and discovering cervical lesions. Even though cytology has undoubted benefits in cervical carcinoma prevention, it is accepted nowadays that some significant lesions can be omitted or underdiagnosed by PA testing due to the limitations of cytology concerning its sensitivity, specificity and predictive values [3, 5, 6]. There are different explanations in the literature for this less satisfactory PA diagnostic assessment in certain cases. One of them is the presence of only few abnormal, *ie* malignant cells in smear which can be easily omitted during examination due to their low frequency. This can usually happen in case of small cell lesions high in the endocervical canal [7]. Moreover, inflammation and bleeding can thwart the assessment [3]. Cohesive tissue fragments of HSIL can sometimes be incorrectly diagnosed as immature metaplastic cells [3]. Furthermore, technical problems occurring while smear is dried are reported [3]. Therefore, it can be recommended that correct smear taking and its optimal handling and cultivation must always be assured. However, patients should also be sent on colposcopical examination.

Colposcopical evaluation and directed biopsy are an essential diagnostic step in treatment of abnormal cytological findings [4]. Colposcopy is a high-quality and sensitive test for detection of CIN and can be considered as integrative and standard basic parts of screening for CIN. Colposcopical evaluation and directed biopsy remain crucial diagnostic procedures for squamous intraepithelial lesions and for identification of those cases that need treatment [8]. However, it must be taken into consideration that performing colposcopy and its occuracy depend in large part on training, experience and skills of the colposcopist. It is usually considered that the limitations of most studies, just like the one we conducted, come from the fact that different colposcopists perform examinations. Nevertheless, an experienced colposcopist's findings can be regarded as precise [4]. Considering that almost all accessible data are based on that principle, we also accepted this standpoint and regarded the findings of our colposcopists as valid. Detected abnormal colposcopical findings, followed by a positive cytological testing, demand for a guided biopsy, under the control of the colposcope in order to avoid obtaining incorrect samples and therefore false negative results.

The main objective of cervical screening is to identify women with HSIL. These women require prompt treatment because of possible disease progression, while those with CIN I can only be monitored as that condition can spontaneously remise. In the literature almost 20% of LSIL was overdiagnosed and between 20% and 30% of HSIL was underdiagnosed [9–11]. In our study such cases were also recorded, which presents a hazard. Synchronized application of colposcopy and cytology gives better chances for detection of those lesions that need treatment. Colposcopy, as the only diagnostic method, is not precise enough, but is useful for evaluation of the lesion stage [12, 13]. In order to choose on adequate treatment biopsy is necessary [12, 13]. Treatment must be based on HP findings due to a possible misinterpretation of both colposcopical and cytological examinations [11]. There are even cases in which mistakes in HP evaluation were made and when CIN was not appropriately dyagnosed [11].

Using the similar methodology as in our studies, the analysis of validity and diagnostic precision of cytological findings of LSIL and HSIL, researchers concluded that PA and HP findings show statistically significant correlation [13, 14]. In the examined population these results were achieved only when a wider categorisation is assessed. Otherwise on both PA and colposcopical examination more malignant changes in comparison with final HP diagnose were obtained. Therefore it can be said that both methods overestimate the stage of the lesion.

The available literature data state that sensitivity is higher than specificity of colposcopy [4, 12], which was also demonstrated in our study. While conducting screening low +PV of colposcopy may result in unnecessary treatment [12]. In our study +PV is also somewhat lower. Colposcopy has higher sensitivity and cytology higher specificity, so their findings are not doubling but supplementing themselves in providing better reliability. Besides, it was also registered that colposcopical findings were more malignant in compari-

son with final HP diagnose and therefore other diagnostic methods should be undertaken.

High sensitivity of colposcopy in the investigated population implies that this method will in most cases recognise malignant changes. On the other hand, cytological analysis has high specificity and –PV, so this method will in most cases disregard benignant changes. It can be observed that our study showed higher values for all the examined parameters (sensitivity, specificity, + and – PV) and therefore is a more reliable diagnostic method. Moreover, as compared with diagnostic categories obtained from different examined methods it can be concluded that PA discovered all malignant lesions, but also had the most false positive findings. Colposcopy was the least reliable and as well had numerous false positive findings. If only benignant and malignant conditions are evaluated, in the widest sense, colposcopical findings were once more the least valid and statistically significantly different from HP diagnoses. Contrary, according to the fact that benignant and malignant PA ad HP findings do not differ significantly, it can be concluded that cytological analysis is a reliable method for differentiation between benignant and malignant findings. For more detailed and reliable diagnostics biopsy of the cervical change with HP analysis of the obtained tissue is still recommended [15].

The roles of cytology, colposcopy and guided biopsy in prevention of cervical cancer are still developing. Regarding the some literature data it can be advised to base the decision on adequate treatment only on the abnormal colposcopical findings [14, 16]. But according to the results of our study it can be concluded that the decision on treatment is best made when based on the findings of all the three methods.

Conclusion

Although both colposcopy and cytology are methods with high sensitivity, specificity, + and – PV, individually they are not absolutely valid. Based on the results of our study colposcopy directed biopsy cannot be recommended due to numerous false results and therefore unnecessary procedures. Cytological analysis is a more reliable method and as such is a necessary diagnostic tool. Therefore, it can be advised that following abnormal colposcopical findings, PA smear should always be taken and only after receiving the cytological results further diagnostics can be planned (biopsy and HP). A final decision on the therapy must be made in accordance with HP findings which are the only method that can lead to the ultimate reliable diagnosis of cervical changes.

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CURRENT TOPICS

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Contemporary aspects of the diagnostics of alcoholic liver disease

Savremeni aspekti dijagnostikovanja alkoholnog oštećenja jetre

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Key words:
liver diseases, alcoholic; diagnosis; biological markers; ethanol; alcohol drinking; alcoholism.

Ključne reči:
jetra, bolesti izazvane alkoholom; dijagnoza; biološki markeri; alkohol, etil; alkohol, pijenje; alkoholizam.

Introduction

Consumption of ethyl alcohol dates back for over fifty thousand years. Alcohol has become an important socio-medical problem lately due to its massive consumption in the world.

In the order of causes of death alcoholism is in the third place, right after cardiovascular and oncological diseases. According to the epidemiological data, the number of alcoholics is about 5% of people in general population, or 10% of adult males [1]. The highest number of alcoholics is in the most productive life period of thirty to fifty years.

Besides the social importance is even greater medical significance of this phenomenon, because it shows a high rate of morbidity. Alcohol through its toxic product, acetaldehyde, induces liver damage that can occur in the form of alcoholic fatty infiltration and alcoholic hepatitis, the changes which are reversible upon termination of alcohol intake, and alcoholic cirrhosis, which presents irreversible liver damage [2]. Cirrhosis of the liver progresses to complications related to central nervous system (the development of hepatic encephalopathy), kidney (the development of hepatorenal syndrome), deposition of iron in the liver (hemochromatosis development), deposition of copper in the organs (the development of Wilson,s disease), disorder at the level of hormones, and disturbances at the level of the lung (development of hepatopulmonary syndrome and portopulmonary hypertension). The effects of alcohol on the degree of liver injury depend on the dose, sex and age, as well on the concentration of alcohol and the length of its usage [3–6].

It is believed that for the toxic effect of alcohol is not important the origin of the drinks, but the concentration of alcohol in it. Permissible weekly dose of alcohol for women is 14 units, while for men is 21 units. The permissible level of alcohol is lower for women because they have lower activity of gastric alcohol dehydrogenase enzyme. It is believed that higher intake of alcohol than allowed, in a time period longer than 5 years, definitely causes damage to various organs.

Lower doses of alcohol have a stimulatory effect on the central nervous system, while higher concentrations cause a dose-dependent depression of the central nervous system. Chronic alcohol intake induces tolerance to toxic effects of alcohol and thus leads to adaptation of the central nervous system to ethanol, and consequently to the development of hepatic tolerance [7].

Diagnostic markers of alcoholic liver injury

Markers of alcoholic liver injury are diagnosed on the basis of a confirmed information about the consumption of alcohol, as well as on liver function tests and liver biopsy.

The hypothesis is that alcohol causes liver damage in patients with chronic and excessive alcohol quantity entries, more than 60 g per day for men, and 40 g per day for women.

The diagnosis can be confirmed by analysis of general markers: prothrombin time, serum bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AP), gamma glutamyl transferase (γ-GT), glutamate dehydrogenase (GDH), mean corpuscular volume (MCV) of erythrocytes lipid and albumin levels [8].

Serum bilirubin is an indicator of liver secretory function. Parenchymal liver diseases, and the damage of the hepatobiliary system caused by longer intake of alcohol, as well as the excessive alcohol intake, increase levels of bilirubin in serum. In the beginning of the disease, when there is small degree damage, conjugated bilirubin is dominated in serum, but later with the progression of the liver disease, and hepatobiliary system disease in general, the level of bilirubin in serum increases. In terminal stage of liver failure, total

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bilirubin is increased at the expense of increased unconjugated bilirubin, when all functions of hepatocytes in the metabolism of bile color are damaged (download, conjugation and excretion of bilirubin). The secretion of the liver function is calculated on the basis of Maddrey discriminant (DF) analysis [9]:

$$DF = 4.6 \times (PT\ control - PT) + serum\ bilirubin,$$

where PT control is the prothrombin time of the control group and PT is the prothrombin time of patients.

In this formula, bilirubin level is given in mg/dL. When the limit is converted into mmol/L it is 17. The value of DF greater than 32 indicates a higher mortality rate, even up to 35% without encephalopathy and 45% with encephalopathy. Prothrombin time is an indicator of synthetic liver function [10].

General markers of alcoholic liver disorders

ALT is mainly localized in cytosol, while AST is mostly localized in mitochondria. Ratio of AST to ALT indicates etiology of alcoholic liver damage. In the serum of healthy people AST/ALT ratio is lesser than 1. When alcohol damages the liver parenchyma, the increase of transaminase activity in serum is moderately elevated.

In alcoholic hepatitis the ratio AST/ALT is greater than 2, because it reduces the activity of ALT. AST is a specific marker for alcoholic liver damage, and the increase in AST levels in liver disease is prolonged in serum.

AST showed elevated values of alcoholic liver damage, as well as in alcoholic myopathy and alcoholic cardiomyopathy.

However, in the progression of chronic hepatitis with pronounced necrosis of hepatocytes, ALT increses up to 5–6 times, and AST activity increases up to 10–20 times above normal.

γ-GT is the most important enzyme for the diagnosis of alcoholic liver damage. In alcoholics with alcoholic hepatitis the acute stage of liver damage is characterized by a rapid increase in γ-GT in serum (at this stage the growth of ALT and glutamate dehydrogenase is slower).

In the initial stages of liver damage, increased γ-GT in serum is the only sign of liver damage. In people with chronic alcohol consumption, and with no damage to the liver, the values of γ-GT in serum were increased by 2 to 3 times above normal. However, in patients with chronic alcohol consumption, and who have liver damage, the value of γ-GT in serum was increased by 10 to 20 times above normal [11, 12].

At alcohol consumption cessation values of γ-GT in the serum are reduced to half of the initial value within 2 weeks. For this reason, γ-GT is used for the detection of chronic alcoholics and to control withdrawal. Studies show that γ-GT is a more sensitive marker for monitoring changes caused by alcohol in men than in women. It was shown that the level of γ-GT in men increases with moderate alcohol consumption [13]. Moderate alcohol intake with obesity shows synergistic effect with respect to increasing values of γ-GT [14].

γ-GT is an enzyme, whose biological function is in the regulation of glutathione concentration. *Via* glutathione the important role in regulating the redox state of the cell is achieved. γ-GT increases in a state of increased production of free radicals, or in a state of oxidative stress, which is basically the pathogenesis of liver damage. For this reason, γ-GT was nominated as the marker of oxidative stress [15, 16] .

Contrary to the increasing value of γ-GT in the serum, drinking coffee in small quantities (one coffee a day), with concurrent use of alcohol, is reducing the value of γ-GT in the serum. Accordingly, it is concluded that coffee consumption has a protective effect in the development of liver cirrhosis [17, 18].

In people who consume moderate amounts of alcohol and in people who are heavy drinkers, the activity of γ-GT in the serum increases with advanced age. In those who abstain, who are over 70 years old, γ-GT in the serum shows declining activity in proportion to age. Also, with the young people who abstain, aged below 30 years, γ-GT activity in the serum decreases [19].

There is a difference in relation to the activity of γ-GT in various countries of the world. So in Scandinavian countries, where alcohol is usually consumed in large quantities, γ-GT in the serum showed the highest activity in middle-aged men even greater than 100 IU (upper limit of reference value is 60 IU) [20].

γ -GT activity in the serum is important for confirmation of liver damages by alcohol. If the period of abstinence lasts 8 to 10 weeks, and the value of γ-GT in the serum constantly persists, then it is an indicator that liver damage is present. Normalization time of γ-GT is 2 to 3 weeks. If the value of γ-GT in the period of abstinence of 2 to 3 weeks, and after continuous intake of alcohol, is returning to normal, it is an indication that there is no liver damage.

The diagnostic sensitivity of γ-GT increased in combination with carbohydrate deficient transferrin (CDT) marker. The combination of these two markers is represented by the following mathematical relation: 0.8 x ln (*γ-GT*) + 1.3x ln (*CDT*). This mathematical relationship is used to detect heavy drinkers, who consume daily more than 40 of alcohol per day. It is also used for tracking control of abstinence, during which the level of the combined markers γ-GT-CDT is showing a continuing decline [21].

MCV is directly relevant to severe alcohol consumption. A MCV marker indicates increased values up to 1 to 2 times compared to the reference values of the consumption of alcohol in less than 40 per day. This marker is used for the detection of long alcohol consumption in individuals without clear clinical signs, which are dependent on alcohol. Ethanol has a direct damaging effect on erythrocytes. Ethanol and its product acetaldehyde bind to the lipid layer of cell membranes affecting the stability of the cell membrane and causes hemolysis of red blood cells. In this way the biological life of erythrocytes reduces. Alcoholics with microcytosis create circulating antibodies which directly impair acetaldehyde-modified complexes of proteins. This suggests that immune mechanisms also play a role in the development of abnormal red blood cells in a state of alcohol-induced [22].

If moderate amounts of alcohol are consummated (one to two drinks a day), high-density lipoprotein HDL has a

protective role for cardiovascular system. If person consummates alcohol in relatively small amounts (about five drinks a day), the level of HDL levels increases. Increased HDL serves as a marker for early identification of problems with drink, and can serve as a marker for monitoring patients who have liver damage.

People who consume alcohol in moderation have a higher value trglycerides.

Persons who in a long run consume small amounts of alcohol also have higher values of ferritin.

In these people, depending on the type of alcoholic drink and the way of alcohol intake, the value of urate increases. In the state induced by alcohol elevated serum uric acid results from the increased uric acid synthesis and also because of decreased excretion of uric acid, which is a consequence of lactate and ketones circulation.

Serum albumin is also significant in the diagnosis of liver damage in heavy drinkers. An increased level of albumin in heavy drinkers without liver damage indicates the increased synthesis of albumin. In contrast, in alcoholics who have liver damage, albumin shows lower than normal value.

Markers and their characteristics are given in Table 1.

Transferrin, CDT, consists of polypeptides bound to two polysaccharide chains. These polysaccharide chains carry the remains of sialic acid. Sialic acid is carbohydrate monosaharid. Depending on the number of chains of sialic acid there are several isoforms CDT. There are monosialo-, disialo-, trisialo- and tetrasialotransferin [23]. Studies show that ethanol affects the value of CDT indirectly, by affecting the transport protein transferrin, and by affecting the activity of the enzyme. Induction or inhibition of enzymes sialyl transferase and enzyme sialidase directly affects the level of CDT in serum.

Chronic alcohol intake reduces enzyme activity of sialyl transferase, and increases the activity of enzymes sialidase. After posttranslational modification of transferrin- glycosylation, transferrin is secreted by exocytosis. Transferrin is a glycoprotein responsible for the transport of iron. Excessive alcohol consumption may affect the synthesis of monosaccharides, and can also partially prevent the installation sialic acid. Ethanol also can enhance the activity of sialidase, which removes the monosaccharides sialic acid from transferrin [24].

CDT is a relatively new marker that has a high specificity and sensitivity in the diagnosis of chronic alcoholics,

Table 1

General markers of alcoholism

Biomarker	Way to consume alcohol	Examples of false positive results	General comments
Aspartate aminotransferase (AST) Alanine aminotransferase (ALT)	Unknown quantity, but often continuously entering a period of several weeks	Excessive coffee consumption may lead to lower values	General marker of diagnosis of alcoholic liver damage. Alanine aminotranferase is a less sensitive marker than aspartate aminotranfferase. Aspartate aminotranfferase / alanine aminotranferase > 2 suggests alcoholic liver disease. The best results are obtained in patients of 30–70 years
Gamma glutamyltransferase (γ-GT)	Probably at least 5 drinks per day for several weeks	At the same time alcohol intake, smoking, obesity, and use of drugs that are metabolized by microsomal enzymes	Primary general marker of alcoholic damage liver. The best results are in individuals of 30–60 years
Mean corpuscular volume (MCV)	Unknown quantity, but often continuous input from the last few months	Liver damage, hemolysis, hematological damage, anemia, folic acid deficiency, hypothyroidism	More sensitive in men alcoholics in comparison to other common markers. It is used for the detection of long and intensive consumption of alcohol (containing less than 40 g per day)
High density lipoprotein (HDL) and triglycerides	Intake of 3 to 5 drinks per day for several weeks		Marker for early diagnosis of problems with drink and monitoring patients who have liver damage. Increase after high doses of alcohol intake, and decreases after 1 week of abstinence
Urates	Intake of small amounts during a period of several weeks	Diseases that lead to increased production of uric acid and kidney disease that lead to decreased excretion of uric acid	Slightly increases the intake of low doses of alcohol. Sensitivity depends on the type of beverage and ways to introduce alcohol
Albumin	Intake of large amounts of alcohol over a longer period of time	In severe liver damage nonalcoholic etiology (cirrhosis)	Marker in the diagnosis of heavy drinkers. Slightly increases in heavy drinkers without liver damage. Decreases in severe liver damage (level < 25 g / L is a bad prognostic sign)

A new diagnostic marker of alcoholic liver damage

CDT is one of the new, specific and sensitive markers to detect early alcohol abuse.

heavy drinkers, as well as those who abstain from drinking alcohol. CDT level in healthy women is higher than in healthy men. The level of CDT in the serum in women depends on the hormonal status that is different in pregnancy,

when taking contraceptive pills, in pre-menopausal and post menopausal. The level of CDT in the serum is directly dependent on iron homeostasis.

Alcohol leads to increased absorption of iron from the intestinal mucosa and causes accumulation of iron in the liver. In people with iron deficiency, the level of CDT is higher if compared to transferrin, since CDT has greater ability than normal transferrin to deliver iron to the tissues and vice versa [25, 26]. It was recorded that CDT in men is in direct comparison with the frequency of consumption alcohol, whereas in women CDT is associated with the intensity of the consume alcohol. Thus, in men who consumed alcohol intensively, increasing levels of asialo- and disialo-CDT are detected, while in women an increased asialo- and monosialo- CDT are registered. In diagnostic terms, for people who apstinate or consume alcohol moderately asialo form is present, while for alcoholics both asialo- and disialotransferin are present.

In treated alcoholics studies have shown that CDT is elevated even in small amounts of alcohol intake. This indicates that CDT may serve as a sensitive marker of return to alcohol or as a marker of dependence. It is shown that one of the advantages CDT has over other markers is that it is neither affected by liver disease, nor under the influence of drugs.

Aldehyde reactive particles and free radicals are produced in condition of high alcohol intake, *ie* in condition of ethanol-induced oxidative stress. Aldehyde particles, products of lipid peroxidation are acetaldehyde, malondialdehyde (MDA), 4 hydroxynenol (HNE), malondialdehyde-acetaldehyde (MAA) and hydroxyethyl radicals. These reactive species attack protein amino acids hence forming modified proteins.

Modified proteins accumulate in the liver and participate in the pathogenesis of alcoholic liver damage. Reactive aldehydes, predominantly MDA, react with proteins of the cell membrane thus changing the functional and structural properties of these proteins, bringing about a change in the stability of the cell membrane, lysis of the cell membrane and finally releasing of enzymes from cells. Aldehyde-reactive proteins also act by reducing the number of receptors on the cell surface that mediate in the endocytosis process [27].

Aldehyde-reactive particles can react with the erythrocyte membrane protein, albumin, tubulin, lipoproteins and collagen, thus changing the functional properties of these proteins. Products MDA and HNE with proteins lead to atherosclerotic changes in the walls of arteries. On one hand reactive aldehydes increases indirectly by stimulating collagen mRNA levels, and on the other hand the level of collagen activation of Ito cells increases. In this way, the process of liver fibrosis is stimulated. Aldehyde reactive protein particles stimulate the immune sensitivity, and stimulate formation of antibodies reactive protein particles, causing anti-acetaldehyde and anti MAA products to form. Under the conditions of oxidative stress expressed in heavy drinkers comes to a breakdown of immune tolerance, or to the formation of auto antibodies. The research shows that the values of anti-modified and anti-aldehyde protein can serve as a marker of expressed alcohol consumption [28, 29].

Metabolites of ethanol

5-hydroxytryptophan (5-HTOL) is a sensitive marker of return to alcohol. The influence of alcohol leads to the shift in the metabolism of serotonin from the normal product, 5-HTOL acetic acid in 5-HTOL, which is why in the urine the value of the ratio 5-HTOL / 5-blunted (%) increases. The urinary 5-HTOL remains elevated 6 to 20 h after cessation of alcohol intake. This marker has high diagnostic value in detecting recent alcohol consumption and to control the return of alcoholism [30].

Ethyl glucuronide (EtG) is formed in the reaction of ethanol and activated glucuronic acid. Little is decomposed in the liver (0.02%–0.06%). EtG remains in circulation 2–3.5 h and even a few days after the cessation of alcohol intake. It is measured in urine. It is present in hair, body fluids (whole blood, serum, plasma, urine, cerebrospinal fluid) and tissues (liver, adipose tissue), which brings additional diagnostic information [31].

Phosphatidyl ethanol (PEth) is an abnormal phospholipid that is found primarily in erythrocytes. PEth is a very specific and sensitive marker in detecting alcohol. In the long-term intake of small amounts of alcohol it is present in circulation, and can be used as a marker of dependence, or a return to alcoholism. This marker remains elevated in serum, more than two weeks after the cessation of alcohol intake. This marker is sensitive to storage so samples must be frozen at temperature of -80 °C [32].

Ethyl esters of fatty acids are present in serum shortly after consuming alcohol and remain in circulation for up to 24 h after alcohol intake. Ethyl esters of fatty acids are present in circulation when the amount of alcohol cannot be measured in blood. In circulation they bind to albumin, are lipophilic, turn into fat, accumulate in tissues. In cells ethyl esters of fatty acids inhibit mitochondrial function and thus lead to cell necrosis [32].

New markers and their characteristics are given in Table 2.

Conclusion

It can be concluded that by analysis of biomarkers, assessments of risk of possible health problems in alcoholics can be performed. Furthermore, analysis of biomarkers contributes to the understanding of the pathogenesis of diseases caused by alcohol, thus improving the treatment and improving the outcome. All this is done in order to develop control for reduced alcohol consumption. The research shows that factors such as gender, age and obesity should be carefully controlled. Since CDT is synthesized, glycolysed and secreted from the liver, analysis of the value of CDT in patients with liver disease may be the area of great interest for further investigations.

Table 2

New markers of alcoholism

Biomarker	Ways to consume alcohol	Examples of false positive results	General comments
Carbohydrate deficient transferrin (CDT)	Probably at least 5 drinks per day for two weeks	Iron deficiency, hormonal status in women, glycoprotein syndrome, fulminant hepatitis C and heavy alcohol damages	As good as gama-glutamyl transferase, but very specific marker in the diagnosis of chronic and heavy drinkers. Sensitive marker for the return of control after a period of alcohol abstinence. Less sensitive in women and young people
The combination of γ-GT and CDT	Probably more than 5 drinks per day for 2 to 3 weeks	Iron deficiency, hormonal status in women, glycoprotein syndrome, advanced chronic liver disease (primary biliary cirrhosis, chronic active hepatitis) and liver damage by medication	Represents the combined mathematical relationship. Increased up the sensitivity in the diagnosis of heavy drinkers (more than 40 g per day) and for monitoring abstinence. It is suitable for routine analysis
Malondialdehyde (MDA), 4 hydroxynenol (HNE), Hybrid malon dialdehyde-acetaldehyde (MAA)	Entering large amounts over a long period	Conditions and diseases caused by severe oxidative stress (chronic severe damage of the liver: biliary cirrhosis, drug induced chronic hepatitis, hepatitis C)	Participate in creating products with membrane proteins. Modified protein marker of alcoholic liver damage. Marker fibrinogeneze to cell activation and collagen synthesis. Marker of immune stimulation sensitivity.
5-Hydroxytryptophan (5-HTOL)		Intake of nutrients that lead to a shift in the metabolism of serotonin	Marker of recent alcohol consumption and restore control of alcoholism. Ratio of 5-hydroxytryptophan by blunted increases sensitivity. It is measured in urine.
Ethyl glucuronide (EtG)	Possible to enter a small amount like just one drink	Unknown, but alcohol is often the medicines, hygienic items, cosmetics, food, etc. It is necessary to examine whether the accident was found alcohol in these funds can significantly affect levels of this marker	A very sensitive direct marker for nonoxidative analysis of alcohol. Small influence of gender and race, and age. Its role will be subject to new research. It is measured in urine.
Phosphatidyl ethanol (PEth)	Probable input 3 to 4 drinks per day for several days	Little is known because few studies performed	Small influence of gender, race, and age. Linearly dependent and associated with the last provided a dose of alcohol. Its role will be subject to new researches

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Electronic health system – development and implementation into the health system of the Republic of Serbia

Elektronski zdravstveni sistem – razvoj i uvođenje u zdravstveni sistem Republike Srbije

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Introduction

Since 1950 information technology has had the potential to impact upon many aspects of the health sector. The ability of communities to access health services is influenced by wider information and communication processes, mediated by information and communication technology (ICT) [1].

Computer technology has been used in healthcare since 1960, but changing and going through various stages [2]:

– First experiments with the new technology in the health system were recorded in sixties. It was the first time to develop computerized tomography, as a new diagnostic method, by combining medical equipment with computers. At that time was one of the first Clinically-oriented Hospital Computer Information Systems (HCISs) established. It was Technicon Medical Information System (TMIS). TMIS development began in 1965 as a collaborative project between Lockheed and EI Camino Hospital in California [3].

– In the 70's the number of hospital information systems was growing rapidly. The first approach to their implementation was in favor of a centralized, integrated, closed system, and relied on large, central (mainframe computer) computers.

– The 80's, in addition to further development and expansion of the concept of information systems in medicine, were characterized by the development of two disciplines: artificial intelligence (divided into expert systems, pattern recognition and neural networks) and methods of information synthesis (with the aspects of a general overview and association data).

– The 90's were marked by the process of integration: integrating the health information system, forming an integrated database of medical and administrative data or knowledge, and communication: a complete communication in the healthcare system and communication of that system with other systems.

– Medical informatics is now accepted as a basic medical science. Analogy with other basic sciences is recognized in the use of previous experience and results to structuring and coding of objective and subjective medical findings, which makes them suitable for analysis, integration and reuse.

Application of ICTs in health care tends to expand the focus of resource management to knowledge management and processes management.

In Europe, integration of information and communication technologies in health care was performed to provide better health services for patients, by achieving mobility of people and providing the opportunity to control and analyse the entire healthcare system in terms of economy and quality, and thus to the possibility of managing large health systems. This brief review shows that there is no common nor unique approach to this area. Depending on its socio-economic opportunities, each country, makes effort to find out the best way to solve problems of management and control of the health system.

The potential of ICT applied to healthcare system can be used to improve health services rendered to citizens, but also to health professionals in order to have safer, higher quality, more rational and better health care. ICTs are a basis for the development of health information system.

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Health information system has a number of features, such as scheduling of examinations, patient registration, record keeping of medical personnel services, electronic patient records, diagnostics, laboratory, pharmacy, statistical processing of collected data, management support.

Electronic health system

The so-called electronic health system (e-health) was created by the application of contemporary ICT, which has fundamentally changed medical practice, enabling a significant increase in quality and efficiency of health service through a more rational and effective use of available resources. The term "e-health" encompasses a wide spectrum of medical services used with the help of information technologies.

E-health is usually defined as the Internet and information technologies use in healthcare system, which improves access, efficiency, effectiveness and quality of medical business processes with the participation of relevant entities (healthcare facilities, medical staff, patients, insurance companies, state) and the aim of improving health condition of a patient [4].

E-health radically changes access to health information, as it allows an easy and quick access to those data, regardless of a user location, taking into account authorization of health professionals who access them. E-health includes: telecommunications systems between healthcare institutions and patients and doctors, and storage electronic medical records collection, processing, keeping electronic medical records, access to healthcare system through mobile communications (a village doctor, ambulance, etc.).

In an E-health system there are the following essential services [4]:

– An electronic medical record is the first step towards more efficient and higher quality healthcare system, and it contains valuable information for all actors in the system. Electronic medical records are usually a computerized legal medical record created in an organization that delivers care, such as hospital and doctor's surgery. An electronic medical record tends to be a part of a local stand-alone health information system that allows storage, retrieval and manipulation of records.

– Telemedicine is a service that involves all types of physical and psychological measurements that do not require a patient to visit a specialist. Owing to this service, a patient does not have to travel often, and a doctor can cover a wider geographical area.

– Evidence-based medicine is a service including a system that contains information about the current state of a patient. A doctor can check whether the diagnosis coincides with the current scientific research achievement. The advantage of this service is that data are always up-to-date.

– Citizen-oriented information provision is a service that enables both physicians and patients to be informed about the latest medical knowledge.

– Specialist-oriented information provision is a service that allows physicians to follow the most recent editions of medical journals, best experience in practice and epidemiological monitoring.

– A virtual healthcare team is a virtual service representing a team of doctors who cooperate with each other and provide necessary information to patients via e-mail (web portals, e-mail, forums).

The main benefits derived from the usage of electronic health system are the following: efficiency in rendering health care – the introduction of electronic communication model between doctors and patients; health care costs reduction; the employee productivity growth; providing the right information in the real time by using the internet; maintenance of medical services quality by using electronic knowledge management.

Due to electronic healthcare system, the resources are used in a more rational way by analyzing the current situation and immediate needs for medical supplies and the usage of hospital capacities.

Electronic healthcare system enables the generation of various reports using all electronic health care records. The analysis of these reports is a way to strategic planning and creating an accurate demographic and health condition of the nation.

Knowledge management system has been implemented with the aim of spreading the expertise of doctors in electronic healthcare system. Thus competence is being improved, which contributes to increasing the total effectiveness and efficiency of healthcare institutions.

Due to the sensitivity of data content in electronic health system, a special attention must be paid to their safety, i.e. protection of integrity, confidentiality and availability of information. The security mechanisms in electronic health system are [5]: authentication, which makes it possible to reliably identify a user via electronic smart card; use of digital signature; protection of confidential data in the system, which is achieved by using cryptographic methods, and access control that provides a controlled access to resources.

Electronic healthcare documentation

One of the basic components is the electronic healthcare documentation (EHD) system, which is based on an electronic healthcare documentation of a particular healthcare consumer unified through a singular identifier throughout a complete healthcare system. The EHD system provides data on basic processes in the healthcare system regarding health care of a particular consumer.

A new approach in conducting business processes in the health information system is the existence of a unified electronic healthcare documentation. The main feature of electronic healthcare documentation is patient orientation. This means that the exchange of information about a patient health is done via the electronic healthcare documentation, thus improving health service and reducing operating costs.

The electronic healthcare documentation incorporates information collected during the entire life of a patient and from various institutions that render health services. This information is available regardless geographical and temporal distance and protected by security mechanisms. This means

that every user of the EHD system controls the access to his/her data, and defines which data could be available to whom.

Figure 1 shows a correlation of the electronic healthcare documentation that is available to all users regardless location. Access to information is strictly controlled using standards for privacy and security of information, modern technological solutions and legal rules.

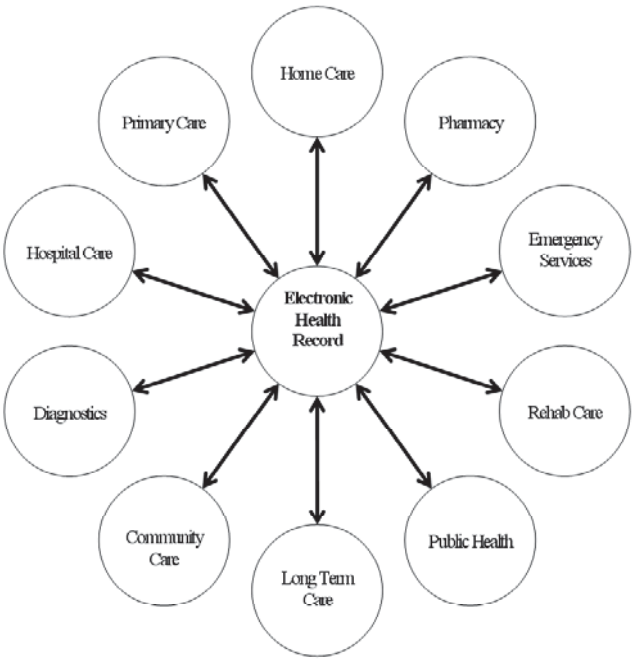

Fig. 1 – Connected electronic healthcare documentation [6]

Electronic healthcare documentation is an information which has been collected and exchanged during regular check-ups by doctors, pharmacists, in hospitals and insurance companies. This means that: all this information will be stored in one centralized place; all healthcare facilities must adopt electronic information systems and use common standards with regard to data in order to enable integration; healthcare organizations and doctors specialists who perform private practice should see themselves as "guardians" of patients' health information, not as the owners of business information; healthcare organizations and other participants in generating EHD have to follow and adopt the best practice to ensure privacy and security of personal health information.

Electronic medical documentation

It is necessary to distinguish between electronic healthcare documentation and electronic medical documentation (EMD). Electronic medical documentation is a software platform for managing detailed medical information collected during a patient's stay in a medical institution. It usually contains a medical history, doctor notes and laboratory and X-ray results, and as a rule is owned by a physician and it is limited to information collected by one doctor and one hospital. An EMD rarely contains information provided by a patient. An EMD is not used by all physicians, and often when a patient changes a doctor or moves to a new surroundings, personal health information does not move with him/her [7].

Electronic patient records

Electronic patient records (EPR), and/or their idealization Electronic Health Records (EHR) are actually the outcome from which both professions (medicine and computer science) build their view on the common goal: building a new system of health services in which the application of technology for knowledge dissemination helps all health professionals to provide personalized service to every patient in accordance with the latest medical standards resulting from the most recent knowledge, and that is knowledge [8].

With the help of the Internet and the set standards of communication between participants in healthcare system, electronic records enable a patient to get a complete insight into the process of solving his/her health problems in electronic form from any geographical location and at any time. Thus, a patient becomes an active participant in his/her treatment not only as a patient, but also as a person who is entitled to make decisions regarding his/her treatment: to choose where to be treated and who by, what level of service quality he/she wants, to seek review of medical expert opinion, etc.

On the other hand, a doctor has a complete overview of medical history, any results, previous diagnosis and prescribed treatment for every patient. It allows him/her to gain a full picture of a patient's health status and to help him/her in the best and most effective way.

Due to multimedia content transfer (digitized images, medical images and documents) *via* the Internet, the conditions for verification of diagnosis by several doctors in different locations have been created, thus reducing the probability of errors in the diagnosing process.

When making diagnosis, doctors have at their disposal the existing diagnoses of patients made earlier by other doctors. In that way, not only a doctor, who improves his/her expertise benefits, but also a patient, who will have the access to consultative opinion of doctors.

The existence of electronic medical records allows medical teams to have an easier access to information, greater interactivity in work through the possibility of telemedicine consultations, and thus the opportunity to solve more cases.

Drugs manipulation is reduced and the possibility of medical errors avoided by the management of electronic records of diagnoses and prescribed medicines. Also, by electronic medical records electronic healthcare system prevents incompatible drugs prescription or drugs that patients are allergic to.

Writing and control of referrals to laboratory analyses are common problem in medical practice. Referrals are electronically sent to a laboratory by the usage of electronic medical records, with the indicated type of analyses and diagnoses, and after processing analysis findings are returned to the doctor. The plan is to enable the same electronic functionality for X-rays, ECG recordings and ultrasound examinations.

A healthcare institution has tremendous benefits of data analysis from electronic medical records of treated patients. Thus, a healthcare institution gets a complete insight into all processes of healthcare personnel work. Patient electronic medical records give the opportunity to accurately detect possible disorders of business process in healthcare system.

So, the essence of the treatment process remains the same, but in an easier way, more efficient, less hazardous to a patient and it has a great impact on shortening the time for diagnosis. According to the same principle, significant savings and benefits in informatics connections between healthcare institutions at different levels of health care are made, mainly due to the ability to have the unique information about each patient.

Electronic health smart card

Healthcare organizations worldwide are implementing smart health cards supporting a wide variety of features and applications.

Electronic health smart card is a basis of successful e-health system functioning. Smart health cards can improve security and privacy of information about a patient, provide a secure carrier for portable medical records, reduce health care fraud, support new processes for portable medical records, allow secure access to emergency medical information, enable compliance with government initiatives and mandates, and provide a platform for implementing other applications as needed by healthcare organizations [9]. There are several types of health cards, but the following three types are the most important [10]: patient data card; health professional card and health insurance card.

Patient data card (PDC) is a mobile patient data carrier. It contains information about a patient that is essential for his/her treatment. Typical data on card chips are: the identity of a patient, information about insurance, emergency data, medical history and electronic prescriptions [10].

For patients mobility means that they have complete and accurate health information at any time. Their critical data are always available when it comes to emergencies. Under normal circumstances, the usage of the card provides data finding and establishes an appropriate treatment for a patient. This prevents excessive medical tests and examinations, and therefore results in urgency and efficiency in solving critical health problems of a patient [11]. For health professionals, the advantage of data mobility is the fact that they work with verified and reliable health information on patients. It is easier to find the best treatment and avoid risk of prescribing potentially dangerous drug combinations with these data.

Typical data on a card are: patient's personal data (name, address, date of birth, telephone number), a digital certificate issued by an appropriate certification body, patient insurance (insurance, social security number, expiry date), a small medical database of a patient (information about diseases, treatment, blood type, allergies, diabetes), prescription data (medication, dosage, date of an issued prescription), an electronic wallet for potential, small amounts of payment in healthcare system, and a patient's personal identification number (PIN) and cryptographic keys for mutual authentication between the card and Smart Card reader [10].

Health professional card (HPC) is an authorized access card which a health professional has. It gives him/her the right to read or write data in fields on patient data card, and it also carries a digital certificate and appropriate cryptographic keys for secure communication. Privacy and data security are guaranteed to patients in accordance with the rules of access, which prevent unauthorized access to their stored medical data [10].

For health professionals, HPC provides a quick and efficient information exchange between health professionals and other users in electronic health system.

Typical data on the card are: identification data of health professionals (name, address, phone number), a digital certificate, individual access rights for reading and/or writing patient's data, PIN to access the card, cryptographic keys for mutual authentication between the card and smart card reader, asymmetric keys to perform digital signature [10].

Health insurance card (HIC) is an ID card with an administrative function. It contains details of the insured, the insurance company ID and information about insurance model.

In some systems, PDC and HIC cards could be integrated into a single PDC card. In this way the administrative procedure for admission to the hospital, i.e. doctors' office is much easier for patients. HIC card increases patient satisfaction and reduces paperwork. Health data of the insured are processed more quickly and accurately. A health professional gets fast, precise, easy and cost-effective data management. This means less paperwork, reduction of transaction costs and more effective payment. Insurance companies benefit because electronic data processing enables data on claims to be processed without error.

Typical data on an insurance card are patient's insurance (insurance, social security number, expiry date), ID insurance, and insurance coverage [10].

Cost-benefit analysis of electronic healthcare system

Cost-benefit analysis in health care is the analysis of resource costs of health care in relation to possible benefits. This analysis is useful and necessary in establishing priorities when choosing between limited resources and desired results.

Costs related to electronic healthcare system

There are two categories of costs related to electronic healthcare system: system costs and induced costs. System costs are the costs of purchasing software and hardware, training, implementation, ongoing maintenance and support. Induced costs are those costs involved in the transition of establishing an electronic system, such as a temporary decrease in service productivity after its implementation.

Software costs are related to the initial purchase of software, with annual maintenance and support fees. The service price includes design costs and system development, interface to existing business systems (planning, laboratory) and periodic updates.

Benefits related to electronic healthcare system

There are much more benefits than costs related to the transition to electronic medical records. The main advantage of introducing electronic medical records is a way of keeping patients' records. Paper documents can be lost, and electronic medical records are stored on a network that is available regardless of location access.

The other benefits of electronic healthcare system implementation are: electronic healthcare system resolves the following issues: paper documents may be incomplete, illegible, and sometimes impossible to find. It is difficult to observe the chronology of patient's disease or to reach the desired information in an efficient way; in electronic systems it is possible to provide an integrated support for a wide range of activities: decision support, monitoring, electronic drugs prescribing, electronic recommendations, processing and results presentation. For instance, the investment in picture archiving and communication system (PACS) is repaid in 1–2 years, which means that from the third year onwards, this system makes great savings in the social security budget; data and information on epidemiological monitoring and control of disease can be easily analyzed, investigated and controlled in electronic systems, and support for continuous medical education.

Obstacles in electronic healthcare system implementation

Electronic healthcare system implementation is hindered due to: technical issues (uncertain quality, functionality, usage, lack of integration with other applications); financial issues (initial costs of hardware and software, maintenance, upgrades, replacement, investment reimbursement); resource issues, training and retraining; resistance from potential users, due to the changes in working practice; and certification, security, ethics, privacy and confidentiality.

Conclusion of cost-benefit analysis of electronic healthcare systems

This analysis shows that net financial analysis of electronic healthcare system is positive in a wide range of assumptions. The main advantage is the reduction of administration costs, the necessary resources and various operational errors.

The described cost-benefit analysis is based on data published in foreign literature. The costs of electronic healthcare system can always be even higher, depending on system complexity. The described costs and benefits are directed towards primary healthcare services.

Not all the advantages of electronic healthcare system implementation can be measured in financial terms. The other benefits include the improved quality of health care, reduced medical errors, as well as better information access.

Cost-benefit analysis is only a part of a complete analysis of the effects of electronic healthcare system implementation. Electronic healthcare system is the key component of the strategic objectives of the Ministry of Health to establish an impeccable care for primary, secondary and tertiary health care.

Electronic healthcare system implementation can lead to positive financial profits in relation to investment in health care organization. The implementation of electronic healthcare systems is a great way to reduce the costs of health organization. Studies have shown that this practice pays off over time, and that it goes towards creating a more efficient healthcare system.

Development of e-health system in the Republic of Serbia

When establishing electronic healthcare system in the Republic of Serbia it all started from the real situation in this area in the country, with a vision of the possible directions in the future.

Generally, healthcare information system in Serbia is mainly old-fashioned and in paper form. There is no coordination and information and communication technologies are rarely implemented.

The objectives of establishing electronic healthcare system in the Republic of Serbia are the following: to modernize healthcare system by applying the appropriate information- communication and telemedicine technologies; to simplify the use of ICT to be available to all participants in the electronic healthcare system, and on the other hand motivate healthcare workers to use computers in order to improve work efficiency; to promote electronic healthcare system as a system of reliable, timely, high quality and available health care which uses modern ICT as its basis; electronic healthcare system can improve monitoring of spreading easily transmitted diseases and warn users about that; to emphasize the importance of continuous medical training, education and research by using ICT; electronic healthcare system will facilitate access to new knowledge in science, profession and content of local concern in order to encourage research in the field of health care and prevention programmes; to encourage a positive attitude of people towards ICT by offering high quality content about healthy lifestyle and disease prevention on an appropriate Internet portal; to respect and protect citizens rights to privacy and security of their health data; to implement international standards in the exchange of health data; and to strengthen and expand initiatives for rendering medical and humanitarian aid in case of disasters or emergency situations based on ICT.

The strategy for the development of e-health system in the Republic of Serbia includes the development of a centralized model of collecting and managing data, which means that the information from all layers and organizations are centralized, standardized and ready for analytical processing at any time.

Taking into account the specificities of the healthcare system in Serbia, Figure 2 shows the main components that make up the "building blocks" of e-health.

Their scope and contents are organizational aspects of Serbian healthcare system, not technological resources. Technology must be used in accordance with present organization, but it also has to be independent and not to disturb

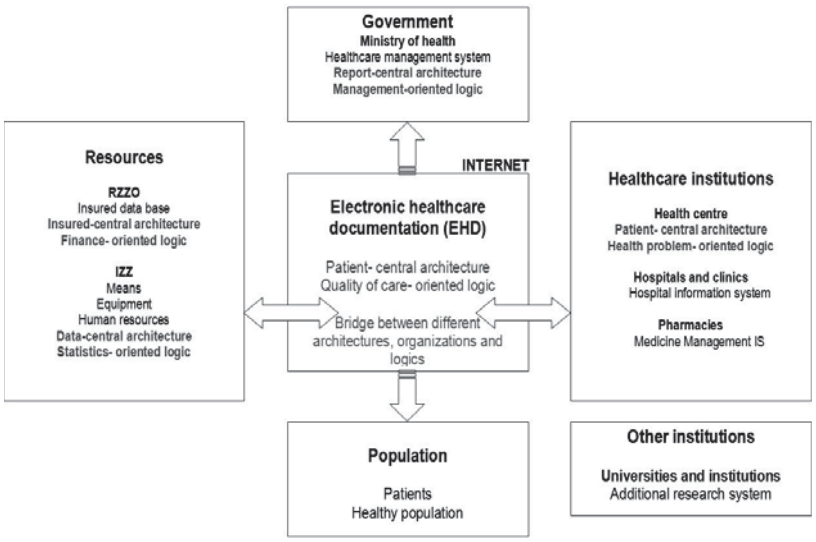

Fig. 2 – Electronic healthcare documentation inside the healthcare system in Serbia[13]

organizational changes, i.e. it has to sustain and support any organizational changes with minimal additional costs.

The development strategy of the integrated e-health system in Belgrade is in compliance with the principles and standards of EU and represents an integral part of the e-health system of the Republic of Serbia. The main goals are to make a comprehensive and integrated e-health system that will enable collection and management of health care, clinical, administrative, and financial information in Belgrade, in a technologically adequate way.

Table 1 shows main participants in the healthcare system, their present roles in the system and improvements to be achieved in the Republic of Serbia [14].

In August 2002, the Ministry of Health of the Republic of Serbia established the International Cooperation and Project Coordination Department. Cooperation with the World Bank and European Union resulted in initiation of several projects. A couple of bilateral projects has been realized with donation support from different countries, European Investment Bank, organizations such as ECHO, UNDP, UNICEF, International Red Cross, EPOS, Global Fund, USAID etc [15].

Since 2002, foreign partners have contributed to making several documents that served as base for the healthcare system reform and those documents are [14]: Policy of Healthcare Protection in Serbia, dated 2002; Vision of Healthcare Protection System in Serbia, also from 2002, and

Table 1

Main participants in the healthcare system

Participant	Role in the healthcare system	Informatics role	Improvements to be achieved
Patient	Healthcare consumer	Stores and transfers healthcare documentation from one place to another	Saving time and energy, Faster and better service, Reduced margin for errors.
Healthcare employee	Provides healthcare services	Reads, transcribes, and checks particular healthcare documentation. Makes notes of important events prescribed by the law (diagnostics and services)	Saving time in prescribing, Reduced margin for errors, More detailed insight into treatment of his/her patients done by other doctors, Automatic markup of important information in the background, Information accessibility and continuous education, Organized provision of healthcare services.
Healthcare institution	Provision of healthcare organization and services	Processes particular data, Submits single and aggregated data to health care office and healthcare insurance fund.	Automated processing of particular results, Electronic reporting to health care office and healthcare insurance fund, Realistic picture of situation for managing purposes.
Health insurance fund	Healthcare system financing and planning	Receives and processes data on provided services submitted by healthcare institutions.	Receiving more accurate data
Healthcare protection office	Organizing and planning healthcare services	Receives and processes data submitted by healthcare institutions	Receiving more accurate data
Ministry of health	Legislation of healthcare services	Interprets reports submitted by health care office and healthcare insurance fund	Making decisions based on more accurate data

Strategic Reform of Healthcare System until the year 2015, promoted in the publication "Better Healthcare for Everybody in the Third Millennium" (2004).

The project "Development of the Healthcare Information System for Basic Healthcare and Pharmaceutical Services" started on November 15, 2004. The main goal of this project is the implementation of Electronic Healthcare Documentation (interconnected EHD) into the Serbian Healthcare Information System (HIS).

Strategic goals of the project are [15]: to contribute to raising the level of responsibility in the Serbian healthcare system, to ease the transition process towards evidence-based healthcare system for the purpose of expenditure control and avoidance of repetition in the process of providing basic healthcare services and drug prescriptions, to establish a national healthcare information system based on e-health principles and adequate standards of medical informatics.

Specific operational goals of the project are [15]: to develop an electronic healthcare information system, as the essence of national healthcare information system, based on European and other international standards on EHD, localized and adopted on the national level, to develop and implement a national center for interconnected EHD in Belgrade and four regional centers for interconnected EHD in Belgrade, Novi Sad, Nis and Kragujevac through the pilot implementation in Pancevo; these centers will ensure data exchange on the patient level as well as generation and dissemination of information through adequate infrastructure, to recommend adequate legislative measures necessary for implementation and proper functioning of the system, with an accent on data privacy, protection and safety, in compliance with European legislative regulations, and to recommend an organizational and institutional frame which will ensure sustainability and enable further expansion of the interconnected EHD system.

Besides the Healthcare Center Savski Venac, few other centers have developed the system, such as Healthcare Center Vranje, Healthcare Center Mladenovac, Healthcare Center Zemun, Clinical Center of Serbia, Clinical Center Kraljevo, Healthcare Center Zrenjanin, Healthcare Center Uzice, etc. Based on previous experience, there emerges the necessity of reaching a consensus, a widely accepted solution on electronic healthcare record contents and development of technical standards that will make these records easily accessible and safe [15].

The results of internal researches in Healthcare Center Savski Venac showed that a large amount of effective working hours is being spent on filling in different kinds of forms, daily and monthly reports (about 30% by doctors and even up to 70% of working hours by nurses). According to the new system, right after the check-in moment on the reception desk, patient's data are being forwarded into the doctor's computer and the doctor is able to see the daily list and examination schedule at every moment. A new approach enabled by the information system is not based only on computer use, but also on the doctor-nurse teams formed according to the latest EU recommendations. For instance, while the doctor is performing medical examination, a nurse enters general data, and while the doctor is prescribing therapy or further specialist examinations, the nurse prepares patient for further examinations. By using the same computer simultaneously, required data are entered only once by one of the team members and on the same location. The stored data are afterwards easily accessible for the statistics and accounting departments and can be easily forwarded to higher instances [16].

This kind of approach reduces waiting time for the patients and improves quality of healthcare services provided. Implementation of the electronic healthcare record does not change examination duration, but does change the effective period of time that the doctor can dedicate to his patient.

Centralized model of data collection and management is being developed and will enable organized and standardized inflow of information from all organizations, ready for analytical processing at any time. This model does not exclude local storage and processing of data, but enables simultaneous transparent availability, both on the centralized and local level. This is achieved by integration and collection of data in real time through the centralized data repository [15].

The development of e-health in Belgrade is currently directed mainly towards development of necessary infrastructure, but implementation of certain applications is expected shortly, such as electronic drug prescription, permanent medical summary, electronic record etc. There are initiatives in progress for the acquisition of necessary equipment for institutions, development of local computer networks and connection with dislocated clinics and computer connection between pharmacies and healthcare centers. Intensive efforts are being made in Belgrade Pharmacy to further develop the present network and create conditions for faster drug disburse, and there are several local computer networks realized with funds from National Investment Plan as well as the complete communication infrastructure of Clinical Center "Dragiša Misović" [15].

Several other projects in different healthcare institutions are being realized in cooperation with the European Agency for Reconstruction (EAR), Health Insurance Fund and Ministry of Health.

In order to speed up the development of e-health in Belgrade and Serbia, it is necessary to ensure extraordinary cooperation between all participants in the project, because the essence of the following reforms in the healthcare system is closely connected to informatics systems.

Figure 3 shows the network infrastructure in Serbia, which includes four regional key-points (Novi Sad, Belgrade, Kragujevac, Nis) and the National Key-Point in Belgrade. It should enable the safe exchange of data on the health of patients.

Each of the four regional key-points includes several districts as defined now (there are 25 districts in Serbia without Kosovo). Accordingly, new levels of management in the healthcare system are being defined.

The key-points are connected in a virtual network of the healthcare system through the national network infrastructure. Centers for electronic healthcare documentation are at the key-points of the national network infrastructure of the

healthcare system. These centers are equipped with servers (Internet/Web, Application & Database) and a large database management system.

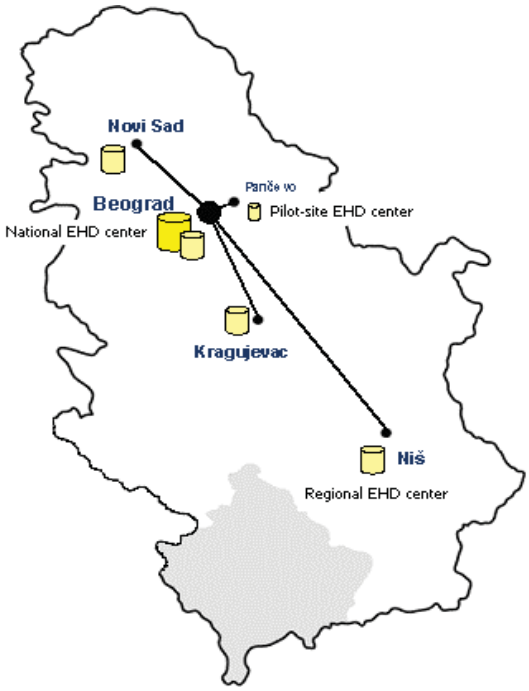

Fig. 3 – Infrastructure of the electronic healthcare documentation (EHD) system network in Serbia

Electronic healthcare system in the Health Center Vranje has been established in the following services: General Medicine Clinic, Pediatrics Clinic, School Clinic, Occupational Medicine Clinic, Women Health Care Clinic. After three months of the pilot project implementation at the Health Center Vranje the following improvements have been noticed in terms of efficiency and cost savings, as shown in Table 2 [17].

In addition to time savings made by patients, medical and administrative staff, the coordination between the Health Center Vranje and Pharmaceutical Institution Vranje is satisfactory, due to the fact that electronic prescriptions patient data are loaded in the pharmacy software for 1 second per prescription (Table 3) [17].

Currently, the Ministry of Defense of the Republic of Serbia is aimed at the development of electronic health system which includes introduction of military electronic health cards, as well as a rapid implementation of certain applications such as electronic drug prescription, durable medical summary, electronic records [18].

The usage of electronic ID cards reduces costs in the Ministry of Defense produced by an inadequate and uneconomical use of available resources – human, material, financial and information. It also increases productivity and data and information safety in information systems.

The card contains two chips – a contact and a contactless [18]. There is an electronic record of data about a card holder in the visual part of the contact chip. The chip has

Table 2

Time of serving patient and data processing in the Health Center Vranje

Serving activities	Time serving	
	Before EHS	Using EHS
Patient time from arrival at the doctor's to departure with the given treatment	24 min	12 min
Time for a doctor necessary to type referral, findings and prescriptions (average)	9 min	2 min
Time for nurses to enter the protocol, write prescriptions, enter accounts for the insured	9 min	2 min
Time used by administrative staff to summarize all reports on a monthly basis	It is not possible to accurately measure	1 min

EHS – Electronic Health System

Table 3

Time of serving patient and data processing in the Pharmaceutical Institution Vranje

Serving activities	Time serving	
	Before EHS	Using EHS
Patient time from arrival to the Pharmaceutical Iinstitution to a prescription issuance	3.5 min	<1 min
Statistical analysis of all prescriptions by services, departments, sectors	It is not possible to accurately measure	1 min

EHS – Electronic Health System

In the pilot project of the Ministry of Health and the Institute for Health Insurance of the Republic of Serbia, the implementation of electronic healthcare system has been made in the Health Center Vranje. Coordination of business processes of the electronic healthcare system implementation project directly depends on three systems, as follows: the Institute for Health Insurance main branch Belgrade, the Institute for Health Insurance branch Vranje and the Health Center Vranje.

such characteristics that it can accept all the other contents needed for record, by using security system to protect those contents from being accessible to unauthorized personnel. In terms of protection, the chip meets the highest standards.

On the body of the card there are the following data: name, identification number, capacity, serial number, personal number of the insured, issuing date and expiry date of the document, whereas the official data such as rank, military

post, place of service, name of unit or institution, which a person with an issued electronic card belongs to, will be filled in the chip [18] (Figure 4).

Fig. 4 – Electronic health card applied at the Ministry of Defense and the Serbian Armed Forces [18]

The introduction of electronic health cards in healthcare system of the military insured is an integrating factor for the entire future military healthcare information system. Their introduction and application will ensure an organized and synchronized connection of military healthcare facilities. The usage of electronic cards and gradual linking of all healthcare institutions in an internal computer network will enable the creation and safe use of a centralized electronic healthcare documentation. The main characteristics of access to the centralized EHD are patient orientation, the exchange of information about health of patients in order to improve health services and reduce treatment costs [19].

The centralized EHD establishment and electronic health cards implementation will enable the linking of medical data from different sources (electronic patient cards from the Military Medical Academy, military medical centers, pharmacies), forming a complete „health picture" of a patient and providing data about a patient, such as allergies, reactions to certain drugs, contraindications, etc., currently available to a doctor in order to make the process of treatment efficient and effective [19–21].

The use of ICT in the Republic of Serbia vs. the European Union countries

In the Republic of Serbia there is an interest and positive attitude of the population to electronic healthcare system introduction. This attitude stems from the fact that ICT are increasingly used in everyday life activities.

The Statistical Office has done research on ICT usage in the Republic of Serbia in 2010, and it includes the territory of the Republic of Serbia (excluding Kosovo) where it was found that 19.7% of citizens connect to the Internet to get health information [22].

In the EU countries the majority of general practitioners use computers at their work, and more often communicate with their patients electronically – according to a survey released by the European Commission on the use of electronic healthcare system. The data show that 87% of general practitioners use computers, out of which 48% have the Internet access. Doctors increasingly use computer for data storage as well as sending laboratory results to patients via e-mail [23].

The use of ICT in health care has enabled the improvement of health services and shortened waiting time for patients, according to a survey conducted in 27 EU countries and in Norway and Iceland. The member of the European Commission for Information Society and Media Vivianne Reding said: "This research shows that the time has come now for everyone in the health sector to use the electronic services because they can significantly contribute to the service quality rendered to patients throughout Europe" [23].

However, within the EU there are great differences in the use of ICT in healthcare. For instance, in Denmark 91% of general practitioners use the Internet, and in Romania only 5%. Denmark is the country with the best access to the Internet, and about 60% of medical practices use e-mail as an usual way of communicating with their patients, while the EU average is only 4% [23].

Only 6% of physicians on average in the EU issue prescriptions over the Internet, while such practice is present only in 3 countries. A total 97% of doctors in Denmark issue online prescriptions, 81% in Sweden and 71% in the Netherlands. As for telemedicine, which enables doctors to have the remote control of disease development with their patients or monitoring chronic diseases, things are still in their infancy. Such services are offered by only 9% of physicians in Sweden and 3% in the Netherlands and Iceland [23].

In 2005 statistical research was conducted in the EU countries regarding the use of electronic medical records in healthcare institutions. The most advanced in this process is Finland, where 95% of physicians used electronic medical records, and the following were Sweden and the Netherlands. In the same year, by the same criterion, the worst in the European Union were Spain, Greece and finally France (17% of physicians who use electronic medical records) [10].

The presented data show that there was still some maladjustment to electronic healthcare system. Most doctors agree that ICT improves the quality of offered services. As the main reason for not using ICT, doctors state the lack of training and technical support [23].

Figure 5 shows the percentage of doctors who used electronic medical records in the EU countries in 2005.

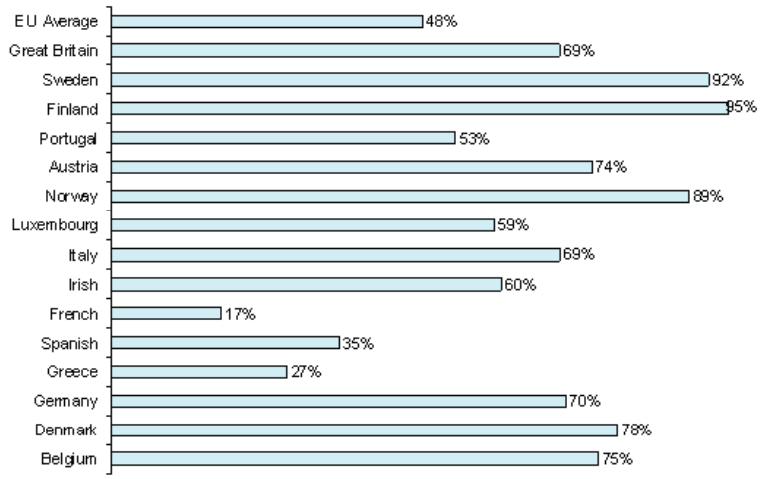

Fig. 5 – The percentage of doctors who used electronic medical records in the EU [24]

The results of electronic healthcare system development in the Republic of Serbia so far

The review of e-healthcare system development in the Republic of Serbia in relation to the Development Action Plan until 2015 shows that there have been made significant IT components and laid the foundations for the future integrated health information system of the Republic of Serbia. The following has been done so far [25]: a central database of the insured has been established; the information network from the Directorate of the Institute for Health Insurance of the Republic of Serbia to all branches and offices has been established; the Central Information Service (CIS) in the Republic Institute for Public Health "Batut" has been made with the established health care resource base. CIS is also a portal that will serve health system users. CIS contains information about all 284 healthcare institutions, 124.000 employees and medical equipment; intensive work on training of final users and testing of CIS functionality; four pilot projects in hospitals (Kraljevo, Valjevo, Vranje and Zrenjanin), have been made with whole ICT infrastructure and purchased computer equipment; a variety of professional, medical and demographic data, information on allergies, medical history, laboratory analyses results, data on received treatments, information about scheduled procedures and examinations are clearly structured, which enables an easy and fast access to the entire patient documentation.

The following is planned in the project continuation: the improvement of software for reporting; the improvement of software for laboratories: it is necessary to connect laboratory instruments and information system, so that the results are automatically sent to an information system; the improvement of software for radiology systems: connection of radiology systems and information system – image scanners, X-ray, magnetic resonance; the implementation of information system related to all health centers (158) in the Republic of Serbia.

Project delivery of improved local services (DILS) of the Ministry of Health needs to complete computerization of the health system by 2011 and that during the 2012 achieve connectivity with other departments. The plan is to integrate the whole system by 2015 in order to better and more accessible health care.

Conclusion

The main objectives of the development of health system are building a comprehensive and integrated electronic healthcare system, which will enable the collection and management of all data relevant to a complex healthcare system of the Republic of Serbia with the help of the latest information and communication technologies.

E-health system provides a foundation for a new approach to organizing and carrying out business processes in healthcare system supported by information and communication technologies. The main features of the new approach are orientation to a patient, health care based on evidence, exchange of information about the health of a patient in order to improve health services and reduce costs.

When you begin to implement electronic health system in Serbia, it is assumed that such a system will increase the capacity of collection, storage, copying, transmission, sharing and manipulation of information, perhaps in a way that people do not expect.

Introduced an electronic health system is of a strategic importance because it will mean a simpler procedure for users of healthcare system services, easier and more reliable operation of health professionals at primary, secondary and tertiary level of health care, more efficient control of the status of the insured and more efficient and effective process of treatment.

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Plastična reorganizacija ljudskog motornog korteksa

Plastic reorganisation of human motor cortex

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Key words:
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Uvod

Ubeđenja prema kojima su svojstvo nepromenjivosti i odsustvo mogućnosti preoblikovanja ili funkcionalne reorganizacije, relevantna obeležja centralnog nervnog sistema (CNS) odraslih sisara, predstavljala su jednu od centralnih dogmi neurobiologije XX veka. Za dugo vreme prevladavao je konsenzus prema kojem razvojno stariji delovi mozga, ali i sam neokorteks, nakon perioda ranog razvoja i maturacije nervnog sistema, predstavljaju stabilne i nepromenjive strukture. Jedini izuzetak, prema takvom konceptu, predstavljali su procesi učenja, praćeni promenama sinaptičke transmisije, koji se dešavaju isključivo u regionima odgovornim za formiranje memorije, poput hipokampusa i girusa dentatusa – lokacijama na kojim i u odraslom dobu dolazi do formiranja novih neurona, drugim rečima, lokacijama sa visokim plastičnim potencijalom. Međutim, kumulacija dokaza iz eksperimenata na životinjama, gde su primenjivane metode invazivne mikrostimulacije i mapiranja moždane kore, već od 80-tih godina prošlog veka donose nova saznanja koja se odnose na plastične promene na različitim nivoima, kako na nivo reprezentacionih mapa, tako i na promene u aktivnosti manjih grupa neurona ili čak i pojedinačnih sinapsi. Korak po korak, usvajani su stavovi prema kojima plastična reorganizacija moždane kore zauzima svoje mesto u permanentnoj interakciji organizma sa spoljašnjom sredinom. Iz takvih shvatanja proistekla je i savremena definicija kortikalnog plasticiteta kojom se obuhvata niz adaptivnih promena funkcionalnih ili morfoloških svojstava moždane kore u procesima interakcije sa spoljašnjom sredinom i/ili nakon patoloških procesa i oštećenja mozga [1].

Motorna kora je zauzela centralnu ulogu u istraživanjima ove vrste, te postala na neki način ogledni poligon namenjen razobličavanju starih dogmi i dokazivanju novih principa. Ne sasvim slučajno, ovaj deo moždane kore, pored visokog potencijala plastične reorganizacije, pruža jedinstvenu mogućnost kontinuiranog praćenja izlaznih signala, sa visokom vremenskom rezolucijom, putem registrovanja amplituda izazvanih motornih odgovora [(motorni evocirani potencijali (MEP)]. Međutim, prepreku prenosu saznanja stečenih u eksperimentima na životinjama, predstavljao je razvoj tehnologije, kao i u brojnim oblastima medicinskih istraživanja. Razvojem metoda neinvazivne kortikalne stimulacije, koje danas obuhvataju transkranijalnu magnetnu stimulaciju (TMS) i transkranijalnu stimulaciju istosmernom strujom (tSIS) (*transcranial direct current stimulation* – tDCS), pokrenut je niz bezbednih eksperimenata na ljudima, u kojima se pokušalo reprodukovati opažanje poreklom iz invazivnih eksperimenata na životinjama, sa ciljem prevazilaženja barijere vrste, i integracije novih saznanja u oblast humane medicine – od fiziologije pa sve do mogućnosti modulacije narušenih funkcija.

Metode neizvazivne kortikalne stsimulacije

Od ove dve navedene metode, kako prema vremenu uvođenja, tako i prema višestrukom značenju ove tehnike, TMS je predstavljala prekretnicu u okviru translacionih istraživanja vezanih uz plasticitet mozga kod ljudi. Pored mogućnosti registrovanja izazvanih odgovora poreklom iz motornog sistema, čime je obezbeđeno kontinuirano praćenje postignutih promena, primenom specifičnih obrazaca ponavljane stimulacije TMS-om podstiču se promene nadražljivosti motorne kore (korelat plastične reorganizacije) koje se održavaju izvesno vreme i nakon prestanka stimulacije. U prvoj nameni prostog registrovanja tekuće moždane aktivnosti, primena pojedinačnog magnetnog pulsa (TMS), polaganjem stimulativnog kalema na glavu ispitanika, u regionu re-

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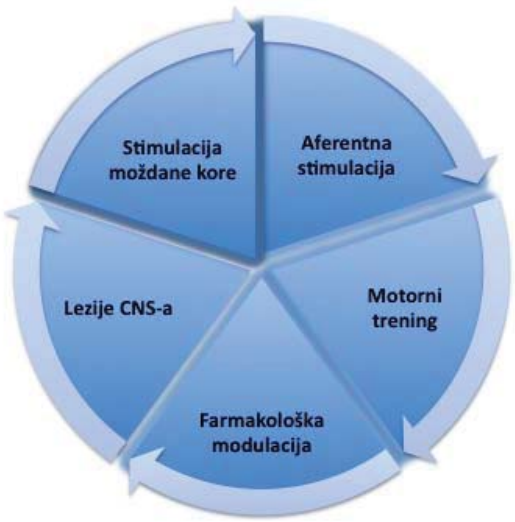
prezentacije primarne motorne kore, u skladu sa Faradeyovim zakonom elektromagnetne indukcije, indukuje magnetno polje, čije su linije toka sile usmerene vertikalno u odnosu na ravan kalema [2]. Ovakvo promenjivo magnetno polje, nadalje, indukuje sekundarno električno polje niskog intenziteta u samim površnim slojevima moždane kore (do dubine 1–2 cm), te na taj način pobuđuje neuralne elemente motornog korteksa [3]. Ovakva bezbolna i neinvazivna stimulacija ima za posledicu niz descendentnih pražnjenja (tzv. I-talasi) duž kortikospinalnih aksona sa visokom frekvencijom (oko 600 Hz) koji vode aktivaciji alfa motoneurona izazivajući pokrete i registrovanje kompleksnog sinusoidnog odgovora sa relativno kratkom latencijom (20–25 ms) u ciljnom mišiću kontralateralne strane tela (elektromiografski signal). Složenija analiza nivoa ekscitabilnosti motorne kore kod ljudi sprovodi se pomoću tehnike primene sparenih magnetnih pulseva (*paired pulse stimulation*) u kratkim interstimulusnim intervalima (ISI) koji se uzastopno oslobađaju kroz isti stimulativni kalem [4]. Pri kratkim ISI (1–4 ms) test puls biva inhibiran pripremnim pulsem (kondicionirajućim), za razliku od dužih intervala (8–15 ms) kada test puls biva facilitiran. Brojni dokazi upućuju na to da test inhibicije pulsa pripremnim stimulusom potpragovnog intenziteta jeste kortikalni fenomen, budući da su serijom eksperimenata isključeni doprinosi sa supkortikalnog ili spinalnog nivoa [5].

Međutim, za drugu namenu TMS-a, kao metode koja intereferira sa moždanom aktivnošću na način da čak može da menja obrasce funkcionisanja, primenjuju se isključivo strukturisani protokoli sa ponavljanjem stimulusa, koji su definisani intenzitetom, vremenskim konstantama koje odvajaju uzastopne pulseve, kao i ukupnim brojem stimulusa. Fiziološki mehanizmi aktivacije neuralnih struktura, u ovom slučaju, nisu ni približno jednostavni kao pri primeni pojedinačnih pulseva koji međusobno ne inteferiraju, budući da ponavljana stimulacija izaziva mešavinu ekscitatornih i inhibitornih efekata, a pored svega pojedini od aktiviranih neuralnih elemenata imaju projekcije ka daljim kortikalnim ili supkortikalnim strukturama, ostvarajući efekte i na udaljenim mestima.

Razvoj novih arteficijelnih metoda manipulacije kortikalnim plasticitetom u procesu oporavka narušene motorne funkcije, zasnovan je na poznavanju relevantnih podsticaja plastičnoj reorganizaciji mozga, kako je to već prethodno utvrđeno u animalnim eksperimentima. Takva istraživanja pokazala su da pokretači plastičnih promena mogu biti različiti oblici eksperimentalnih intervencija dajući primarni značaj bihejvioralnim manipulacijama (slika 1): izmenama u prilivu aferentnih ulaznih signala u senzomotorni korteks (poreklom bilo iz taktilnih ili proprioceptivnih projekcija); iskustvu vezanom uz vršenje pokreta usmerenih ka sticanju motorne veštine (motorni trening ili motorno učenje), tzv. plasticitet podstaknut upotrebom; ali u isto vreme ne zapostavljajući niti sagledavanje preostalih mogućnosti: farmakološka modulacija plasticiteta primenom lekova sa specifičnim delovanjem na neurotransmiterske sisteme CNS-a; plasticitet podstaknut lezijama i patološkim procesima u okviru CNS-a; plasticitet podstaknut stimulacijom moždane kore.



Sl. 1 – Pokretači kortikalnog plasticiteta

Manipulacije senzornim iskustvom

Somatosenzorne ulazne informacije neophodne su prilikom obavljanja kompleksnih motornih zadataka, kao i tokom procesa usvajanja novih motornih veština [6]. Veoma dugo je poznato da aferentni signali poreklom iz kutanih i mišićnih receptora mogu menjati nadražljivost neuronskih populacija senzorimotorne kore mozga kod viših primata [7], ali i kod ljudi [8]. Značaj aferentnih ulaznih signala definisali su eksperimenti u kojima su pojedine strukture u okviru ovih ascendentnih projekcija bile ledirane. Tako je započeto sa pokušajima unilateralne deaferentacije ekstremiteta kod majmuma, presecanjem zadnjih korenova spinalnih nerava, što je razvijalo kod životinja sklonost da ne upotrebljavaju deaferentovani ekstremitet [9]. Komplementarni pravci istraživanja obuhvatali su invazivna mapiranja somatosenzitivnog korteksa nakon presecanja perifernih nerava [10], amputacija prstiju [11] i veštačke sindaktilije (spajanje susednih prstiju životinja uz pomoć hirurških šavova) [12]. Ova istraživanja potpomogla su nastanak koncepta receptivnih polja (grupe perifernih receptora koji usmeravaju aferentni dotok informacija sa senzornih "površina" ka "pojedinačnim" neuronima korteksa) iz čega su pretpostavljene mogućnosti topografske reorganizacije somatosenzitivnog korteksa. Nedostajuća potvrda ovih mogućnosti kod ljudi uskoro se pojavila kroz magnetoencefalografsku (MEG) studiju kortikalne reorganizacije kod sedamnaestogodišnjaka, koji je u saobraćajnoj nesreći doživeo nadlakatnu amputaciju [13]. U ovom detaljnom prikazu bolesnika data je reorganizacija kortikalne reprezentacije šake i podlaktice, tako što je bolesnik prilikom dodirivanja kože lica doživljavao percepciju dodira izgubljenog ekstremiteta. Sumnje nije više moglo biti – fenomen kortikalne reorganizacije kod ljudi postao je činjenica.

Međutim, manipulacija dotokom senzornih informacija započeta je pojačanjem aferentnih somatosenzitivnih ulaznih signala. Ponavljana kutana stimulacija distalnih falangi (jagodica) jednog ili više prstiju (pritisak na rotirajući disk sa

neravnom površinom) majmuna tokom 60–90 dana, pokazalo se, vodila je ka uvećanju mapa kortikalne reprezentacije stimulisane šake na somatosenzitivnom korteksu [14]. Opservacione studije, ponovnom primenom MEG, prikazale su da se slični fenomeni dešavaju i kod ljudi u slučajevima pojačane profesionalne upotrebe šake. Tim putem, utvrđeno je postojanje izrazite hemisferne asimetrije mapa somatosenzorne reprezentacije šaka kod profesionalnih muzičara na žičanim instrumentima, budući da leva šaka odgovara visokozahtevnom motornom zadatku hvatova na vratu instrumenta [15]. Na osnovu ovih saznanja vezanih za plastičnu reorganizaciju somatosenzitivnog korteksa pristupilo se različitim modelima arteficijelne stimulacije aferentnih somatosenzitivnih projekcija poreklom iz perifernih receptora, primenom električkih ili vibratornih stimulusa [16–19]. Primenjivost ovakvih modela pojačane aferentne modulacije u skorije vreme testira se i u kliničkim pilot studijama [20, 21].

Suprotno ovom, deprivacija aferentnih somatosenzitivnih ulaznih signala nije sagledavana u okviru mogućnosti primene u cilju oporavka motorne funkcije kod ljudi, s obzirom na poznate činjenice, da se redukcijom dotoka ovih informacija, nakon primene lokalne anestezije remeti motorna kontrola čak i kod zdravih ispitanika [22]. Međutim, koncept smanjenog dotoka aferentnih infromacija, u početku sasvim zapostavljen kao moguće terapijsko sredstvo, vremenom je, kroz patološke studije na ljudima, dobio novu dimenziju. Širenje kortikalne reprezentacije šake na štetu regiona lica, kod bolesnika sa facijalnom paralizom, bio je jedan od prvih nalaza u ovom smeru [23]. Dakle, usvojeno je saznanje prema kojem i redukcija dotoka aferentnih informacija u somatosenzitivnu koru može voditi ka porastu kortikalne ekscitabilnosti susednog regiona – preduslovu plastične reorganizacije. Eksperimentalne studije na ljudima koristile su model privremene ishemijske deaferentacije podlaktice naduvavanjem manžetne sfingomanometra iznad nivoa sistolnog pritiska, čime je izazivan porast MEP amplitude u mišićima proksimalno u odnosu na blok [24]. U kliničkoj studiji koja se poslužila istim principom, motorni trening sprovođen neposredno nakon regionalnog anestetičkog bloka proksimalnog dela brahijalnog pleksusa, kod osoba sa parezom šake, koje su moždani udar pretrpele pre više godina, rezultovao je značajnim poboljšanjem motorne funkcije [25]. Model dieferentacije zasnovan je na kompeticiji susednih telesnih regija (npr. nadlaktica *vs*. šaka) za teritoriju reprezentacije senzorimotornog korteksa, pri čemu je ovaj efekat posebno izražen u slučaju uporednog motornog treninga paretične grupe mišića.

Plasticitet podstaknut upotrebom

U svakodnevnom životu čovek primenjuje niz raznovrsnih motornih veština koje je sticao tokom razvoja, kroz kontinuirana ponavljanja i interakciju sa sredinom koja ga okružuje. Usvajanje novih veština postiže se kroz ponavljana izvršavanja motornih zadataka (motorni trening), koji nadalje vode ka poboljšanju pokreta [26]. Opisane vrste adaptacije u procesu savladavanja pokreta, smatraju se danas jednim od najsnažnijih stimulusa koji pokreću funkcionalnu reorganizaciju motornog korteksa.

Ovo se pre svega odnosi na učestala i ponavljana izvođenja pojedinih pokreta, sa pažnjom usredsređenom na motorni zadatak, u sklopu sticanja i/ili održavanja profesionalne motorne veštine (vrhunski sportisti, muzički virtuozi).

Suprotno tome, u uslovima produžene redukcije senzorimotorne aktivnosti, kakva se viđa kod imobilizacija ekstremiteta (prelomi, distorzije i sl) koje za posledicu imaju izrazitu hipotrofiju, odnosno redukciju mišićne mase i snage, dolazi i do opadanja veštine motornog izvođenja. U nekoliko dosadašnjih studija prikazana je reorganizacija primarnog motornog korteksa kao posledica dužeg inaktiviteta, kod ljudi nakon imobolizacija ekstremiteta usled fraktura [27, 28]. Studija Liepert i sar. [28] prikazala je redukciju mapa kortikalne reprezentacije za mišiće koji su bili imobilizovani. S druge strane, u radu Zanette-ija i sar. [27] amplitude MEP ispitanika se umanjivala nakon prinudne redukcije upotrebe, ali u isto vreme bez promena ekscitabilnosti na spinalnom nivou, čime je razrešena mogućnost plastičnih promena u segmentnoj distribuciji kao posledici inaktiviteta.

Mehanizam plasticiteta podstaknutog upotrebom u nastanku promena kortikalne reprezentacije pojedinih pokreta kod ljudi upoznat je kroz seriju fizioloških eksperimenata, u kojima je TMS primenjivan u kombinaciji sa farmakološkim agensima za koje je poznato da interferiraju sa sinaptičkim plasticitetom. Blokada plasticiteta zavisnog od upotrebe postignuta je primenom lorazepama, pozitivnog alosteričkog modulatora na receptorima tipa $GABA_A$ i dekstrometorfana, leka koji blokira aktivnost NMDA-tipa glutamatnih receptora, neophodnu za indukciju fenomena dugoročne potencijacije (DP) u motornoj kori. Suprotno ovome, primena D-amfetamina vodila je jačanju plasticiteta zavisnog od upotrebe na način da su promene postajale dugotrajnije [29].

Farmakološka modulacija plasticiteta

Eksperimenti na životinjama u kojima je razmatrana modulacija plasticiteta farmakološkom manipulacijom različitim neurotransmiterskim sistemima označila je noradrenergičku i dopaminergičku stimulaciju, kao potencijalne promotere kortikalnog plasticiteta, suprotno primeni agenasa sa GABA-ergičkim delovanjem, koji jačajući inhibiciju okludiraju plastične promene [30]. Naime, noradrenalin potencira fenomen DP u vizuelnom korteksu pacova, primenom specifičnog obrasca repetitivne stimulacije koje oponaša teta ritam hipokampusa (*theta-burst*), čime se povećava depolarizujući odgovor na tetaničku reakciju, i nadalje, u toku trajanja tog odgovora, povratno povećava membransku provodljivost kontrolisanu NMDA tipom glutamatnih receptora [31]. U motornom korteksu pacova noradrenalin, nadalje, povećava ekscitabilnost velikih piramidalnih ćelija sloja V slabljenjem sporih K+ struja, i jačanjem perzistentnog influksa Na^+ [32], što je verovatno dovoljno za promovisanje fenomena DP u motornom korteksu. Međutim, u kliničkoj praksi, neposredna primena noradrenalina nije moguća, usled niza neželjenih efekata, a primena amfetamina takođe je ograničena u primeni, s obzirom na kardiovaskularne rizike ili eventualne mogućnosti razvoja adikcije [33]. Stoga, pažnja je posebno usmerena ka mogućnostima pospešivanja dopaminergičke tran-

smisije u procesima oporavka i kortikalne reorganizacije, na šta upućuju i pojedine kliničke studije [34]. Ovakve pretpostavke odnedavno su našle uporište i u fiziološkim studijama, primenom neinvazivne kortikalne stimulacije kod ljudi [35, 36].

Plasticitet podstaknut lezijama

Plasticitet podstaknut lezijama nervnog sistema obuhvata čitav niz poremećaja funkcija nervnog sistema, bilo u vidu već opisanih izmena priliva aferentnih ulaznih signala sa nivoa perifernih receptora ili sa segmentnih nivoa (oštećenja spinalne medule) ili neposrednih lezija supkortikalnih i kortikalnih struktura (infarkt mozga, trauma, multipla skleroza). Ovaj podsticaj verovatno odražava teleološko značenje kortikalnog plasticiteta budući da „sistem" brzo odgovara reorganizacijom, u pokušaju ponovnog zadobijanja kontrole nad oštećenim ili izgubljenim funkcijama. Upravo ishemijski infarkt mozga predstavlja bolest – model sagledavanja plasticiteta podstaknutog lezijom u procesima oporavka, istražujući istodobno sinergističko delovanje molekularnih, sinaptičkih i regionalnih mehanizama plasticiteta [37]. Nizom istraživanja pokazano je na animalnim modelima i kod osoba koje su doživele moždani infarkt, da neoštećeni regioni korteksa, u okolini lezije (penumbra), mogu prihvatiti (u većoj ili manjoj meri) senzomotorno procesiranje, koje je ranije pripadalo zonama nepovratno oštećenim ishemijom [38]. Na eksperimentalnom modelu pokazane su dugotrajne promene u smislu porasta ekscitabilnosti neurona, uz porast glutamatergičke aktivnosti posredovane putem NMDA i ne-NMDA tipova receptora do četiri nedelje nakon eksperimentalne okluzije *a. cerebri mediae*, kao i indukcije DP fenomena, koja je u perilezionalnom korteksu pojačana do sedmog dana nakon akutnog razvoja moždane ishemije [39]. Takođe, utvrđeno je i postojanje dugoročnog oštećenja gabaergičke inhibitorne transmisije, kako u neposrednom okruženju fokalne ishemije, tako i u kontralateralnoj hemisferi [40]. Sumarno i dugoročno praćenje promena kortikalne ekscitabilnosti pokazalo je da se vrhunac promena meri trajanjem u nedeljama, ali da perzistira i mesecima nakon inicijalnog insulta. Naime, za period tzv. dugoročnog perioda oporavka nakon moždanog infarkta (≥ 6 nedelja), na animalnom modelu pokazana je pojačana sinaptogeneza, na apikalnim dendritima piramidnih neurona sloja V u regionu periinfarciranog korteksa (na rastojanju kraćem od 0,5 mm u odnosu na granicu sa ishemijskim tkivom) [41]. U istom smislu, već od ranije prisutna su zapažanja o zavisnosti procesa aksonske regeneracije (mereno ekspresijom GAP 43) sa ishemijom tokom prve dve nedelje [42]. Međutim pored jačanja sinaptogeneze, anatomske studije su pokazale da i lokalne i distalne intrakortikalne projekcije bivaju izmenjene ishemijom, što se smatra svojstvom intrinzičke plastičnosti samog korteksa [41].

U proučavanju funkcionalnih mehanizama nakon infarkta mozga poseban doprinos pružile su studije u kojima je primenjivan TMS. Kod bolesnika sa visokim stepenom motornog hendikepa u akutnoj, ali i hroničnoj fazi nakon moždanog udara, opisana je redukcija inhibicije kako za oštećenu [43], tako i za neoštećenu hemisferu [44–46]. Objašnjenje zapažanja vezanih za redukciju intrakortikalne inhibicije oštećenog motornog korteksa, u akutnoj fazi, moglo bi biti povećana senzitivnost gabaergičkih neurona na ishemiju, ili što je još verovatnije – kompenzatorni mehanizam „popuštanja" toničke gabaergičke inhibicije u nastojanju da se demaskiraju intrakortikalne horizontalne veze na putu reorganizacionih promena kortikalnih mapa senzorimotornog korteksa. Naime, longitudinalno praćenje ovih bolesnika pokazuje da se redukcija inhibicije tako izražena u akutnoj fazi, ipak postepeno normalizuje tokom vremena [46, 47].

Plasticitet podstaknut stimulacijom moždane kore

Pojavom neinvazivne tehnike TMS dobijena je metoda kojom su se mogle oponašati invazivne stimulacije na eksponiranom korteksu eksperimentalnih životinja ili, još dalje od toga, na modelima pojedinačne neuronske sinapse. Usled toga, prilikom elaboracije pojedinih modela neinvazivne kortikalne stimulacije upotrebljavaju se termini poreklom iz bazične neurofiziologije. Otkriće prolongiranog pojačanja sinaptičke transmisije nakon primene tetaničke stimulacije, fenomen poznat kao DP – *long term potentiation* (LTP), označilo je tokom poslednjih 40 godina jednu od najznačajnijih oblasti istraživanja u neuronaukama – plasticitet zavisan od aktivnosti (*activity-dependent plasticity*), sposobnost mozga da se preoblikuje u smislu memorije, učenja, poboljšanja motornih i kognitivnih funkcija [48]. Međutim, za razliku od jednostavnih modela stimulacije, izučavanjem vremenske specifičnosti asocijativne sinaptičke modifikacije u regionu hipokampusa utvrđeno je suštinsko značenje redosleda pre- i postsinaptičkih pražnjenja [49]. Ukoliko presinaptičko pražnjenje prethodi postsinaptičkom unutar vremenskog „prozora" od nekoliko desetina milisekundi, dolazi do indukcije DP, za razliku od obratnog redosleda (*post*-pre) čime se izaziva slabljenje sinaptičke transmisije, fenomen poznat kao dugoročna depresija (DD) – *long term depression* (LTD). Stoga, ovakav oblik DP/DD plasticiteta zavisnog od aktivnosti naziva se danas plasticitet vremenski zavisan od pražnjenja (*spike timing-dependent plasticity*) [50], a savremeni protokoli neinvazivne stimulacije korteksa upravo nastoje da repliciraju navedene obrasce. Ipak, ovaj translacioni koncept i do danas trpi kritike. Naime, sagledavajući u celini strukturnu i organizacionu kompleksnost cerebralnog korteksa, nije jednostavno uspostaviti neposrednu analogiju između animalnih modela i primene na ljudima. Površna analogija govorila bi da frekventno-zavisna kortikalna stimulacija primenom repetitivne (rTMS)-a može na kortikalnim sinapsama ljudi podstaći promene koje su na mehanicističkom nivou nalik onima koje viđamo pri indukciji DP/DD fenomena na eksperimentalnim životinjama. Ove pretpostavke, naravno, podržane su zapažanjima prema kojima najdelotvorniji TMS protokoli oponašaju prethodno uspešne obrasce stimulacije u eksperimentima na životinjama. Dalja analogija, koja se i upotrebljava kao argument, odnosi se na farmakološku modulaciju indukovanih fenomena. Naime, ukoliko pojedini farmakološki agens (sa poznatim delovanjem na neurotransmisiju u CNS-u) prevenira indukciju DP ili DD kod glodara, pretpostavlja se slično delovanje i na induktivne protokole kod ljudi. Međutim, praćenjem promena MEP amplitude kao

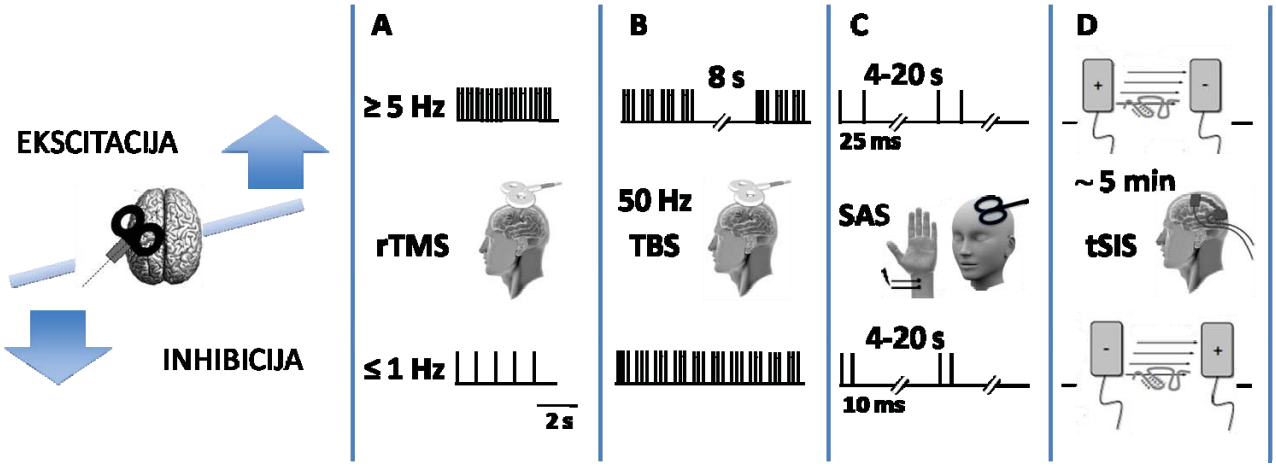
osnovnog pokazatelja plastične modulacije – izlazne informacije iz sistema, treba imati na umu da su originalno mehanizmi DP i DD monosinaptički događaji, dok je MEP amplituda kao posredni efekat, udaljena od mesta stimulacije čitave tri sinapse. Dakle, bez sumnje, optimalni način praćenja promena indukovanih stimulacijom bilo bi registrovanje „događaja" već na prvoj sinapsi, što je za sada rutinski nedostupno. Studije u kojima se obavljaju ove vrste tzv. direktnih registrovanja kod ljudi, uz pomoć elektroda položenih u epiduralni prostor ispitanika, nose dimenziju invazivnih ispitivanja, i primenjuju se samo u eksperimentima verifikacije pojedinih fizioloških principa (*proof of principle studies*). Ipak, primena metoda neinvazivne kortikalne stimulacije, uz puno razumevanje ograničenja koje donosi, predstavlja najbolju aproksimaciju sinaptičkih događaja kakvu danas poznajemo.

Uporedo sa razvojem niza protokola TMS, došlo je do ponovnog „buđenja" i tehnike nefokalne stimulacije korteksa istosmernom strujom niskog intenziteta (1–2 mA), tzv. (tSIS; tDCS). Suprotno pojedinačnom magnetnom pulsu koji izaziva MEP u ciljnom mišiću, transkranijalna primena istosmerne struje niskog intenziteta (1–2 mA) uslovljava modulaciju kortikalne ekscitabilnosti, fiziološkim mehanizmima različitim u odnosu na TMS, a bez neposrednog izazivanja elektrofiziološki merljivog odgovora na periferiji [51]. Suštinska razlika ovih dvaju tehnika, pa tako i njima srodnih primena, odnosi se na činjenicu da magnetni puls primenjen nad korteksom odgovara natpragovnom (*suprathreshold*) nadražaju sa fenomenološkim efektom izazivanja MEP u ciljnom mišiću. Dakle, reč je o neurostimulativnoj tehnici koja, uz odgovarajući broj ponavljanja (obrasci repetitivne stimulacije), uzrokuje i neuromodulatorni efekat. Za razliku od TMS, pri kortikalnoj primeni električne struje izazivamo isključivo neuromodulatorni efekat, budući da je stimulacija potpragovna (*subthreshold*) i ne uzrokuje MEP već isključivo interferira sa moždanom aktivnošću.

Pionirske studije primenom magnetne stimulacije korteksa kod ljudi, sprovedene sredinom 90-tih godina, potvrdile su princip uzlazne modulacije ekscitabilnosti motorne kore rTMS pri frekvenciji od 20 Hz [52], kao i silaznu modulaciju primenom obrasca niskofrekventne stimulacije od 1 Hz [53]. Međutim sprovođenje originalnih protokola kakve poznajemo iz animalnih eksperimenata (npr stimulacija frekvencijom 100 Hz tokom 1 sekunde), nisu, naravno, bile moguće zbog tehničkih ograničenja (pregrejavanje kalema magnetnog stimulatora), pre svega zbog toga što bi ovakva stimulacija kod osetljivih osoba mogla izazvati „nekontrolisani" porast ekscitabilnosti i eventualne epileptičke napade. Ovo su razlozi zbog kojih studije kod ljudi ne predstavljaju autentične replike visokofrekventnih protokola stimulacije, na način na koji se oni primenjuju na životinjama. Stoga, pored obrazaca monotone kortikalne stimulacije, koji su definisani isključivo frekvencijom, razvijeni su i TMS protokoli u kojima se primenjuju strukturisani obrasci stimulacije, ili kortikalna stimulacija sparena sa aferentnom stimulacijom u strogo definisanim ISI.

U cilju boljeg razumevanja fizioloških osnova intervencionih protokola sa primenom TMS, moguće su analogije prema fiziološkim obrascima neuronalne aktivnosti od nivoa pojedinačnih neurona do čitavih suppopulacija: tonička pražnjenja (*tonic spiking*), karakterisana unimodalnom distribucijom intervala između pojedinačnih pražnjenja; pražnjenja u salvama (*bursting*), dinamičko stanje u kojem neuroni opetovano okidaju u diskretnim grupama ili salvama pražnjenja, iza kojih sledi period mirovanja (*quiescence*) (u zavisnosti od broja pražnjenja u salvama ovi nizovi se nazivaju dubleti, tripleti, kvadripleti itd); kao i prelaznim stanjima, između dva navedena osnovna funkcionalna moda.

Sledeći navedene analogije, protokoli rTMS koji se aktuelno primenjuju mogu se podeliti na (slika 2): I – frekventno-zavisne (analog plasticitetu zavisnom od aktivnosti –



Sl. 2 – Protokoli neinvazivne kortikalne stimulacije – mogućnosti bidirekcionalne modulacije plasticiteta. Panel A pokazuje obrasce visoko- (gornji deo) i niskofrekventne repetitivne transkranijalne magnetne stimulacije (rTMS) (donji deo); panel B pokazuje *theta-burst* stimulaciju (TBS), u gornjem delu facilitatorni protokol intermitentne TBS (obratiti pažnju na postojanje pauza), u donjem delu inhibitorni protokol kontinuirane TBS; panel C prikazuje sparenu asocijativnu stimulaciju (SAS) uz interstimulusne intervale (ISI) 25 ms (gornji deo) pojačanje ekscitabilnosti motornog korteksa, za razliku od inhibitornog protokola sa ISI 10 ms (donji deo); panel D – transkranijalna stimulacija istosmernom strujom (tSIS), anodni oblik (gornji deo), katodna stimulacija (dole)

activity-dependent plasticity) – obrasci ritmičke i toničke stimulacije moždane kore: a) sa unimodalnom distribucijom ISI – niskofrekventna TMS (< 1 Hz), visokofrekventna TMS (> 5 Hz) i b) sa multimodalnom distribucijom ISI intervala (strukturisana stimulacija); pr. theta-burst TMS – obrazac stimulacije moždane kore pražnjenjem u salvama (multimodalna distribucija interstimulusnih intervala i intervala između salvi) [54] – kontinuirani *theta-burst* TMS (kTBS); intermitentni *theta-burst* TMS (iTBS); i II – intervalno zavisni protokoli rTMS (plasticitet vremenski zavisan od pražnjenja – *spike timing-dependent plasticity*): a) kombinovana kortikalna stimulacija rTMS i periferna električna stimulacija i protokol sparene asocijativne stimulacije (SAS), kombinovanjem nisko frekventne rTMS i periferne aferentne stimulacije u striktnom ISI [55] i b) repetitivni TMS u intervalima periodiciteta I-talasa (*spike-timing dependent plasticity*) – primena parova stimulusa [56], primena tripleta stimulusa [57] i primena kvadripleta stimulusa [58].

U pogledu dosadašnje primene predloženih protokola izdvajaju se TBS i SAS protokoli, gde prvi odgovara interveniconom protokolu, kojim se oponašaju prirodni (inherentni) ritmovi mreža neuronskih populacija, kao što je slučaj sa *theta*-ritmom (5 Hz) hipokampusa [59]. Originalni TBS protokol Huang-a i sar. [54], tzv. intermitentni obrazac teta-pražnjenja podrazumevao je 600 magnetnih pulseva, niskog intenziteta (80% vrednosti praga podražaja) u 20 epizoda od po tri stimulusa (frekvencije od 50 Hz, što odgovara intervalima između pojedinačnog stimulusa od 20 msec), uz pauze od po 8 sec, što je vodilo ka porastu MEP amplitude u periodu od oko 20 min. Suprotno ovom, ukoliko se pauze izostave, model nazvan kontinuiranim obrascem teta-pražnjenja, vodio je ka padu MEP amplitude.

Pored navedenog obrasca "čiste" kortikalne stimulacije, u upotrebi je i SAS protokol, koji oponaša obrazac tzv. Hebb-ovog asocijativnog plasticiteta, prema kojem snaga sinapsi može biti modulirana usaglašenom aktivnosti poreklom iz dva izvora, u striktnoj vremenskoj korelaciji – model plasticiteta vremenski zavisnog o pražnjenjima. Prva eksperimentalna replika ovog principa, primenom metoda neinvazivne kortikalne stimulacije kod ljudi upotrebila je periferni električni stimulus (niske frekvencije, a trostruko višeg intenziteta u odnosu na perceptivni prag) prezentovan ispitaniku iznad *n. medianus* u predelu ručnog zgloba, iza čega usledi magnetni puls nad kontralateralnom hemisferom u odgovarajućoj motornoj prezentaciji ciljnog mišića tenara, pri ISI od 25 milisec [55]. Postintervenciono praćenje pokazalo je da su promene odražene porastom amplitude izazvanih motornih odgovora (DP – sličan efekat) maksimalno izražene tokom narednih sat vremena, da se na preintervencione vrednosti vraćaju kroz 24 časa, da su striktno topografski specifične, te da zavise o aktivaciji NMDA receptora [60]. Testiranjem spinalne ekscitabilnosti (registrovanje F-odgovora) i električnom stimulacijom moždanog stabla potvrđeno je kortikalno poreklo opaženih fenomena. Naknadni eksperimenti koji su pratili isti model utvrdili su depresiju amplitude MEP, u trajanju od oko 90 min, ukoliko bi se ISI skratio na 10 milisec (DD – sličan efekat). Efekat se može blokirati primenom NMDA antagonista (dekstrometorfan) ili antagonista voltažno-zavisnih kalcijumskih kanala (nimodipin) [61]. Ukupno uzevši, u nizu sprovedenih eksperimenata izvedeni su zaključci da procesima sličnim DP ili DD u regionu primarnog motornog korteksa kod ljudi (*in vivo*) upravljaju striktna pravila Hebb-ovog modela učenja. Ovaj protokol je danas namenjen prvenstveno analizi fizioloških mehanizama plasticiteta [62, 63] i patofizioloških abnormalnosti plasticiteta kod neuroloških oboljenja [64].

Poznavanje navedenih pokretača kortikalnog plasticiteta u patološkim stanjima i razumevanje mehanizama njihove aktivacije u željenom pravcu, predstavlja osnov strategije obnove neuroloških funkcija. Posebno značenje ovog koncepta usmereno je ka potencijalu kompenzacije hroničnih motornih deficita, nastalih više godina unazad, čime se napušta dugi period terapijskog nihilizma. Naposletku, u budućim istraživanjima je neophodno posvetiti pažnju visokoj interindividualnoj varijabilnosti promena kortikalne nadražljivosti kod bolesnika, kao i činjenici da klinički ispoljen deficit često predstavlja neto efekat uporednih kortikalnih i supkortikalnih oštećenja. Stoga, pred nama stoji put u pokušaju što egzaktnijeg definisanja obrazaca funkcionalnih abnormalnosti, sa ciljem razvoja terapijskih programa prilagođenih pojedincu. Razvoj kompleksnih neinvazivnih protokola kortikalne stimulacije i modulacije funkcije, u sinergiji sa odgovarajućim farmakološkim agensima i programima motornog treninga, otvaraju nove mogućnosti u tom pravcu.

Zaključak

Plasticitet motornog korteksa odnosi se na reorganizacione adaptivne promene pod uticajem relevantnih interakcija sa spoljašnjom sredinom. Pored plasticiteta pokrenutog lezijom, funkcionalna svojstva motornog korteksa kod ljudi mogu biti menjana putem bihejvioralnih i farmakoloških manipulacija, kao i specifičnih obrazaca neinvazivne kortikalne stimulacije. Transkranijalna magnetna stimulacija i tSIS predstavljaju inovativne, bezbedne i neinvazivne tehnike modulacije nadražljivosti humanog motornog korteksa, u pokušaju oponašanja stimulativnih protokola izvedenih iz sinaptičke fiziologije. Pored toga, tehnika TMS prikazala se prikladnom u proučavanju reprezentacionog plasticiteta na sistemskom nivou kod ljudi. Svrsishodna modulacija plastičnih promena motornog korteksa primenom različitih rehabilitacionih strategija zasnovanih na detaljnom proučavanju pokretača plasticiteta otvara novu nadu za one sa hroničnim motornim deficitom.

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GENERAL REVIEW

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Radionuclide treatment of metastatic disease in patients with differentiated thyroid carcinoma

Lečenje metastatske bolesti radionuklidom kod bolesnika sa diferenciranim karcinomom tiroideje

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Key words:
thyroid neoplasms; thyroidectomy; iodine; elements, radioactive; drug therapy; radiotherapy; radionuclide imaging; risk factors; prognosis.

Ključne reči:
tireoidna žlezda, neoplazme; tireoidektomija; jod; elementi, radioaktivni; lečenje lekovima; radioterapija; scintigrafija; faktori rizika; prognoza.

Introduction

In general, the therapy of differentiated thyroid carcinoma (DTC), includes initial treatment and follow-up of patients. Nowadays, there is no universal accepted consensus regarding initial treatment of DTC patients. Several countries have their own guidelines and recommendations for treatment of DTC [1–5]. Beside all controversies, mostly accepted recommendation regarding initial treatment of DTC includes total or "near" total thyreoidectomy followed by the therapy with radioactive iodine (^{131}I). Radioiodine ablation of postoperative thyroid remnants is usually recommended in all DTC patients regardless their stage (low or high risk of cancer-specific mortality and risk of relapse), due to easier monitoring of thyroglobulin (Tg) [6]. Thyroglobulin is a glycoprotein that is produced by normal or neoplastic follicular thyroid cells. In the absence of thyroglobulin antibodies (TgAb), undetectable Tg after the thyroid stimulating hormone (TSH) stimulation is a valid parameter of remission and the absence of metastases. On the other hand, detectable or increasing Tg during follow-up indicates the appearance of metastatic disease. After radioiodine ablation, a life-long suppressive therapy with L-thyroxine should be prescribed to all DTC patients. Rarely, a palliative therapy including external beam radiation therapy and chemotherapy is recommended [7].

After the initial treatment, all DTC patients should be monitored life long, with the aim to detect persistent disease or recurrence. Each check-up should include laboratory analyses (thyroid hormones, TSH, Tg and TgAb) and ultrasonography of the neck. The result of diagnostic whole-body scintigraphy (WBS) with ^{131}I (^{131}I-WBS) is influenced by thyroid carcinoma affinity to accumulate ^{131}I in the presence of high concentration of TSH achieved by one-month L-thyroxine withdrawal or with intramuscular application of human recombinant TSH [7]. Whole-body scintigraphy is routinely performed as a routine check-up (a year after the radioiodine ablation), and thereafter in cases suspected for recurrence only [8]. Magnetic resonance imaging (MRI) and computed tomography (CT) are useful for detection of neck and mediastinal metastases [9]. Magnetic resonance is useful especially in non-iodine-avid and mediastinal metastases [10]. Fluorodeoxyglucose (^{18}F-FDG) positron emission tomography fused with computed tomography (^{18}F-FDG-PET/CT) is a modern diagnostic procedure that is important in detection of non-iodine-avid metastases [11]. Computed tomography is useful in visualization of small lung metastases, but is rarely performed due to iodine contrast interference with iodine therapy [12].

Local and regional metastases in differentiated thyroid carcinoma patients

Local recurrence and/or regional neck metastases usually appear during the first years of follow-up in approximately of 5%–20% DTC patients. Regional neck metastases represent about 60%–75% of all neck metastases. They are usually detected by neck ultrasound (in about 94% of cases), or by increased Tg levels or WBS (in 50% of cases) [13]. However, these recurrences are not palpable if they are soft, small or located in a central neck compartment or behind the great neck vessels. Metastatic neck lymph nodes appear at ultra-

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sound as round, hypoechoic, with microcalcification and cystic components, hypervascularized at Doppler ultrasound which can detect metastatic lymph nodes in early stage of disease if they are a few milimeters sized only. Fine needle aspiration (FNA) of lymph node suspicious of recurrence is important in detection of regional metastases, since Tg determination in the aspirate increases accuracy of cytologic report [9].

The Tg serum level is not detectable in about 20% of patients with isolated lymph node metastases on L-thyroxine therapy. Thyroglobulin level remains undetectable after TSH stimulation in approximately 5% of these patients. Whole body scintigraphy detects metastases in about 60%–80% of patients with clinical neck lymph node recurrences (Figure 1). Mediastinal lymph node metastases are usually combined with distant lung metastases. Recurrences in soft tissues or invading aero-digestive tract appear in less than 10% of all neck metastases [9].

Distant metastases in differentiated thyroid carcinoma patients

Distant metastases appear approximately in 27% of DTC patients [18]; metastases presented at the time of diagnosis (early metastases) occur in 9% of them, while metastases which appear during the course of disease (late metastases) occur in 18% cases [19]. According to our results, distant metastases appear in 21.2% of DTC patients; the frequency of early distant metastases is 8.5%, while late distant metastases appear in 7.02%. Early metastases are more frequent in papillary carcinomas, while late metastases occur more often in follicular carcinomas. Appearance time of distant metastases does not significantly affect disease-specific survival (DSS) of DTC patients [20].

Patients with high risk for distant metastases appearance are younger than 16 years, older than 45 years, those with histological subtypes of papillary carcinoma (tall cell, columnar cell, diffuse sclerosing) and follicular carcinoma (widely invasive and poorly differentiated), patients with bulky tumors, those with tumors extended beyond thyroid capsule and with nodal metastases, patients who underwent less extensive surgery than total or near total thyreoidectomy, or those with no post-surgical administration of radioiodine ablation [9].

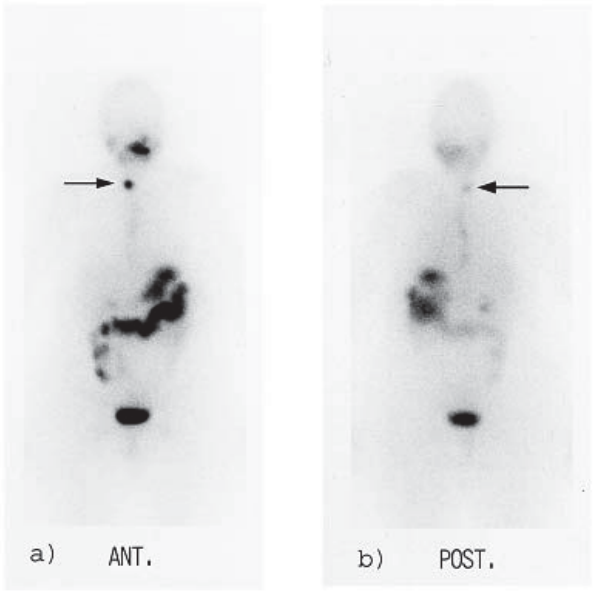

Fig. 1 – Posttherapeutic ^{131}I-WBS (whole-body scintigraphy) detects regional metastasis in the lymph node on the lateral right side of the neck (a – anterior view; b – posterior view)

The most important treatment of locoregional recurrences is surgical removal of metastatic tissue. A mediastinal dissection with additional radioiodine therapy should be performed in case of bulky mediastinal metastases (even in the presence of micrometastases of the lungs). The best effect of ^{131}I therapy is obtained when is a diameter of metastatic lymph nodes is less than 1 cm. Some authors suggest surgical treatment as additional procedure after the ^{131}I therapy as initial treatment of recurrences [14]. External beam radiation therapy is recommended only in patients with non-iodine-avid metastases, those with incompleted surgery and patients with invasion of aero-digestive tract and soft tissue [15]. A combination of external radiation and chemotherapy (doxorubicin in small doses of 10 mg/m^2 weekly) is suggested in extensive and nonoperable recurrences [16].

Tubiana et al. [17] reported the ten-year survival rate of 62% in DTC patients with local and regional recurrences.

Lung metastases are often combined with lymph node recurrences in central neck and mediastinal compartment (Figure 2). Papillary carcinomas usually extend lymphogeneously to the lungs, while follicular carcinomas extend hematogeneously to the lungs and bones. Distant metastases are usually located in lungs (57%), bones (24%), spine, pelvis, long bones, ribs, sternum, the base of the scull. One third of metastases in bones represent solitary bone metastases. Lung metastases associated with bone metastases occur in 16% patients, while metastases in liver, brain and skin appear in 3% of the patients [21].

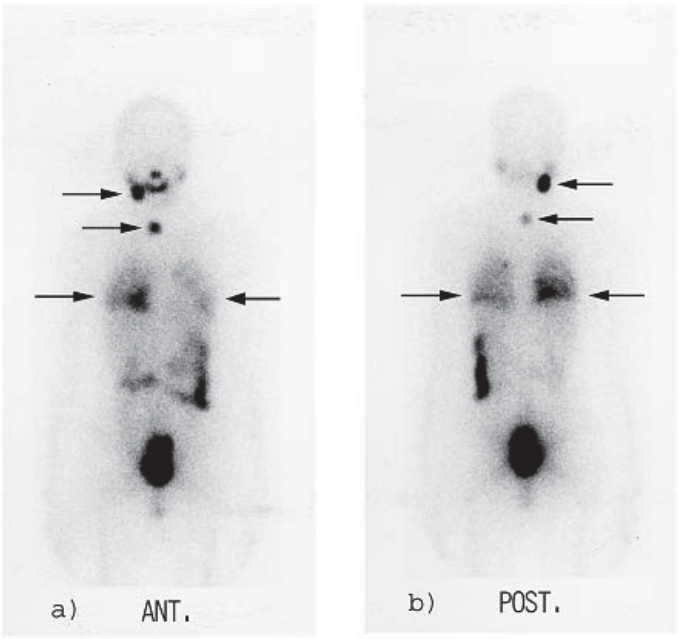

Fig. 2 – Posttherapeutic ^{131}I-WBS (whole-body scintigraphy) shows regional recurrence in submandibular lymph node on the right side, and distant metastases in the upper mediastinum and both lungs (a – anterior view; b – posterior view)

Surgery should be the primary treatment of bone metastases. This treatment is not recommended if multiple lung metastases are present. Radioactive iodine is accumulated only in 2/3 patients with distant recurrences, but is able to destroy only a small tumor foci. Radioactive iodine is performed in activity ranged from 5.55 to 7.4 GBq in adults, every 6 months during the first 2 years, and thereafter annually until complete ablation of residual uptake on posttherapeutic ^{131}I-WBS. Most patients are cured with cumulative activity of ≤ 18.5 GBq. Even the fact that risk of secondary carcinoma and leukemia increases with higher cumulative activity of ^{131}I, there is no limit for cumulative activity which can be performed in DTC patients with metastatic disease. If there is no uptake on posttherapeutic ^{131}I-WBS, any further radioiodine therapy is useless (Figure 3) [9, 22]. In these patients with so-called non-iodine-avid metastases, the exact localization of tumor deposits is possible with ^{18}F FDG-PET/CT (Figure 4).

Fig. 3 – Posttherapeutic ^{131}I-WBS (whole-body scintigraphy) of the patients with increased thyroglobulin serum level does not detect radioiodine uptake due to the presence of non-iodine-avid metastasis (a – anterior view; b – posterior view)

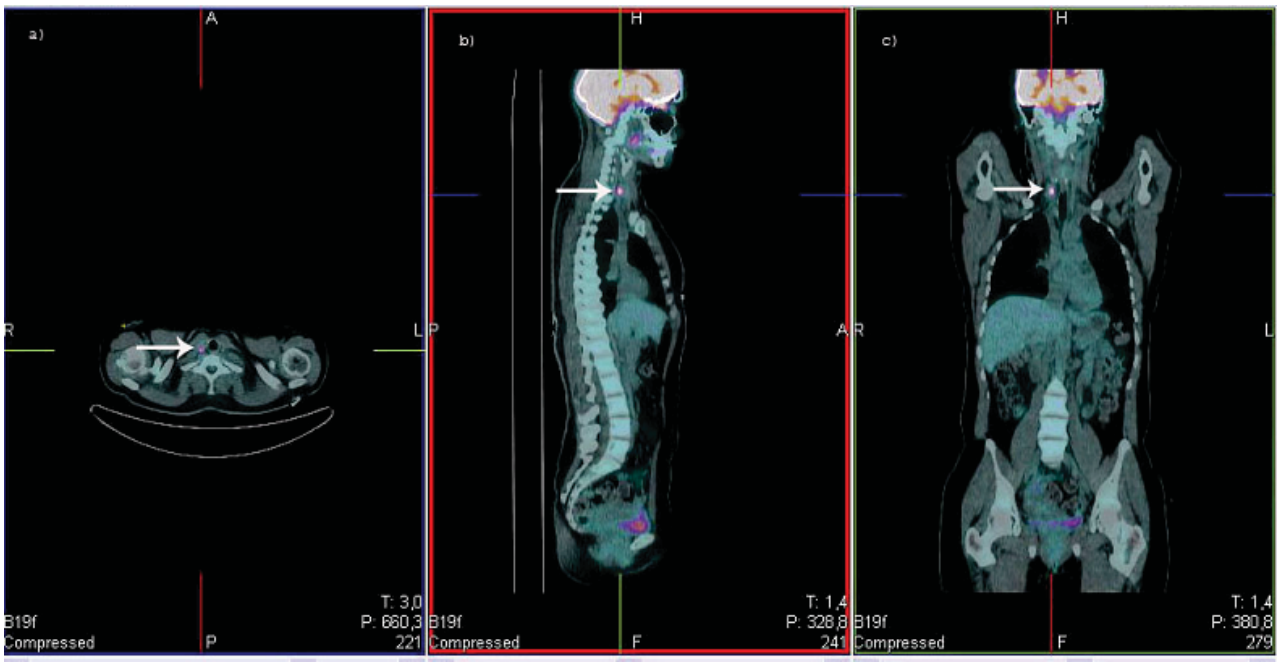

Fig. 4 – The FDG PET/CT (fluorodeoxy glucose positron emission tomography/computed tomography) of the same patient (Figure 3), demonstrating the hypermetabolic FDG focus localized in jugular lymph node on the right side, is compatible with recurrent disease

Complementary treatment of DTC includes external beam radiation therapy and chemotherapy. External radiation therapy should be performed in patients with non-operable and non-iodine-avid bone metastases. The metastases are located in vertebral column, near the base of the scull, sites where pathological fracture would cause a serious disfunction. In patients with iodine-avid bone metastases, a combined therapeutic protocol should be performed: radioiodine therapy followed by external radiation therapy, and afterwards additional ^{131}I therapy should be applied in the interval of 3 to 6 months. The doses of radiation should be 30 Gy for 15 days, or 40 Gy for 28 days. Chemotherapy should be performed in patients with progressive recurrent disease refractory to ^{131}I. In about 33% patients, there is a response to doxorubicin treatment (dose of 60 mg/m^2 every 3–4 weeks). Combination of doxorubicin-cysplatine has similar response, but greater toxicity. Treatment with interferon-α, interleukin-2 (alone or associated with doxorubicin) and somatostatin analogs usually result with no treatment response [9].

Complete remission (CR) after radioiodine therapy occurs in 33%–50% of DTC patients with distant metastases which accumulate radioiodine, and in 83% patients with normal chest radiography at the time of detection of recurrences, in 53% patients with micronodular lung metastases and in 14% patients with macronodular lung metastases [21].

Overall survival after 10 years from the detection of distant metastases is 25% to 40%. Prognostic factors such are iodine-avid distant metastases, younger age at the time of distant metastases diagnosis and metastases limited in extension indicate better prognosis [9]. The study performed in our institution from 1977 to the end of 2005 included 75 DTC patients with distant metastases treated by ^{131}I therapy. Our results suggest few prognostic factors which significantly affect the disease-specific survival (DSS) of DTC patients with distant metastases: age, histological type of the tumor and initial treatment. We found that the survival of DTC with distant metastases is significantly shorter in patients of 45 years or older than in patients below 45 years, with a highly statistically significant difference ($p = 0.0001$). According to the tumor histology, patients with papillary metastatic thyroid carcinoma have significantly longer survival than patients with follicular metastatic thyroid carcinoma ($p = 0.0138$). Our data also suggest that patients who underwent adequate initial treatment (including total or near total thyroidectomy followed by ^{131}I therapy) show significantly longer survival compared to patients initially treated inadequately (nodulectomy, lobectomy, loboisthmectomy or subtotal thyroidectomy, alone or combined with ^{131}I therapy, $p = 0.0351$). On the contrary, we detected that the gender of DTC patients with distant metastases has no influence on disease-specific survival ($p = 0.2046$) [23].

The ability to accumulate ^{131}I is also important prognostic factor. In our study, the probability of DSS in patients with iodine-avid metastases is 67% after 5 years, 55% after 10 years and 45% after 15 and 20 years, while DSS in patients with non-iodine-avid metastases is 18% after 5 and 10 years ($p = 0.0006$) [24].

Conclusion

Patients with DTC should be adequately and optimally initially treated including total or "near" total thyroidectomy followed by radioiodine therapy. Those patients should be monitored lifelong in order to detect recurrences on time. The survival of DTC patients with distant metastases is short, but optimal treatment provides better quality of life.

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CASE REPORT

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Possibilities of thermovision application in sport and sport rehabilitation

Mogućnosti primene termovizije u sportu i sportskoj rehabilitaciji

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Abstract

Introduction. Infrared thermography or thermovision is increasingly applicable in sport and sport rehabilitation. Thermic forms, thermic imprints, temperature and isotherm distribution, temperature gradient change are the terms that are more and more often met in sport medicine and medicine, in general. **Case report**. We presented two examples of thermovision application: in detection of muscle injury and changes of the feet exposed to low temperature. In the first example the thermovision method was used for analysing heat distribution in an athlete with back muscles injury. With a special original method of local cooling the place and degree of injury was precisely localized and determined, respectively, regardless high environmental temperature. In the second case the thermovision method was for the first time applied in a runner whose feet was exposed to low temperature. Significant hypothermia of the feet was detected by the method and appropriate treatment was performed. Thanks to this the athlete had no harmful consequences. **Conclusion.** Thermovision is fast and efficient in detecting different kind of injuries, so its increased use in the future can be expected.

Key words:
sports medicine; rehabilitation; athletic injuries; thermal conductivity; treatment outcome.

Apstrakt

Uvod. Infracrvena termografija ili termovizija ima sve veću primenu u sportu i sportskoj rehabilitaciji. Termičke forme, termički otisci, temperaturna i izotermalna distribucija, promene gradijenta temperature jesu pojmovi koji su sve češće prisutni u sportskoj medicini i medicini uopšte. **Prikaz bolesnika.** Prikazali smo dva primera korišćenja termovizijske metode: za otkrivanje povrede mišića leđa i promena na stopalima izloženim niskoj temperaturi. U prvom slučaju termovizija je korišćena u analizi distribucije toplote kod sportiste sa povredom leđnih mišića. Zahvaljujući specijalnoj, originalnoj metodi lokalnog hlađenja, precizno je lokalizovano mesto i određen stepen povrede. U drugom slučaju termovizija je po prvi put upotrebljena u otkrivanju promena na stopalima trkača izloženim niskoj temperaturi. Zahvaljujući ovoj metodi ustanovljena je značajna hipotermija stopala, preduzet je odgovarajući tretman, tako da sportista nije imao štetnih posledica zbog hipotermije stopala. **Zaključak.** Termovizija je brz i efikasan metod u otkrivanju različitih vrsta povreda, pa se može očekivati njena sve veća upotreba u budućnosti.

Ključne reči:
medicina, sportska; rehabilitacija; povrede, atletske; provodljivost, toplotna; lečenje, ishod.

Introduction

Body temperature is determined by heat production generated in metabolic processes and mechanisms that enable the process of thermoregulation. The skin is particularly important as a barrier between the outside and the inside of the body. Normal temperature of the body is between 36.2 and 37.8 ºC. In normal conditions the inside body temperature is several degrees higher than on the skin surface. Temperature starts dropping about 2.5 cm deep into the skin creating a temperature dissipation gradient. Peripheral tissues, like muscles, fat, skin, are able to function in a wider temperature range (20ºC to 40ºC), than inner organs that need lower temperature variation, *ie.* more stable temperature. Temperature changes on the skin have influence on blood circulation, on the receptors for heat in the skin and in the hipotalamus. Heat is lost through the following mechanisms: 60% through radiation in infrared (IR) spectar, 25% through an evaporation, 12% through air circulation, and 3% through conducting.

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In 1977, Clark et al. [1] reported temperature changes on the skin during running. Infrared thermography was used for skin temperature visualization in two athletes during stillness and during running at the air temperature of 20ºC and 11ºC, respectively. Temperature distribution was recorded on the film and analyzed. Paralelly, a method of measuring temperature with thermopar was used. It was concluded that during running the average skin temperature above muscles is significantly different from the average skin temperature during stillness. Both methods of measurement were identical within 1ºC–5ºC. In 1979, Veghte et al. [2] did thermovision measurements of temperature changes during training sessions. That study analyzed dynamic temperature changes on the skin connected to vascular changes following running and other exercises. They noticed rising in temperature (with maximum increase by 1.7ºC) with the increasing difficulty during the exercise, as well as a significant increase in the temperature of the skin on the challenged leg in comparison with the rested leg. Furthermore, Torri et al. [3] and Nakayama et al. [4] noticed an increase in temperature when intensity of the exercise was increased by 20%, 50% and 80%, as well as a significant increase in the temperature of the leg skin that was challenged in comparison with the rested leg. They did studies to determine increase and drop of temperature in different sports, such as running, swimming, and cycling. The initial temperature drop was analyzed on the bicycle in ten healthy males. The examination was done under the weight of 50W–150W in the ambience of a chamber with the temperature ranging from 10ºC to 40ºC and relative air humidity from 45% to 55%. Temperature was measured thermographically and with a thermopar. A drop in tempeature during the exercise did not depend on the season of the year, although perspiration was greater at 40ºC than at 30ºC. They concluded that the temperature drop was not influenced by perspiration but by vasoconstriction, probably caused by non-thermic factors.

First articles on thermovision application to injuries monitoring and treatment were published about thirty years ago [5, 6]. Their authors concluded that injuries can be recognized as a local hypothermia, if an injury is not deep in the tissue.

Case report

We presented two examples of thermovision application: in detection of muscle injury and changes of the feet exposed to low temperature.

The applied protocol included control of room temperature and humidity before thermal recording, as well as 20 min rest and termal body equilibrium (during termal recording, patient must be without movement).

Basic functions of thermal camera M3 were: All the pictures presented in LCD in black and white or in the pallette of 256 colours; picture performances; Spectral range: 8-14 μm; Thermal sensitivity ≤ 120 mK, 30°C; Temperature range -20°C - +250°C, Resolution: 0.1 °C

Modes of measurement were: auto hot-spot trace, spot, area, line profile, and isotherms.

The first case

Thermovision measurement was done on a 19-year-old athlete, 181 cm high, weighing 75 kg. The athlete, a javelin thrower, was chosen after he had injured back during training in the gym, when he had been lifting weights.

The athlete was still after he had taken off his T-shirt so that the body temperature became balanced. Air humidity was 45%, and the air temperature was 28.5ºC. *Musculus erector spinae* was injured. In order to measure the degree of back injury in the acute phase of the injury, pictures were taken immediately and there was no waiting in order to lower the temperature in the room, because the precious time would have been lost.

We applied an original, new method of local cooling of the back region by using spray for cooling injuries, and in that way the first therapy was done. With even movements at the distance of twenty centimeters cooling spray was applied. The technique of even spray application can be easily trained using autospray, where even colour application was practiced. The same technique was applied for local cooling of the body. Soon after the application of cooling spray, regions that were warmer heated the lower temperature of the spray and clearly pointed out the temperature contrast between the injury and the surrounding tissue. It was necessary to determine the extent of injury as soon as possible and locate it precisely in order to start the therapy, as with this type of injury the most important period is several hours in the acute phase.

There were successive thermal pictures made in the time intervals of 1 minute after applying the cooled spray (Figure 1). Application of cooled spray enabled us to use the method of local cooling at the high temperature conditions of 28.5ºC. In that way we were able to precisely localize and determine the extent of muscle injury, and at the same time immediately apply the first therapy.

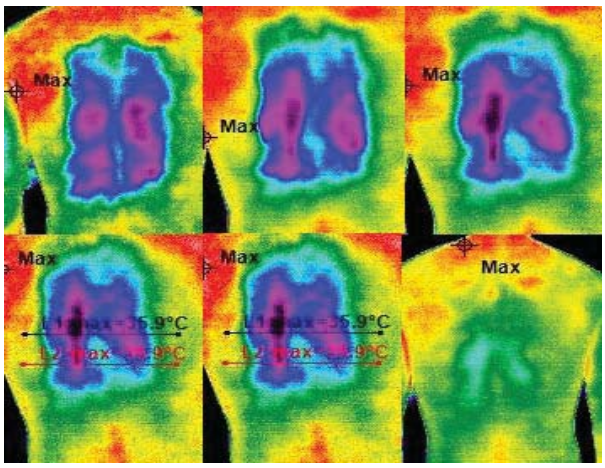

Fig. 1 – Thermal presentation after the application of cooling spray

Gradual heat domineering of the injured muscle that points out the traumatized area (light blue region along the backbone). A temperature region that is light blue, surrounding

the cooled area, is a normal phenomenon of heating of the borders of both the cooled and the non-cooled region. We are interested in the light blue region that appears within the treated region. It shows localization and the extent of injury.

Thermic picture was the same as the clinical picture of the athlete. Figure 2 shows a graph of thermal distribution

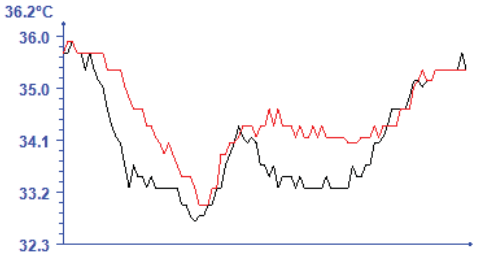

Fig. 2 – A graph of thermal distribution

along the lines L1 and L2 (black and red lines). On the line L1 there is a temperature difference of simmetrical points on the muscle of 0.5ºC, and on the line L2 of 1.2ºC. At the same time it shows the direction of the injury that extends into the lower part of the back where the focus of the injury is. In recording 6 (Figure 1) there is the thermal picture of temperature distribution after 30 minutes. The injury is still clearly noticed.

The second case

In second case, termovision was applied after running. Thermovision measurement was done in a 45-year-old half-marathon runner, 182 cm high, weighing 78.5 kg. The trainers for running made by a branded manufacturer were used. The socks were made from special materials chosen for running, so-called "dry-fit". The procedure was as follows: expose feet at room temperature after runnning, rest 5 min in sitting position, take thermovision photoes. Measurement was done after 10 km of running at the temperature of -2ºC. Fresh, wet snow had fallen before. Immediately after the run, there was a measurement with thermovision camera, done inside. Checking and making photos for comparison were done at one of the following days in the ambience at similar temperatures, but in dry weather, when feet were not wet.

In this case, a thermovision camera registered hypothermia on the feet, especially on the toes, mostly on the thumb on the right foot. This type of measurement was also new, and had been never recorded before. Thermal picture when feet were exposed to the temperature of -2ºC and humidity, is given in Figure 3. The coolest point was registered at the top of the toe-thumb (14.8ºC). Set squares on thermal pictures automatically find the coolest points. In Figure 4, a temperature gradient along the line L1 from Figure 3 is given. Figure 5 represents a histogram with temperature distribution in the marked square. It can be seen that there was a significant hypothermia in that region. This hypothermia was quickly sanated and did not leave any consequences, except redness and numbness feeling in the next 48 hours. Figure 6 shows a termal picture of the feet, that were dry, at the temperature of -2.5ºC. A significant difference can be seen in the foot temperature (the lowest registered temperature was 25.2ºC).

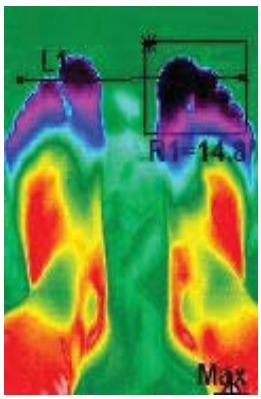

Fig. 3 – Thermal presentation of the feet

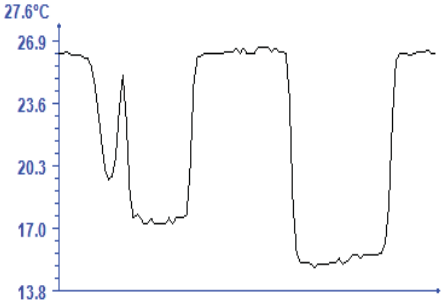

Fig. 4 – Temperature gradient along the line L1 shown in Figure 3

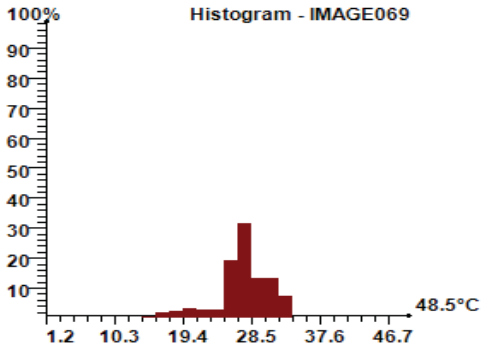

Fig. 5 – Distribution of the training temperature

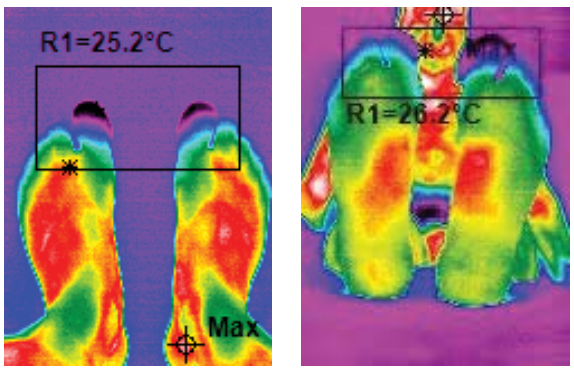

Fig. 6 – Temperature distribution in the feet after training at -2.5 ºC

It is interesting that again the upper part of the right toe-thumb was the coolest point. It can be concluded again that there was a modest disturbance in peripheral circulation in the right foot in this runner, the same as was niticed in his medical history (the runner had modestly varicose veins on the right leg, as a consequence of operation on the vermiform appendix). Besides, in the left leg there was also a significant local hypothermia of 16.8ºC.

Discussion

In the first case thermovision measurement of back injury (*musculus erector spinae*) determined the extent and localization of the injury. A new original method was applied, a method of local cooling that enabled the measurement although the environmental temperature was high. In such a situation measurement must be applied quickly. That is a limitation of the method. Other limitations include conditions when an injury is deep inside the tissue, or when it is impossible to get appropriate enviromental condition.

In the first case presented, thermal picture, distribution of the temperature gradient and clinical picture of the injured athlete were completely the same. The thermal pictures clearly show that the injury was asymmetrical (the injury was localized on the right part of the backbone). Local cooling provided the first therapy and also allowed recording in the high temperature conditions.

In the second case, the method detected local hypothermia of the feet exposed to the temperature of -2ºC and humidity. Under the same ambiental conditions, but with dry feet, there was no hypothermia. The feet were again cooler, but the impact of lower temperature was insignificant. Graphical representation of topology and thermal distribution on the upper part of the right foot point out that at the temperature below zero and if feet are wet, during the long runs (half-marathon, marathon) frostbites of the first degree would occur. The wind influence would additionally aggravate the situation because, according to the chilly scale with the wind blowing at the speed of 10 m/s, it would feel the temperature like that of -10ºC. At the same speed of the wind and temperature of -8ºC, chilly temperature would be -18ºC [8]. Additionally, thermal disbalance was detected, as a direct consequence of the difference in peripheral circulation of the left and right runner's leg, which was the same as in the runner's existing history.

Conclusion

Thermovision is a fast and efficient method in detecting different kind of injuries. Using a new cooling metod it is possible to record termovision pictures even in high enviromental temperatures. Increased use of this method can be expected in the future.

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CASE REPORT

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Heroin addict with gangrene of the extremities, rhabdomyolysis and severe hyperkalemia

Heroinski zavisnik sa gangrenom ekstremiteta, rabdomiolizom i teškom hiperkalemijom

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Abstract

Introduction. Long-time consumption of narcotics leads to altered mental status of the addict. It is also connected to damages of different organic systems and it often leads to appearance of multiple organ failure. Excessive narcotics consumption or abuse in a long time period can lead to various consequences, such as atraumatic rhabdomyolysis, acute renal failure and electrolytic disorders. Rhabdomyolysis is characterized by injury of skeletal muscle with subsequent release of intracellular contents, such as myoglobin, potassium and creatine phosphokinase. In heroin addicts, rhabdomyolysis is a consequence of the development of a compartment syndrome due to immobilization of patients in the state of unconsciousness and prolonged compression of extremities, direct heroin toxicity or extremities ischemia caused by intraluminal occlusion of blood vessels after intraarterial injection of heroin. Severe hyperkalemia and the development of acute renal failure require urgent therapeutic measures, which imply the application of either conventional treatment or a form of dialysis. **Case report.** We presented a male patient, aged 50, hospitalized in the Emergency Center Kragujevac due to altered mental status (Glasgow Coma Score 11), partial respiratory insufficiency (pO_2 7.5 kPa, pCO_2 4.3 kPa, SpO_2 89 %), weakness of lower extremities and atypical electrocardiographic changes. Laboratory analyses, carried out immediately after the patient's admission to the Emergency Center, registered the following disturbances: high hyperkalemia level (K^+ 9.9 mmol/L), increased levels of urea (30.1 mmol/L), creatinine (400 μmol/L), creatine phosphokinase – CK (120350 IU/L), CK-MB (2500 IU/L) and myoglobin (57000 μg/L), with normal levels of troponin I (< 0.01 μg/L), as well as signs of anemia (Hgb 92 g/L, Er 3.61 × 10^{12}/L), infection (C-reactive proteine 184 μg/mL, Le 16.1 × 10^9/L) and acidosis (base excess – 18.4 mmol/L, pH 7.26. Initial examination of the patient revealed swelling and paleness of the right lower leg, signs of gangrene of the right foot and the 1st and the 4th toes of the left foot. The patient had normal values of arterial pressure (130/80 mmHg) and heart rate (64/min^{-1}); roentgenographic lungs examination and computerized tomography (CT) brain examination did not reveal pathological changes in lung and brain parenchyma; toxicological analyses confirmed the presence of heroin in patient's organism. The patient was treated by intensive conventional treatment (infusion of crystalloid solutions, 8.4% solution of sodium bicarbonate, *iv* infusion of diuretics, calcium gluconate and short-acting insulin), and also by antibiotics and anticoagulants. Normalization of kalemia and fast regression of electrocardiographic changes were registered. The patient refused the suggested surgical treatment (fasciotomy, foot amputation). After stabilization of kidney function and improvement of his mental state, the patient agreed to undergo surgical procedure. Therefore, on the day 30 of hospitalization the above-knee amputation of the right leg was performed, and on the day 38 the transmetatarsal amputation of the left foot was carried out. After 46 days of hospital treatment, the patient was released and sent to home treatment. **Conclusion.** The routine laboratory diagnostics, which implies determining of the levels of potassium, urea, creatinine and CK in the serum of all hospitalized heroin addicts can contribute to timely detection of hyperkalemia and acute kidney weakness and undertaking of appropriate therapeutic measures.

Key words:
heroin; overdose; rhabdomyolysis; hyperkalemia; gangrene; foot; diagnosis; differential.

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Apstrakt

Uvod. Upotreba narkotika u dužem vremenskom periodu dovodi do promena psihičkog stanja zavisnika. Ona je, takođe, povezana sa oštećenjem različitih organskih sistema i često dovodi do pojave multiorganske insuficijencije. Ekscesivna upotreba narkotika ili njihova zloupotreba u dužem vremenskom periodu može dovesti do različitih posledica, kao što su atraumatska rabdomioliza, akutna bubrežna slabost i elektrolitski poremećaji. Rabdomioliza se karakteriše oštećenjem skeletne muskulature i posledičnim oslobađanjem intracelularnog sadržaja, kao što su mioglobin, kalijum i kreatin fosfokinaza. Kod heroinskih zavisnika rabdomioliza je posledica razvoja kompartment sindroma zbog nepokretnosti bolesnika u besvesnom stanju i produžene kompresije ekstremiteta, direktne toksičnosti heroina ili ishemije ekstremiteta izazvane intraluminalnom okluzijom krvnih sudova nakon intraarterijske primene heroina. Teška hiperkalemija i razvoj akutne bubrežne slabosti zahtevaju neodložnu primenu terapijskih mera, koje podrazumevaju primenu konvencionalnog ili nekog od oblika dijaliznog lečenja. **Prikaz slučaja.** Prikazali smo muškarca, starog 50 godina, hospitalizovanog u Urgentnom centru Kragujevac zbog izmenjenog stanja svesti (*Glasgow Coma Score* 11), parcijalne respiratorne insuficijencije (pO_2 7,5 kPa, pCO_2 4,3 kPa, SpO_2 89%), slabosti donjih ekstremiteta i atipičnih elektrokardiografskih promena. Laboratorijskim analizama učinjenim neposredno po prijemu bolesnika u Urgentni centar registrovani su sledeći poremećaji: hiperkalemija teškog stepena (K^+ 9,9 mmol/L), povišene vrednosti uree (30,1 mmol/L), kreatinina (400 μmol/L), kreatin fosfokinaze – CK (120350 IU/L), CK-MB (2500 IU/L) i mioglobina (57000 μg/L), uz normalne vrednosti troponina I (< 0,01 μg/L), kao i znaci anemije (Hgb 92 g/L, Er 3,61 × 10^{12}/L), infekcije (C-reaktivni protein – CRP 184 μg/mL, Le 16,1 × 10^9/L), acidoze (bazni eksces – 18.4 mmol/L, pH 7,26). Inicijalnim pregledom bolesnika uočeni su otok i bledilo desne potkolenice, znaci gangrene desnog stopala i 1. i 4. prsta levog stopala. Bolesnik je imao normalne vrednosti arterijskog pritiska (130/80 mmHg) i srčane frekvence (64/min^{-1}), rendgengrafskim pregledom pluća i kompjuterizovanom tomografijom mozga nisu uočene patološke promene u plućnom i moždanom parenhimu, a toksikološkim analizama potvrđeno je prisustvo heroina u organizmu bolesnika. Bolesnik je lečen intenzivnom primenom konvencionalnog lečenja (infuziona primena kristaloidnih rastvora, 8,4% rastvora natrijum bikarbonata, *iv* primena diuretika, kalcijum glukonata i insulina kratkog dejstva), kao i primenom antibiotika i antikoagulantnih lekova. Registrovano je normalizovanje kaliemije i brza regresija elektrokardiografskih promena. Bolesnik je odbijao predloženo hirurško lečenje (fasciotomija, amputacija stopala). Nakon stabilizovanja bubrežne funkcije i poboljšanja psihičkog statusa prihvatio je hirurški zahvat, tako da je 30. dana hospitalizacije učinjena natkolena amputacija desne noge, a 38. dana transmetatarzalna amputacija levog stopala. Nakon 46 dana hospitalnog lečenja, lečenje bolesnika je nastavljeno u kućnim uslovima. **Zaključak.** Rutinska laboratorijska dijagnostika koja podrazumeva određivanje vrednosti kalijuma, uree, kreatinina i CK u serumu kod svih hospitalizovanih heroinskih zavisnika može doprineti pravovremenom otkrivanju hiperkalemije i akutne bubrežne slabosti i preduzimanju odgovarajućih terapijskih mera.

Ključne reči:
diacetilmorfin; predoziranost; rabdomioliza; hiperkaliemija; gangrena; stopalo; dijagnoza, diferencijalna.

Introduction

Upper normal levels of potassium (4.5–5.4 mmol/L), regardless the presence of other diseases, are associated with the increase of cardiovascular mortality [1]. The risk of appearance of "malignant" cardiac arrhythmia and cardiac arrest rises with the increase of potassium concentration in serum, and for kalemia level above 9 mmol/L the undertaken therapeutic measures do not always give positive result. Narcotics abuse is among less frequent causes of hyperkalemia occurrence. Opiates, psychotropic medications, alcohol and analgesics represent substances which are often abused. In different ways, both directly and indirectly, they lead to disturbance of organic systems functioning and to appearance of diseases [2]. In addition to common complications which occur at long-term heroin consumption and heroin overdosing, such as disorders of consciousness, respiratory depression and altered mental functions, these patients may develop numerous neurologic disorders and rhabdomyolysis [3–5]. Severe atraumatic rhabdomyolysis results in a release of intracellular contents and subsequent increase of potassium and myoglobin concentration in serum [6]. Myoglobinuria leads to development of acute renal weakness which must be treated in intensive care units by applying either conventional treatment or a form of dialysis [4, 5].

Case report

A male patient, aged 50, was hospitalized in the Emergency Center due to altered mental status (Glasgow Coma Score 11), respiratory insufficiency (pO_2 7.5 kPa, pCO_2 4.3 kPa, SpO_2 89%), weakness of lower extremities and electrocardiogram changes (Figure 1). Ten hours prior to that, the patient had been admitted to the Psychiatric Clinic with altered mental status (Glasgow Coma Score 10) and suspected heroin overdosing. After the initial examination, there were no indications for application of antidotes, while the signs of severe electrolytic disorders were the reason for continuing the patient's treatment in the Emergency Center.

The patient had been treated in the Psychiatric Clinic for heroin addiction for approximately four previous years by methadone application (prior to the beginning of treatment, the patient had been a heroin user for 15 years). The patient demonstrated a lack of motivation for undergoing detoxication treatment (methadone application), and during previous hospitalization in the Psychiatric Clinic (three months earlier), signs of renal weakness of the second degree (levels of urea of 11.6 mmol/L and creatinine of 145 μmol/L) and initial right foot ischemia had been registered in the patient.

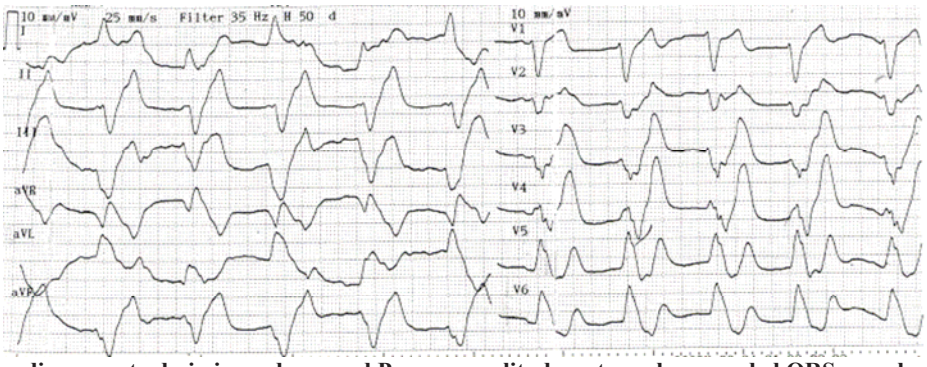

Fig 1. – Electrocardiogram at admission – decreased P-wave amplitude, extremely expanded QRS complexes – above 0.16 s and increased T wave amplitude

Pathological findings were not registered by the initial physical examination of heart and lungs during hospitalization in the Emergency Center. The patient had normal values of arterial pressure (130/80 mmHg) and heart rate (64/min^{-1}). Swelling and paleness of the right lower leg, as well as the signs of gangrene of the right foot and the 1st and the 4th toes of the left foot, were registered in the patient. Laboratory analyses revealed signs of anemia (Hgb 92 g/L, Er 3.61 × 10^{12}/L), infection (creactive protein – CRP 184 μg/mL, Le 16.1 × 10^{9}/L) and acidosis (base excess – 18.4 mmol/L, pH 7.26). Until the admission to the Emergency Center, the patient had oliguria (diuresis lower than 20 mL/hr) and initial laboratory analyses revealed severe hyperkalemia (K^+ 9.9 mmol/L), increased levels of urea (30.1 mmol/L), creatinine (400 μmol/L), creatinine phosphokinase – CK (120350 IU/L), CK-MB (2500 IU/L) and myoglobin (57000 μg/L), with normal levels of troponin I (< 0.01 μg/L). The elevated levels of aspartate transaminase (AST) – 720 IU/L, alanine aminotransferase (ALT) – 235 IU/L and lactate dehydrogenase (LDH) – 3860 IU/L were registered in the patient's serum, with normal values of bilirubin. The initial concentration of fibrin degradation fragment (d-Dimer) in the patient's serum was 2970 μg/L, and prolongation of prothrombin time (INR 1.8) was registered as well. The presence of anti-HCV antibodies was registered in the patient's serum, and toxicological analyses (rapid immunochromatographic Bio Gnost® assay) revealed the presence of heroin, methadone and benzodiazepines in patient's organism. Radiographic lungs examination and computerized tomography (CT) brain examination did not reveal pathological changes in the lung and brain parenchyma. Ultrasound examination of right leg arteries revealed sclerotic changes of walls and locally calcified lesions on femoral artery, with normal flow all the way to its distal parts. From that part, distally, in popliteal and tibial arteries the flow was not registered; instead, a complete occlusion of those arteries by hyperechogenic thrombi (old thrombosis) was detected. The patient was treated by intensive conventional treatment (infusion of crystalloid solutions, 8.4% solution of sodium bicarbonate, *iv* infusion of diuretics, calcium gluconate and short-acting insulin), and also by antibiotics and anticoagulants. There was no need for applying mechanical ventilation; instead, oxygen was applied by nasal catheter. During the first 24 hours of hospitalisation in the Emergency Center, mental status was normalised, as well as values of arterial blood gasses. Since the registered diuresis was satisfactory, with gradual decrease of kalemia (Table 1) and rapid regression of electrocardiographic changes (Figure 2), the application of a form of dialytic treatment was abandoned. From the 7th until the 23rd day of hospitalization the patient was treated in the Clinic for Urology and Nephrology. Ultrasound examination did not reveal any changes of position, size and shape of kidneys, but the presence of bilateral calculosis was observed. On the 8th day of hospitalization, creatinine clearance was 22 mL/min. Despite the existing gangrene on lower extremities, on the tenth day of hospitalization the decrease of CK to the level below 500 IU/L was registered. The patient kept refusing the suggested surgical treatment, although he was treated in the Center for Cardiovascular Surgery since the 23rd day of hospitalization. After stabilisation of the patient's mental status, he agreed to undergo the suggested surgical procedure. Therefore, on the 30th day of hospitalization above-knee amputation of the right leg was performed, and on the 38th day the transmetatarsal amputation of

Table 1

Serial presentation of laboratory analyses

Time	K^+ (mmol/L)	CK (IU/L)	CK-MB (IU/L)	Urea (mmol/L)	Creatinine (μmol/L)	Base excess (mmol/L)	Myoglobin (μg/L)
At admission	9.9	120350	2500	30.1	400	-18.4	57000
After 8 hours	8.2	112000	1700	33.9	489	-5.6	58200
After 24 hours	6.6	87260	987	34.5	502	-2.1	52300
After 48 hours	5.7	51072	473	27.5	460	-3.2	–
After 5 days	5.2	2760	62	26	382	+2.6	–
After 10 days	4.6	486	24	23.5	288	+2.1	–

K^+ – potassium; CK – creatine phosphokinase; CK-MB – creatine phosphokinase-MB

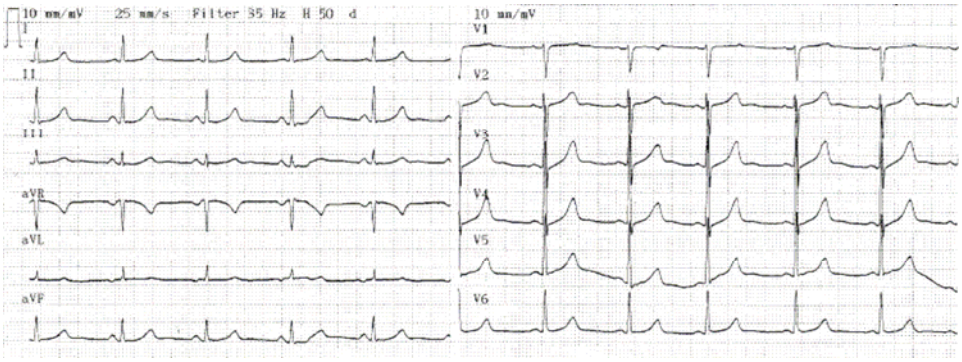

Fig. 2 – Electrocardiogram registered 12 hours after the initial examination

the left foot was carried out. After 46 days of hospital treatment, the treatment was continued in home environment.

Discussion

Heroin addiction leads to nervous system damages, as a consequence of psychic functions disturbance, and also to numerous, seemingly unusual somatic disorders. Acute rhabdomyolysis is a syndrome which rarely occurs, but since it involves injuries of integrity of muscle cells plasma membrane and release of toxic intracellular contents into the circulatory system, it is characterised by potentially serious complications [6, 7]. Rhabdomyolysis may occur due to excessive physical exertion, muscle injury, endocrinologic disorders, infections and exposure to various medications and toxins [3, 4].

Pathophysiology of rhabdomyolysis associated with heroin addicts is obscure. Most authors who study this disorder indicate that pathogenesis of rhabdomyolysis is multifactorial and that it occurs either due to acidosis, hypoxia, muscle compression, direct toxicity and immunologic reactions caused by heroin and various contaminants or due to infections or blood vessels damage caused by intravenous / intraarterial injection of heroin [5, 6, 8–11].

Approximately one third of patients with rhabdomyolysis develop acute renal failure [12]. Unlike pathophysiologic mechanisms cocaine overdosing, where vasospasm of renal arteries and malignant hypertension are responsible for the development of renal insufficiency, heroin, through rhabdomyolysis, leads to massive myoglobinuria, renal tubules obstruction and development of acute renal failure [3, 13]. These patients develop hyperkalemia due to release of potassium from myocytes and the development of acute renal failure. Besides conventional treatment, hyperkalemia often calls for application of some form of dialysis (continuous venovenous dialysis, hemofiltration or hemodiafiltration) [12]. The fact that only in the United States of America there are around 100,000 new registered heroin users in a year emphasizes the importance of treating acute and chronic complications caused by heroin consumption [2].

Hyperkalemia is a potentially fatal condition and is defined as a concentration of potassium higher than 5.5 mmol/L. The risk of appearance of cardiac arrhythmia is directly dependent on hyperkalemia level. In extreme hyperkalemia, fatal arrhythmias such as ventricular fibrillation and asystole are often registered. However, with the application of adequate therapy, the fatal outcome can be avoided even in patients with serum potassium concentration above 10 mmol/L [14]. In patients with severe hyperkalemia electrocardiograms can be different – from normal electrocardiographic records to records which may imitate the existence of ventricular tachycardia or myocardial infarction [15, 16]. Therefore, severe hyperkalemia must be treated in line with its etiology and accompanying disorders.

Our patient had the signs of severe hyperkalemia and acute renal failure. During previous hospitalizations in the Psychiatric Clinic, signs of foot ischemia and renal function decline had been registered in the patient. Since the patient was a long-time heroin addict, he had most probably developed heroin nephropathy over the years. American authors point out the fact that long-time consumption of cocaine and heroin leads to development of chronic renal failure through the appearance of segmental glomerulosclerosis and membranoproliferative glomerulonephritis [2].

In addition to that, long-time intravascular application of heroin and other drugs leads, initially, to damage of small diameter veins, and, over time, damage of large diameter veins and arteries; therefore, in addition to vasospasm, heroin addicts develop many vascular complications on extremities blood vessels, ranging from trombophlebitis, aneurysms and arteriovenous fistulas to occlusions of blood vessels by thrombus or embolus [10, 17].

A preexisting renal failure in our patient, his rejection of addiction treatment by application of methadone and recurring use of heroin resulted in the appearance of severe somatic disorders, such as extremities ischemia, rhabdomyolysis, acute renal failure and potentially fatal hyperkalemia. Aggressive application of infusion solutions, urine alkalization and acidosis correction led to stabilization of renal function and correction of electrolytic disorders even without dialytic treatment. Normal troponin levels, regardless of enormously high CK levels, as well as rapid regression of electrocardiographic changes made possible the exclusion of the presence of acute coronary syndrome. Surgical treatment was suggested (extremity amputation), which the patient accepted only after intensified psychiatric treatment.

In this paper, we have shown that timely application of conventional treatment of severe hyperkalemia in heroin addict with preexisting renal failure and gangrene of the extremities may result in rapid regression of electrocardio-

graphic changes, normalization of kalemia and positive long-term prospects.

Conclusion

Consumption of heroin may lead to rhabdomyolysis and myoglobinuria, subsequent renal function decline and severe hyperkalemia which sometimes results in sudden appearance of asystole and fatal outcome. The routine laboratory diagnostics which implies determining of the levels of potassium, urea, creatinine and creatine phosphokinase in serum of all hospitalized heroin addicts can contribute to well-timed detection of these severe complications and undertaking of appropriate therapeutic measures.

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CASE REPORT

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Elevation of troponin values in differential diagnosis of chest pain in view of pulmonary thromboembolism

Određivanje vrednosti troponina pri diferencijalnom dijagnostikovanju bola u grudima sa stanovišta pulmonarne tromboembolije

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Abstract

Introduction. Acute coronary syndrome, as unstable form of ischaemic heart disease, beside clinical presentation and electrocardiographic abnormalities, is characterized by increased value of troponin one of cardiospecific enzimes. Although troponin is a high specific and sensitive indicator of acute coronary syndrome, any heart muscle injury may induce its increasing, so there are some other diseases with the increased troponin value. **Case report.** We presented a female patient with chest pain, admitted because of suspicioun of acute coronary sindrome. Performed coronarography excluded ischemic heart disease. Considering symtomatology, electrocardiographic abnormalities, increased troponin and D-dimer values, as well as echocardiography finding we considered pulmonary embolism as a differential diagnosis, which was confirmed by pulmoangiography. **Conclusion.** Isolated increased troponin values are not enough for diagnosis of acute coronary syndrome.

Key words:
coronary disease; diagnosis, differential; pulmonary embolism; chest pain; troponin I.

Apstrakt

Uvod. Akutni koronarni sindrom, kao nestabilni oblik ishemijske bolesti srca, pored kliničke slike i elektrokardiografskih promena, karakteriše i porast vrednosti jednog od kardiospecifičnih enzima – troponina. Ipak, bez obzira na to što je troponin visokospecifičan i senzitivan indikator akutnog koronarnog sindroma, svako oštećenje srčanog mišića može dovesti do njegovog porasta, pa postoji određen broj drugih bolesti gde se posledično javljaju povišene vrednosti troponina u perifernoj krvi. **Prikaz bolesnika.** Prikazana je bolesnica hospitalizovana zbog bolova u grudima i sumnje na akutni koronarni sindrom. Urađena je koronarografija kojom je isključeno postojanje ishemijske bolesti srca. S obzirom na simptomatologiju, promene u EKG-u, pozitivne vrednosti troponina i D-dimera, kao i ehokardiografski nalaz, diferencijalno dijagnostički razmatrana plućna embolija, koja je dokazana pulmoangiografijom. **Zaključak.** Povišene vrednosti srčanog troponina ne mogu izolovano obezbediti dijagnozu akutnog koronarnog sindroma.

Ključne reči:
koronarna bolest; dijagnoza, diferencijalna; pluća, embolija; bol u grudima; troponin I.

Introduction

Any cross-striped muscle fiber is composed of several hundred to several thousand myofibrils, each of which contains 1,500 myosin and 3,000 actin filaments. Actin filament is composed of three different protein components: F-actin, tropomyosin and troponin (Tn). Troponin achieves its physiological role in controlling the contraction of cardiac and skeletal muscle thanks to its structure, since it consists of three loosely related protein subunits: troponin I (TnI), troponin T (TnT) and troponin C (TnC) [1]. Cardiac troponins (cTnT and cTnI) highly sensitive and specific indicators of myocardial damage, because it leads to the increase of troponins in peripheral blood only 3 to 4 hours after the necrosis of cardiac muscle cells, reaching a maximum within 12 to 24 h, and after that it returns to the initial value in 7 to 10 days [2] (cTnI < 0.01 ngmL^{-1} – laboratory Clinical Center Kragujevac).

In addition to troponin as markers of cardiac damage creatinine phosphokinase (CK) and its isoenzyme CK-MB

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are also used, with their values increased in the peripheral blood only 8 to 12 h after myocardial necrosis. While CK-MB is highly specific for myocardial tissue necrosis, the specificity of CK is very questionable since the value of this marker rises in the necrosis of the brain, peripheral muscle and kidneys, too [3, 4]. Furthermore, in the detection of myocardial necrosis myoglobin plays an important role thanks to its great sensitivity (90%). However, myoglobin is not sufficiently specific because it is released from damaged heart, but from skeletal muscle and the damaged tissue, too [3–5]. Similar characteristics of myoglobin are shown by a low molecular weight protein, fatty-acid binding protein (FABP) [3].

It should be noted that all the above markers, with troponin in the end, belong to the late acute coronary syndrome (ACS) detectors [2]. Today, more and more attention is paid to early detectors of ACS, such as leukocyte myeloperoxidase (MPO) [6] or ischemia modified albumin (IMA) [7], whose values rise in myocardial ischemia in the absence of myocardial necrosis, too. According to the latest research histamine plays more important role in early detection of cardiac ischemia [8].

Case report

A 46-year-old female patient, was observed in the Emergency Department of Clinical Center Kragujevac, because of chest and abdominal pain, 2 hours before admission, with transitory loss of consciousness during hard physical work. The patient had been diagnosed psychosis since many years ago. At admission, the patient was afebril, tachypnoic and pale. Auscultation of the chest revealed normal breath sound with late expiratory cracks on both side from the lower parts. Initial tachycardia was registered (about 100 beats/min.) Heart sounds were normal, blood pressure was 140/90 mmHg. Other internal and neurological examinations revealed no signs of a disease.

Electrocardiogram (ECG) revealed sinus rhythm, frequency was about 100 beats per minute, ST depression horisontal type 0.5 mm in leads II, III, aVF, V5 and V6 and negative T wave in aVL (Figure 1a). Basic laboratory analyses revealed reduced values of hemoglobin (105...108 g × L^{-1}) and other results were in optimal range. Second ECG revealed significant evolution such as sinus bradycardia and ST elevations 0.5 mm in leads II, III, aVF, negative T waves in leads I, aVL, V2 i V3 with biphasic T in V5 and V6 (Figure 1b). After this ECG evolutions, although there were referent values of cardiospecific enzymes (cTnI < 0.01 ng·mL^{-1}, CK-MB 10 ng·mL^{-1}), a working diagnosis of ACS was set up. We expected elevations of cTnI and CK-MB considering appearance of pain and first laboratory analyses from peripheral blood had been taken not more than 2 h before. Double antiplateled and anticoagulant therapy was prescribed.

The surgeon was consulted since the patient had abdominal pain. Surgeon excluded acute surgery disesase and prescribed H^+ pump blockers. Repeated laboratory analyses revealed significant elevations of cTnI 0.18 ng·mL^{-1} and CK-MB was in optimal range, so the patient was admitted to the Cardiology Department with the diagnosis of unstable angina. Performed echocardiography showed referent left ventricle (LV) systolic function, with no wall motions abnormalities and LV hypertrophy. LV was normal and right ven-

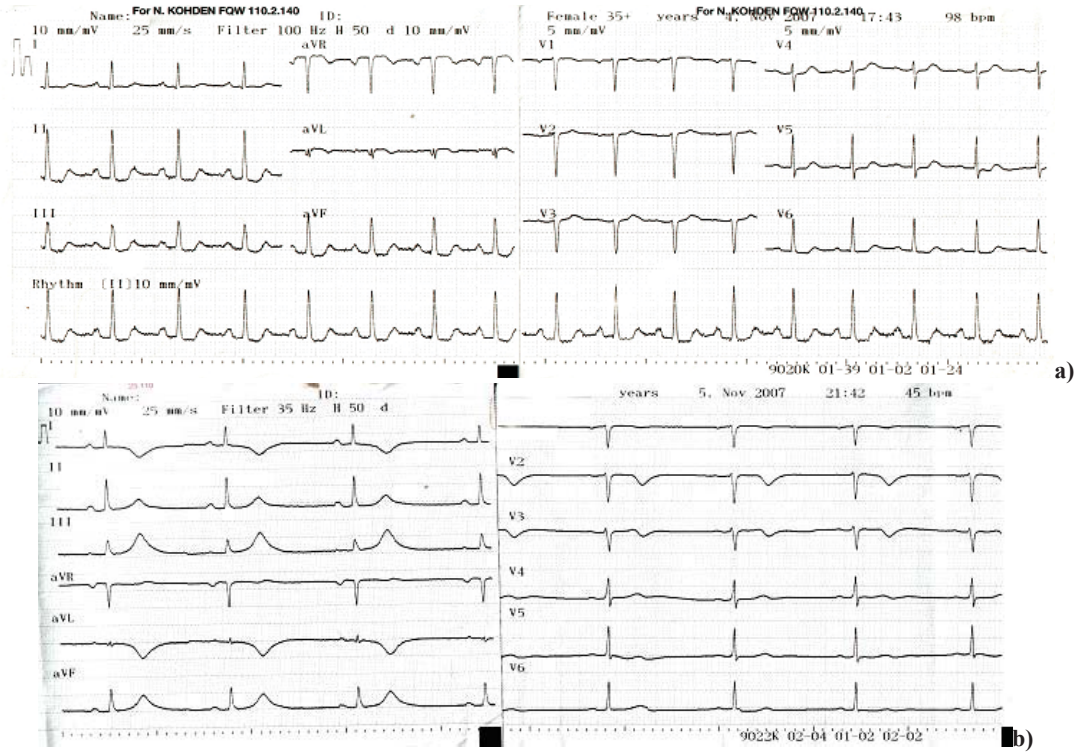


Fig. 1 – Electrocardiograms (ECG) of the presented patient: a) the first ECG; b) the second ECG

tricle (RV) was bvot borderline size (30 mm) with overload pressure at pulmonary artery and RV (42 mmHg) (Figure 2).

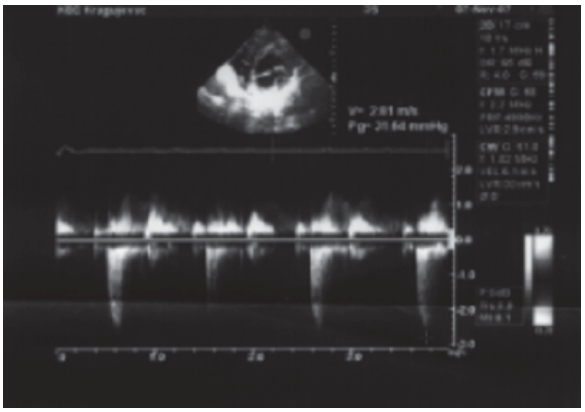


Fig. 2 – Transthoracic echocardiogram of the presented patient

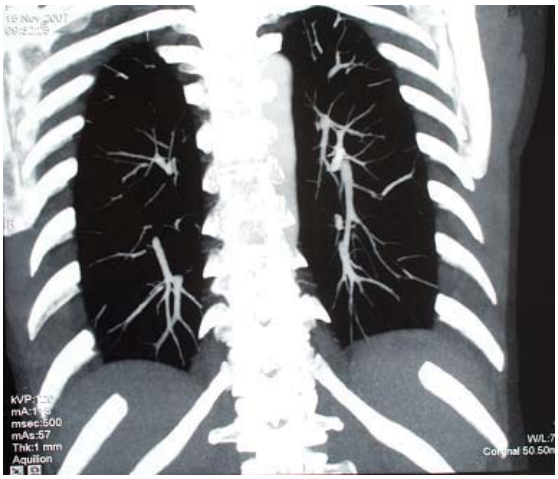
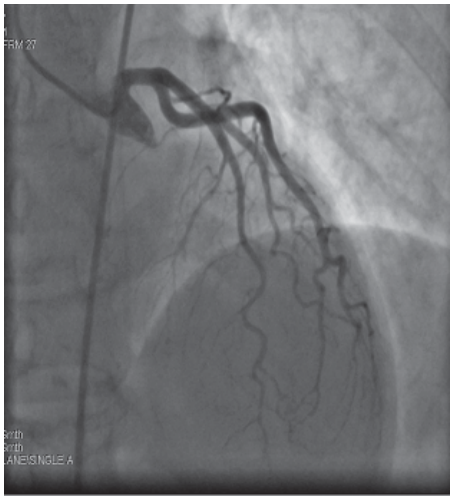


Fig. 4 – Pulmoangiographic finding of the presented patient

Repeated cTnI CK-MB analysis showed further elevations of cardiac troponin I (0.25 ng·mL^{-1}). Considering clear clinical signs, laboratory tests and ECG, the diagnosis ACS was confirmed, and urgent coronarography was indicated (Figure 3a and b). Performed coronarography showed angiographically normal lesions-free coronary arteries, and excluded ischemic heart disesae. Further diagnostic procedure was directed to other disesaes with positive cTnI values. Performed laboratory analyses showed significant elevations of D-dimer value (first value was 2,720 ng/mL, and repeated one 2,220 ng/mL). A new working diagnosis was set up – pulmonary embolism (PE) and confirmed by computed tomography (CT) pulmoangiography (multidetector computed tomography – MDCT) (Figure 4). Coumarin anticoagulants were introduced into the treatment to maintain international normalized ratio (INR) within the therapeutic range (2–3).



a)

b)

Fig. 3 – Selective coronarographic findings of the presented patient: a) left coronary artery (LCA); b) right coronary artery (RCA)

Deep venous doppler of the pelvic and lower extremity was made and the findings were normal. The patient neither used contraceptives nor gave information about the conditions that would make her lie in bed for long (recent surgery, pregnancy, extensive injuries, etc.). An additional laboratory tests confirmed the presence of elevated values of lupus anticoagulant (1.33) and the necessity of hematological and rheumatoid test was pointed to the patient. After two weeks the patient was discharged in good condition with recommendation for the appropriate therapy.

Discussion

Elevated values of cardiac troponins, with appropriate symptoms and ECG abnormalities, usually make a physician to suspect of ACS. In contrast to conventional enzymes, which have their baseline levels, cardiac troponins are virtually immeasurable in healthy individuals, so that the least damage of the heart muscle can be easily detected. The combined analysis of four studies, estimating the predictive properties of individual values of cardiac troponin I for acute myocardial infarction, found a sensitivity of 39% and specificity of 91%. Serial cTnI increased the sensitivity of 90% to 100% [3].

However, despite the fact that troponin is highly specific and sensitive indicator of ACS, any damage of heart muscle (and not only of ischemic etiology) may lead to its

increase: renal failure, supraventricular tachycardia, acute heart failure, pericarditis and myocarditis, PE, takotsubo cardiomyopathy, sepsis, stroke, heart contusion, heart surgery, a distinct physical exercise (eg marathon), and so on [2].

There are various mechanisms that lead to increased cardiac troponins in peripheral blood. Most often mentioned is ischemia, which, if lasts enough, leads to irreversible damage of heart muscle cells, *ie* necrosis. It can be caused by mechanical or dynamically narrowing of coronary arteries (pathophysiological basis of ACS) [2, 3] or a sudden overload blood preasure in the pulmonary artery (RV damage mechanism in PE) [9]. On the other side, repairing of ejection fraction of the LV after sepsis or myocarditis, in which the values of troponin were elevated, indicate the possibility of reversible damage of heart muscle cells [2, 10]. Studies show that troponins have high sensitivity in early detection of minor damage of cardiomyocytes in PE associated with RV dysfunction, but not in differentiation of cardiac from non-cardiac chest pain, because, in some patients presenting with PE, elevated troponin I concentrations above the normal range are observed, as well [9].

In our case, starting from clinical signs, ECG abnormalities as well as laboratory findings, it was logical to suspect ACS. We were directed to PE as differential possibility by cardiac ultrasound which showed a borderline dimension of the RV which is an independent predictor of mortality and non-fatal clinical complications in PE [11] and enlarged values of D-dimer after performed coronarography, although our patient had intermediary Geneva (3 poens) and low Well (0 poen) score [12]. We should say that appearing of opposite T waves in precordial leads, was shown in our case, could be one of signs of PM [13]. The reported sensitivities and specificities for the diagnosis of PE of spiral CT vary (45%–100% and 78%–100%), and depend on the type of CT (single or multi-detector spiral CT). MDCT allows evaluation of pulmonary vessels down to sixth-order branches and significantly increases the rate of detection of PE in segmental and subsegmental levels [14].

Enlarged troponins values in patients with PE are present because of acute RV pressure overload, impaired coronary blood flow, and severe hypoxemia and they are independent predictors for in-hospital mortality. Limitation of pericardial expansion in the presence of dilated RV together with leftward shift of the interventricular septum appear to contribute to the diminished LV preload and resultant decreased cardiac output. Hypoxemia, systemic arterial hypotension, and cardiogenic shock may further increase the propensity to ischemic damage and pre-existing cardiopulmonary abnormalities may contribute to both the hemodynamic alteration and the risk of ischemia and infarction induced by PE [15].

Conclusion

Elevated values of cardiac troponins cannot absolutely indicate diagnosis of ACS, because laboratory is not a singular arbiter. Together with clinical signs, ECG evolution, coronarography and echocardiographic searching it could help in setting up the right diagnosis. If MDCT is available, then CT pulmonary angiogram can be used as the first-line imaging investigation for the diagnosis of PE.

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The Spanish Flu – Part II: the second and third wave

Španska groznica – II deo: drugi i treći talas

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Key words:
influenza, human; world war I; disease outbreakes; history, 20th century; serbia.

Ključne reči:
grip, humani; prvi svetski rat; epidemije; istorija, 20-ti vek; srbija.

The second wave

The second wave of influenza pandemic of 1918 represents a period in which the Spanish Flu showed its full deadly potential. It is usually said that this wave struck in autumn 1918, although the disease had spread even before this time.

A U.S. naval intelligence officer received a telegram on August 3, 1918 which he immediately stamped as a secret and classified document. While indicating that his source was reliable, he reported to the competent authorities:

„I am confidentially advised ...that the disease now epidemic throughout Switzerland is what is commonly known as the black plague, although it is designated as Spanish sickness and grip“ [4].

The comparison of the Spanish Flu with plague was not a rarity already at the beginning of the second wave of the pandemic [*]. Doctors reached this conclusion, that it was a question of plague, based on the appearance of the lungs in autopsy. Until then, flu did not leave this kind of a picture, thus many believed that it was a question or either a new disease or lung plague. An increase in the frequency of the ill-stricken with flu occurred in some places with mutual distances of thousands of kilometers in August 1918, but this time with a large number of severe cases. An epidemiological study, written in the States, relatively shortly after the pandemic, indicated that a progressive increase in the number of flu cases was observed in the American military bases in the week ending August 4, 1918, whereas pneumonia cases started appearing in the week ending August 18, 1918 [4].

The very day when the British command proclaimed the end of the epidemic on August 10, there were so many ill soldiers in the French port Brest, that the overcrowded naval hospital was forced to stop admitting the newly ill-stricken. The increased death rate in Brest caused by flu, was observed already in July among the American troops, which had arrived from the military base in Arkansas [4].

Severe forms of the disease appeared on the African continent also in mid August 1918. Military ships would get their coal supplies in Freetown, today’s capital of the Republic of Sierra Leone, on the Atlantic coast. On August 27, 1918 the crew of the British military ship „HMS Africa“ was forced to load coal by itself, as the majority of African workers from the coal supply company were ill. Within a couple of weeks, 51 crew members of that ship died of the Spanish Flu, which was 7% of the manpower. They got the disease from those African workers who were still not affected with the disease and with whom they were working, but who were already in the incubation period [4].

A practically prophetic heading appeared in „The Serbian Newspaper” on August 16/29, 1918:

„INFLUENZA, FLU – It seems that the world is going to be overwhelmed again by this infection this year“. The following was also included under this heading, signed by Dr. Sima Petrović: „We have already had this serial spread in one unit here on Corfu a few months ago, where in just a few days everyone fell ill, however they also all recovered easily and happily in a couple of days. Further spread of the infection among us was terminated by energetic isolation. However, it seems now that it is present among the civilians of the town and that it will thus be easily brought in to us from there and from other sides. According to newspaper writings, it seems that this year’s spread has been more severe and dangerous in Spain, Switzerland and Germany, which have already been overwhelmed by the disease. However, here in

[*] During the syphilis pandemic also, at the end of the XV and in the XVI century, when the second stadium of the disease was violent and deadly, many believed that it was a question of – the plague!

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the south, at least until now, the infection has had a light form.“ [16].

It is possible to conclude from the text above that there had not been any victims of the first pandemic wave among the Serbian soldiers on Corfu. However, considering other sources, this should not be taken for granted. The same writing, on the other hand, testifies to the probable presence of the disease on the island at the end of August.

The end of August and beginning of September marked the beginning of mass deaths throughout the world caused by the Spanish Flu. Millions were to die of this disease in the last months of World War I.

The dying itself of the Spanish Flu was terrible, so terrible that the need of humankind to forget this pandemic, is practically understandable. Before presenting the picture of the flourishing pandemic in this text, a description will be given of the knowledge about the flu at the beginning and in the course of the duration of the pandemic, and then of the severe form of the disease, the form of it that claimed so many lives.

Dr. Aleksa Savić wrote at the time when the disease had already widely spread:

„The influenza is caused by contagious germs, found in the nose, throat and lungs of the diseased. There are various views about the cause of the influenza and that issue remains unresolved in the discussion. While the German school maintained always, that the influenza was caused by a minute, motionless, short and very tiny bacillus, found by Pfeiffer in 1890, French authors kept claiming that this bacillus was not the cause of the disease. The truth is, according to the reports from all countries and observations made on this front in the central bacteriological laboratory of the Eastern Army, that this bacillus was only found in a certain minor number of cases. It is particularly interesting to note that this bacillus was never found in the severe influenza cases, in which there are bronchopneumonic processes.“ [8].

Richard Friedrich Johannes Pfeiffer (1858–1945) believed in 1892 that he had discovered the cause of influenza. His authority did not leave much room for doubt; a great majority of scientists of that time believed that Pfeiffer’s bacillus – *Bacillus influenzae*, today known as *Hemophilus influenzae*, was quite certainly the cause of the flu. However, the text written by Dr. Aleksa Savić indicated doubt about Pfeiffer’s bacillus being the cause of influenza, which was the stand of a minor number of doctors at that time.

Dr. Aleksa Savić concludes in his description of the experiments made by French scientists:

„Thus, according to this latest belief, the cause of the influenza would be an invisible microorganism, the so-called 'Virus filtrant', as it is the cause of, for example, varicella (chickenpox) and variola (smallpox), scarlet fever and measles.“ [8].

It turned out that Dr. Aleksa Savić was wrong in the previous sentence in speaking about scarlet fever, but that he was absolutely right about the influenza. More than decade after the Spanish Flu pandemic in 1931 Dr. Jovan St. Kujačić wrote that:: „the bacillus Pfeifferi s. b. Influenzae is still for the time being the most important biological cause of influenza“. He also pointed out the possibility of the disease being caused by a virus [17]. It was in this year that the influenza virus was isolated from swine, and two years later, so was the human virus.

A clinical picture of the Spanish Flu was well depicted by Dr. Dimitrije Antić on a poster printed in Kragujevac in October 1918 (according to the Julian calender):

„There is almost no one who cannot be infected by the Spanish Flu, if just exposed to the danger of being infected. Maybe the spared ones are those who already had the same disease in 1889 and 1890, which had also spread throughout the world at that time. Thus, the old and the young, men and women fell ill equally. What are the symptoms of the Spanish Flu? It takes usually 2–3 days from the moment of entry of the contagious germ into the body till the manifestations of the Spanish Flu. The first signs of the disease are: feeling cold, sometimes strong shivering, later fever, general weakness, headache, loin and joint pain, nausea sometimes with vomiting, appetite loss, cold, cough, bloodshot eyes and sometimes throat pain; the patient is usually constipated, having rarely diarrhea; his nose bleeds sometimes, the tongue is lined, dry, the patient frequently becomes deaf later on. It is understood that all of the indicated signs may not appear in all patients and that some may not manifest. The fever and the other signs of the disease last 3–5–7 days, after which the fever starts decreasing and disappears completely in 2–3 days, and with it the other signs of the disease. If the fever is not very high, many of the patients do not become bedridden, but drag around and do their work. But many get a very high temperature, reaching as much as 39–40 or more degrees and they feel so bad, that they have to go to bed, the inflammation which had started in the throat and trachea, lowers down to the larger, and then tinier bronchial branches, and very often also into the lung alveoles, causing thus pneumonia. Sometimes the influenza begins immediately with pneumonia, whereas it follows only after a few days of illness in most cases. It is not rare that patients get rid of the high temperature first and feel quite well for 3–5 days and in some cases, even get out of bed; when all of a sudden, the fever gets back again with a high temperature, which are an introduction to severe pneumonia. Pneumonia is very dangerous in case of influenza and ends after 3–5–10 days, very frequently in death.“ [18].

The Spanish Flu claimed many human lives through primary viral and secondary bacterial pneumonia. People died more frequently of secondary bacterial infections, which were the result of bacterial invasion on the tissues already damaged by virus. Death caused by primary viral pneumonia is still what makes the Spanish Flu special, what caused people to believe that it was a question of a new disease, even – plague. The diseased would die quickly, most frequently after two to three days from the manifestation of the first symptoms, and the deadly outcome followed terrible suffering of the diseased. The manner of dying was extremely striking for the people in the vicinity of the diseased, even more so since this was the way in which mostly young and strong people died, the ones who were believed to be the most resistant ones. There is a well-known description of the

Spanish Flu to be found in the letter written by Dr. Roy Grist, in the American military base Camp Devens on September 29, 1918:

„These men start with what appears to be an ordinary attack of LaGrippe or Influenza, and when brought to the Hosp. they very rapidly develop the most vicious type of Pneumonia that has ever been seen. Two hours after admission they have the Mahogany spots over the cheek bones, and a few hours later you can begin to see the Cyanosis extending from their ears and spreading all over the face, until it is hard to distinguish the coloured men from the white. It is only a matter of a few hours then until death comes... It is horrible." [19] (Figure 1). The appearance of cyanosis on the cheeks and ears was an evil premonition. The body would not get enough oxygen through lungs. It was really very difficult to understand how it was possible for lungs to become useless in such a short time. It is believed today that the young, strong people, the very ones who had had perfect health until then, developed an extremely intensive inflammatory response to the antigenically new influenza virus. The occurrence of this strong inflammatory reaction in lung tissues, was the main obstacle to their normal functioning. Doctors who did autopsies, noticed that these young people had actually suffocated in their own blood. It is believed today that they suffocated in the products of an intensive inflammatory reaction, which is called „cytokine storm".

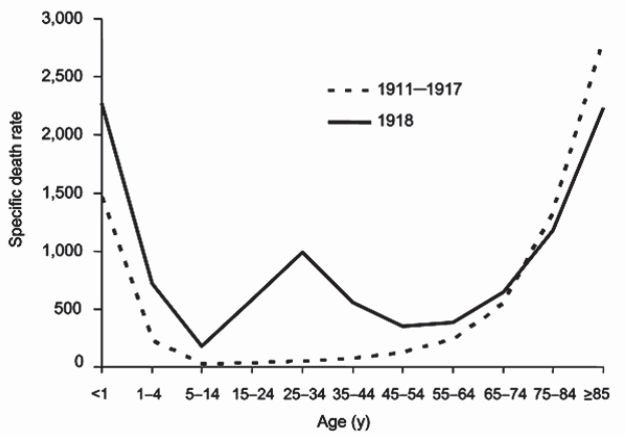

Fig. 1 – The above graphic presentation shows the difference in the age specific death rate for influenza and pneumonia per 100,000 persons in each age group, USA, in the interpandemic years (the dashed line – the so-called "U curve") and in the pandemic year (solid line – the so-called "W curve") [6]

At the beginning of September 1918 the Spanish Flu was present in many countries. The disease appeared in each country in certain places, and took its toll. One gets the impression that it spread in a mysterious and unstoppable way. It appeared on broader and broader terrain, reaching every place, every family. By rule, the disease would still appear firstly in military bases and barracks, to be brought to the civil population, as a result of contacts with the members of the army. Embraces of spouses, who had not seen each other for months, kisses of fathers, who had just come back from the front, were ways in which the deadly virus spread. Practically by rule, the disease could be found firstly among soldiers, before it spread into local environments.

Camp Devens, a military base from which Dr. Roy Grist wrote the already mentioned letter, has an important role in the United States. This base near Boston had around 45,000 soldiers on September 6, 1918. Like other military bases in the country, it was overcrowded with people, considering that it was planned for some 10,000 soldiers less. Starting from August there is an increase in the number of those suffering from pneumonia in the base. The soldiers kept falling ill, but this did not prevent normal operation at the beginning. Intensive transport of people among bases and between America and Europe, was favourable for the spread of the virus. What happened in Camp Devens was to follow practically everywhere. Around September 20, the Spanish Flu almost caused havoc in this military base. Around 20% of soldiers fell ill on September 22. Cases of pneumonia and deadly outcomes became increasingly numerous. A total of 342 soldiers were diagnosed with pneumonia, just on September 24. The medical staff, who had also begun to fall ill and die of the same disease, were so overburdened, that a decision was made on September 26, about not admitting any new cases into the hospital! Dr. Roy Grist indicated in his letter from this base, that a large number of doctors and medical nurses had already succumbed to the Spanish Flu. A shortage of coffins also occurred, and as for the long lines of stacked corpses, Dr. Roy Grist pointed out that such picture was more striking than any other, that could be seen in France, after the worst battle. Excruciating scenes were described by other doctors, who visited this camp at that time. An immense number of soldiers were lying in hospital. In its premises hard coughing echoed, the foul smell of feces and urine penetrated the area, many patients had the ominous indicator – bluish face colour, many cough up blood... One of the most esteemed American doctors of the time, Dr. William Henry Welch (1850–1934) upon visiting the influenza stricken Camp Devens said: „This must be some new kind of infection or plague" [4].

The Spanish Flu appeared at the beginning of September in its severest form throughout America. The disease appeared in the States in every town, taking its toll everywhere. The number of the dead of the Spanish Flu in this country has been estimated to 675,000 [7].

The town Philadelphia was highlighted as an example of the conflict between public health and war propaganda interests. The Big Parade, the purpose of which was collection of money from the citizens (the so-called Liberty Loan Parade), was supposed to be organized in Philadelphia on September 28, 1918, although the Spanish Flu was already present in the town since the beginning of September. The flu was brought by sailors from Boston. The disease had already claimed many lives, just before the parade. Doctors tried to prevent the parade from taking place, but the state war logic differed and persistently incited the city authorities to organize the parade. The parade was thus held. It was afterwards described as „magnificent", but its effect on health condition of the population was catastrophic. Just three days

after it, every patient bed was occupied in thirty-one city hospitals. Hundreds of residents of this town died daily, already at the beginning of October. Terrible scenes could be seen. Corpses stayed in homes with the survivals, due to the shortage of coffins and paralysis of the mortuary services [4].

The Philadelphia case during the Spanish Flu pandemic is highlighted even today as an example of disastrously bad public health measures. Efficient preventive measures entailed, primarily, quarantine isolation, with a series of rigorous regulations, which it was not possible to implement in the largest part of the planet. Philadelphia was repeating throughout the world.

The United States represented the crucial factor which gave the Allies the decisive advantage over the Central Powers. The Central Powers had almost won the war during the first wave of the flu pandemic in 1918. However, the situation changed in September 1918. The great German offensive did not succeed, and hundreds of thousands of American soldiers were arriving each month to Europe.

„The Serbian Newspaper" wrote about this on September 8/21, 1918: „Reports from London say that 313,000 soldiers have been transported from the States to Europe in the course of August." [20]. There were already around two million American soldiers in Europe in September. The entire United States were fully dedicated to the victory of the Allies, and the country functioned as an enormous war machinery. Democracy and human rights were suppressed onto the second level. Rigorous laws were in force for prosecuting and penalizing those who dared criticize the authorities. Every citizen had to contribute to the victory of the Allies.

The situation was similar in Europe, in which 2,640,000 people died of the Spanish Flu, which was 1.1% of the European population of the time [21]. The number of deaths was particularly high in October and November 1918. The war was still going on, thus censorship of information among the European nations was of the same intensity as it was in the States. There are even claims that it was not rare that French doctors diagnosed incorrectly, on purpose, the Spanish Flu, calling it cholera or dysentery, in the aim of covering up the actual situation [4]. Still, the authorities closed down the schools in Paris, fearing that everything else could reduce war efforts. There were thousands of deaths.

The mayor of Cologne of that time, Konrad Hermann Joseph Adenauer, (1876–1967), the future chancellor of the Federal Republic of Germany, said that the Spanish Flu was exhausting so much thousands of sick people, that it made them incapable of hatred [4]. Life was strongly disrupted in the neutral Spain during the pandemic. The death rate caused by the influenza amounted to 3.8% in the course of October 1918. The death rate was significantly higher in some places. The death rate amounted to 10.1% in Zamora, a town in the west of Spain in October. The mayor of Barcelona asked for help from military forces for transport and burial of the dead, as the available mortuary services had become insufficient. The first 4–5 pages of the Spanish papers consisted of obituaries, during the peak of the pandemic [1]. The disease took its toll in every European country. The European allies ignored the disease as much as they could in the last months of the war. The Central Powers were being given the final blow and there was no room for drastic prophylactic and hygienic measures, which would stop or at least slow down the spread of the pandemic. The war logic was also against health interests in the countries faced with a foreboding of defeat.

Absolute chaos resulted following the defeat of the Central Powers, out which nothing good could have resulted in respect of public health either. While the ever present masks dominated on the American photos of the period, which were by the way useless, even that could not be seen in Europe: the flu was ignored to the greatest possible extent. In the photo of London celebration on November 11, 1918 on the occasion of the signature of armistice, there was not any mask, but only happy people everywhere.

Mass gatherings of this kind helped to spread the virus in the same manner as had already happened in Philadelphia, end of September.

It is also not possible to see anything in the photos of the Serbian soldiers, after the penetration of the Thessaloniki front, which would indicate any protection against the Spanish Flu.

The disease was particularly cruel in isolated human communities, which is explained by the absence of contact of the people from these environments with earlier forms of the influenza virus, thus the Spanish Flu virus was absolutely new for them in antigenic respect. Some Eskimo settlements were almost completely devastated. The death rate in many Eskimo communities was even above 70%. Out of 80 people 72 died in Brevig Mission, a settlement in which search was to be made, many decades after, for preserved lung tissues of the dead, for the purpose of getting the virus genetic material. Out of 300 people 176 died in another Eskimo settlement. The disease paralysed many Eskimo settlements. Many died because no one could take care of them in their illness, give them food and light the fire. A hard fate befell also many tribes in Africa, then the indigenous tribes in South America, as well as the population of the Pacific islands. The actual data will never be known.

A total of 8% of Europeans died of the Spanish Flu in Gambia, and a British man noted down the situation he found in the Gambian countryside:

„I found whole villages of 300 to 400 families completely wiped out, the houses having fallen in on the unburied dead, and the jungle having crept in within two months, obliterating whole settlements".

A total of 4% of the population died of the influenza in Cape Town. The virus killed almost 5% of the indigenous population on the Pacific island Guam, 14% of the population died on the Fiji islands just between November 25 and December 10 in 1918. 22% in Samoa.

The case of American Samoa was, however, an exception in the course of the Spanish Flu pandemic. Considering extremely strict quarantine, no death cases were recorded in this country! Evasion of the catastrophe by implementation of an extremely strict quarantine was also noted down in several minor American environments.

A total of 10% of the entire population died of the Spanish Flu in the Mexican state of Chiapas. The pandemic

took many lives in Russia, China, India... The real number will never be known. Recent sources point out several millions of victims in India [4], while 390,000 people died of this disease in Japan [22].

Reliable statistical data can only be found in rare environments, whereas it is possible to conclude about the Spanish Flu pandemic in the greatest part of the world just based on incomplete data, memories, memoir writings, newspaper articles and graves.

Medical science was already significantly developed at the time of the appearance of the Spanish Flu. It was known that microorganisms cause different diseases, and it was also known that there are also even smaller infectious particles than the bacteria visible through a microscope. Vaccines and serums for prevention and treatment of infectious diseases were already being made. Antibiotics were still not invented. The ways in which diseases were transmitted were known for a significant number of infectious diseases, and one of these diseases was also influenza. Thus, although some scientists believed already then, that a virus could be the cause of influenza, it was Pfeiffer's bacillus, which was still considered as the scientifically proven etiological factor.

While writing in Kragujevac at the peak of the Spanish Flu, Dr. Dimitrije Antić, listed the following preventive measures:

1. Do not visit patients nor those who have already died; 2. Isolate the patient immediately preferably into a separate room and prevent any kind of contact between the healthy and the ill as well as with the infected objects from his room; 3. Make the patient spit only into the spittoon, and by no means on the floor or walls, as is the custom of our people in the country. Put lime wash into spittoons and empty them either into lavatories or into dug out and filled up holes in the yard.; 4. Put immediately patients' scarfs, towels, dirty clothes and bed linen into a container with lye, and only afterwards boil and wash them; 5. No one should stay for quite some time in the rooms in which patients had stayed and then recovered or died, the walls of such rooms should be whitewashed, the floors scoured with hot lye and windows left open for several days; 6. Restaurants and inns should not be visited as long as the disease is spreading and people falling ill, gatherings in general in closed premises should be avoided and schools should be closed down. Those who have the Spanish flu or have just recovered from it, should not mix with people for quite some time, unless they absolutely must; 7. The dead should be buried without the usual burial ceremony (it is of course understood, that all contacts with the dead are absolutely out of the question). The usual memorial servings of food and drinks should also be left out; 8. The drunk and the exhausted get ill more easily and recover with more difficulty." [18].

Dr. Aleksa Savić pointed out that particular attention should be given to mouth, nostril and throat care. He stressed the necessity of rinsing the nose every morning and evening with a mild disinfectant device, brushing teeth several times a day, and added that the „doctors and nurses should use small face masks, besides capes." [8].

The use of masks is ever-present in the American photos from this period. They were really widely used in the States. Yet, it is believed that their impact on the spread of the disease was very low or nonexistent. Masks were also used in other environments with developed public health systems, for example in Australia in 1919, the country which the pandemic circumvented in 1918 due to the efficient quarantine isolation of passengers. Schools, somewhere also cinemas and theatres, were closed throughout the world, mass gatherings were forbidden. Spitting, coughing, sneezing were particularly forbidden in the States, somewhere also hand shaking or entry into public transportation means without masks (Figure 2). In an analysis which made a comparison of the impact of the early introduction of public health measures and mortality caused by the Spanish Flu in 23 American towns, it was found that such measures did have a significant impact on the reduction of the number of deaths. The mortality was significantly lower in Saint Louis thanks to the early and consistent implementation of preventive measures than in the previously mentioned Philadelphia [23].

Fig. 2 – A tram conductor in Seattle not allowing the man without a mask to get on the tram, because of the ongoing Spanish Flu pandemic

According to the instructions given by Dr. Antić, the treatment of the Spanish Flu should follow these steps:

„1. As soon as you feel any one of the above mentioned signs of the Spanish Flu, go to bed straight away; 2. The patient's room should be clean with only the most essential

things in it, whereas all unnecessary furniture should be removed and taken to other rooms; windows in the room should be opened as frequently as possible, so that the patient can get as much fresh air as possible; the room should be moderately warm and not overheated; 3. It is advisable for the patient to sweat all the time, he should therefore be tucked in well and given every 2 hours warm linden flower tea or the chamomile tea or warm milk or sugared water for children; 4. The patient should frequently rinse his mouth with lukewarm chamomile tea or lukewarm salt water; 5. The food should include: milk, yogurt, chicken soup with egg or beef soup, cooked fruit (apples, pears, plums). The patient is allowed to drink water and when he gets pneumonia it is good to give adult patients a glass or two of old wine or 3 small glasses of strong brandy per day; 6. When the coughing is strong and when pneumonia begins, then compresses should be placed around the chest and crosswise over each shoulder using stale water from the room mixed with vinegar. Compresses with brandy also have a good effect. Dry cloths should be placed over the wet ones and this should be changed every 2 hours. Similar compresses on the head and around the neck are also good for the patient. If the fever is too high, then it is possible to wipe the whole body with a thick towel dipped in vinegar and water, repeatedly every 2 hours; 7. during the illness, also in case of pneumonia it is good to give the patient as a good refreshment, nutrient and strengthener the following drink: cook a little cinnamon with a glass of water, filtrate it, stir into the filtrated water 2 egg yolks, pour in 3 spoons of cognac or strong brandy and add sugar until you get a drink with a pleasant taste. A spoon of this should be given every hour; 8. It is not advisable to bathe adults, children can take baths, depending on the fever 2–3 times per day; 9. Upon recovery from the Spanish Flu, one should take care for quite some time and avoid any kind of body exertion, because due to a weakened heart, sudden death may result even after the recovery.“ [18].

The following have also been used in the treatment of the Spanish Flu: digitalis, aspirin, kinin, venesection... People used alcohol compresses, garlic and everything else which was believed to possibly have certain medicinal properties. All this was in vain, there was no medicament against the Spanish Flu. The chances for a patient to recover increased if he went to bed, had good care, stayed in bed long enough even after the relief of the symptoms and signs of the disease.

A lot of effort was made to find and get a vaccine and serum during the pandemic. People, volunteers, above all among prisoners were also used in the experiments, conducted in search for the cause [24]. This enormous effort was doomed to fail because of the wrong idea about the etiologic agent. Even if the cause had been experimentally proven then, medicine was not able at its level of development of the time, to produce an efficient vaccine against flu. Newspapers of the time reported frequently about proofs of the successfulness of new vaccines, but the purpose of such news was just to maintain an optimistic spirit in that terrible period (Figure 3).

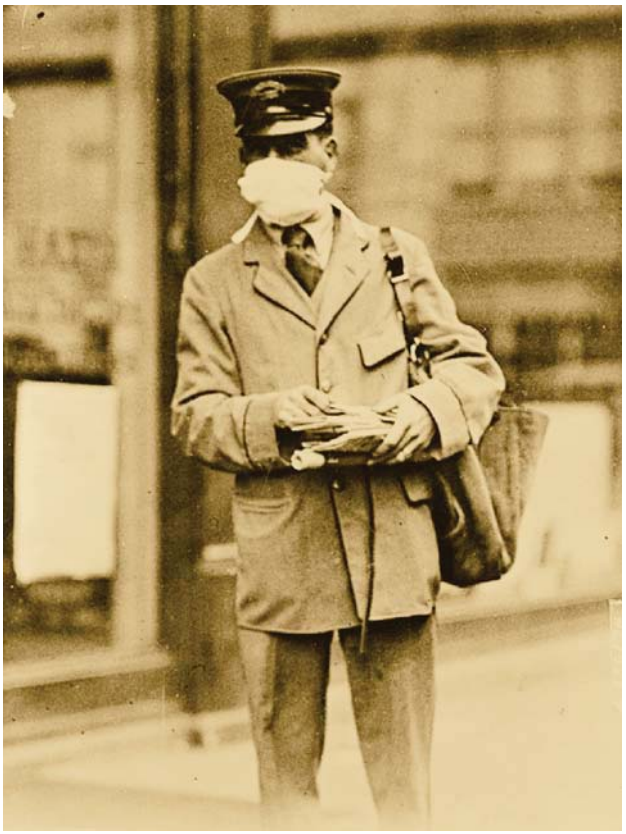

Fig. 3 – A postman in New York on Oct. 16, 1918

The second wave in Serbia

Serbia was an occupied country at the time of the second wave Spanish Flu appearance. The disease was present on both sides of the Thessaloniki front on the day of the beginning of it's penetration. In the memoir writing of a Serbian woman, the following is said about the presence of flu in the occupied Serbia:

„The Spanish Flu flourished that autumn, making all my children ill, the younger ones caught a milder form, whereas the elder had a more severe and dangerous form of it. Thus, my eldest daughter caught the Spanish Flu with complications, she was ill for a long time, and to her great regret, was not able to welcome our army upon liberation. My mother got also ill and died, just two days before the end of the war at the age of sixty-two“ [25].

The Serbian army began the liberation of the fatherland on September 15, 1918 (according to the Gregorian calender). The enemy was not able to withstand anymore the onrush of the Serbian troops, thus Serbian soldiers were successfully liberating foot by foot their exhausted country.

In summing up the military medical corps experiences of those days Dr. Aleksandar Nedok pointed out that the appearance of flu burdened extremely the medical corps units of the advancing Serbian army. „The flu epidemic, which was spreading in these regions from Albania through the population and moving troops, became a rage in a short time, causing significant difficulties in the work of the French and Serbian medical corps units, which was worsened by the lack

of background reinforcement...“ The organized field surgical hospitals did not succeed in following the shifting front due to inadequate transportability, and the presence of the Spanish Flu paralysed additionally the Serbian military medical corps. Thus, for example, the field hospital of the Timok Division with a large number of flu patients was left in Veles a few weeks, only to catch up later with the division in Kraljevo [26]. Serbian soldiers performed, thus, their liberation mission during the very peak of the pandemic.

Many Serbian soldiers were to face their tragic fate in the just liberated fatherland. A significant number of those who had survived hard battles, typhus, the „Albanian Golgotha“, hunger, malaria, became victims of the pandemic flu virus. Dr. Aleksandar Radosavljević noted down:

„Following the penetration of the Thessaloniki front, I went with my medical corps unit all the way to Sarajevo. We saw some sudden diseases appearing among our soldiers on our way from Thessaloniki *via* Skoplje, but we did not know that these diseases would become big epidemics. Only upon arrival in Raška, I sow that the local hospital was full of diseased citizens and soldiers, and that signs of „influenza“ had appeared, as this disease was called at the time. I felt the severity and deadliness of this epidemic particularly when I came to Kraljevo. I remember one of my good war friends, an active lieutenant, a serene and joyful man, born in Kraljevo. Everybody called him 'Tića the God' because of his joyful and serene nature. He had also passed through Albania with the Timok division of the first call-up from his native Kraljevo and reached the Thessaloniki front alive and healthy and following the penetration of this front, he arrived with us back to his native Kraljevo, glad to see his mother. He saw his mother, however having caught the Spanish Flu, he died two days later.“ [11].

A widespread view occurred among the people that the enemy had poisoned the wells and the food while retreating, and that this was the cause of the disease. However, Serbian doctors knew that it was a question of a microorganism which had been present among the soldiers even before the penetration of the Thessaloniki front, but the war excluded the possibility of an active fight against the infection. Military victories had priority. Anyway, that was the rule in all armies in those crucial, final months of the war. There were probably some protection measures among the Serbian soldiers who were not involved in war actions. „The Serbian Newspaper“ published in the same issue in which it reported that Belgrade had been liberated, a text under the heading „Flu“, and from the witty content of this text, it is possible to conclude, that prophylactic measures had been implemented at least among the remaining Serbian soldiers on Corfu. It is possible to read in this paper, which was still being published on Corfu, in the issue dated October 23/November 5 as follows:

„At this time, when the greatest kindness is needed among people, a furious unkindness is recommended. Instead of gathering in theaters, concert halls, cinemas – the favourite amusement places of the world of both genders and both national costumes – you are forced to avoid each other, you must look for lonely places, preferably forests. The time has come for people to become highland rebels. As soon as someone sneezes in your company, you are taken over by a deadly fear, soaked in cold sweat“ [5]. Anyhow, this kind of writing could not have been written on liberated Serbian soil, as the reality was far too cruel.

Dr. Dimitrije Antić wrote in Kragujevac about the disease which „has taken over in a short time the entire Europe, thus also our fatherland, so that people are catching it in turns in all regions, with a large number of victims on a daily basis, most of them being in their best years“ [18].

Only military rule governed Serbian towns and villages immediately after the liberation, whereas the other elements of the state were waiting to be established. It was not possible to properly keep statistic data, thus it was not possible to easily get data on the dead.

The hospital staff in just liberated Vranje consisted mainly of women doctors and medical nurses from Australia and New Zealand. These brave women represented the personnel of the third field surgical hospital, which was the only one which managed to efficiently follow the liberation army [26]. It is possible to see from their memoir writings what the Spanish Flu did in this just liberated town.

A great majority of hospitals on the territory of Serbia of that time were found in absolutely devastated, the worst possible condition [*]. Thus, the hospital in Vranje had partly been organized in the premises of the military barracks, some time before the arrival of the Australians. The second bandage facility of the Drina division was already working there with its staff and doctors. The sanitary hygienic condition was still terrible, to say the least.

According to the records kept by the above mentioned women doctors and medical nurses, 87 patients suffering from the Spanish Flu were admitted and treated in the Vranje hospital in October, 114 in November, and 62 in December. There is also evidence for the same period of those suffering from „pneumonia, bronchitis and tuberculosis“, malaria, typhus... In total 334 suffering from the Spanish Flu, and 500 suffering from „pneumonia, bronchitis and tuberculosis“ were treated from October to April. However, these data do not speak of the total number of the diseased on the territory of the municipality of Vranje, who quite certainly constituted a significantly greater number [28].

Many Serbian soldiers from this region came home to tragic scenes, their dearest ones had died just a day or two before their return. „Laments and cries were heard almost everywhere, instead of laughter and joy“ [28].

It is possible to conclude from the memoir writings of Živadin T. Čokić (1894–1988) that the number of the dead was also very high in Belgrade: “A disease named the Spanish Flu has started to strike ... There are not enough doctors and even less medical material. Those who fall ill go to the (Main) Military Hospital on Vračar, however few come out of it...” Živadin had himself had the flu: „I felt myself a high temperature one morning. I did not go to the doctors, because

[*] Mihailo Mika Petrović, the father of Serbian war surgery, wrote in his diary: „8.11.1918. According to Subotić, everything has been taken away, everything demolished in the Belgrade and Niš hospital..“ [27]

I knew where they would send me...“ He decided to report to the commander and ask him to let him go home as he was ill, which the commander agreed to. His countryman Dika, also ill, came along with him. Both of them were, quite obviously, spreading the disease. „Dika started to slow down, already in Belgrade and finally sat down. I saw him turning red in the face... He put his arms on his knees, leaned his head on his arms and started crying. *Bon Voyage*, Živadin. When you come back from your home, you will not find me among the living“. Živadin got well, and looked for Dika’s body on the New Cemetery in Belgrade: „... a grave-digger pointed out a shed where all those who had died in the past six days were still located... They were lying naked... I could not believe that so many had died... There were thousands thrown into the shed on a heap, just like pumpkins. When we arrived, the civilians had started to take them out and throw them into a big hole“ [29].

Dr. Aleksandar Radosavljević, who had collected memories about the Spanish Flu in Belgrade, writes:

„...the old Belgrade residents remember seeing burial processions passing every day, particularly through the street 27. marta, at that time Ratarska street. Besides dead residents, dead officers and soldiers were very often taken to the Belgrade cemetery, and military music with burial marches caused great mourning amongst the Belgrade residents” [11].

Serbs fell ill and died of the Spanish Flu even far away from their fatherland. It seems that „The Serbian Newspaper“ published more freely obituaries for those people who died far away from the Serbian government and army. The August 16/29 issue announced about the death of a Serbian student in Switzerland, who died on August 9/22 „following a short and severe flu at the age of 28, and is temporarily buried in the chapel of Saint George’s cemetery in Geneva, from where he will be taken to Jagodina, upon the liberation of our beautiful fatherland and buried in the family tomb“ [30]. There is an obituary in the issue dated October 9/22 dedicated to a Serbian woman „who was not destined to see the Serbian sun after great suffering, instead of which she died of flu in three days at the age of 43 in Ajaccio on Corsica, between September 14 and 15 of the current year“ [31]. The same issue reported that the Serbian prime minister, Nikola Pašić, had fallen ill with flu in Paris.

The tasks of the Serbian army did not end with the liberation of the fatherland. Following the orders given by Louis Franchet d’Esperey, (1856–1942), the supreme commander of the Eastern Army, units of the Serbian army were supposed to go pass onto the territory of Austria-Hungary and occupy certain regions on behalf of the Entente. This order dated October 30, 1918 was in agreement with the war goals of the Kingdom of Serbia from 1914 which entailed liberation of the Southern Slavs and establishment of a common state [26, 32].

At the beginning of November, the Serbian army took over part by part of the Austro-Hungarian territories of the time. However, the Spanish Flu was already largely present in these regions. Schools were closed down in Zagreb on October 10, 1918, considerably before the entry of Serbian troops and a day later in Osijek and Sarajevo [14]. Schools were closed down throughout Austria-Hungary and also in those regions which are part of the present day Serbia. Schools were closed down in the village Tovariševo in Bačka on October 23 [33]. 300 death cases were registered in Zemun in October 1918, whereas that number reached 408 in Stara Pazova. A Croatian newspaper of that time wrote mid October, that doctors in Split hardly manage to visit all patients, that there are 8 to 10 funerals per day. The Croatian paper „Obzor“ reported on October 13, 1918 that almost half the newspaper boys had fallen ill with flu, so that subscribers are kindly asked to come and get their copy of the newspaper at the newspaper office. The same paper reported on October 19, that the state railway was forced, due to the illness of the employees, to reduce the number of train lines. Zagreb horse cab drivers refused to transport Zagreb doctors, for fear of the disease, which was the cause for the intervention of the municipal administration. It is possible to see in the preserved documentation of the military administration of Bosnia and Herzegovina, that around 40,000 people fell ill in October and that around 4,000 died, and that this disease became more frequent by the end of October [14]. Of course, all these data should be taken as the lower figure of the ill and dead cases, because the Spanish Flu could certainly not be registered in less accessible regions.

Serbian soldiers thus performed their liberation mission in the period of greatest mortality caused by the pandemic. The disease was present among the soldiers before the beginning of the liberation actions, they came back to find the disease in the liberated fatherland, and the Spanish Flu was also largely present on other territories of the future new state. Serbian soldiers were thus dying of the Spanish Flu also on these new territories. On the other hand, the state interest imposed that no attention be paid to the pandemic, as this would slow down the victorious advancement and would endanger the long desired goal. Austria-Hungary capitulated on November 3, 1918.

A photo of the entry of Serbian soldiers into Novi Sad on November 9, 1918 shows a multitude of soldiers and civilians, densely crowded, which illustrates excellent conditions for the spread of the disease. The disappearance of the old state and the establishment of a new one, created a public health vacuum, even chaos. People unavoidably came in contact with the army, gathered on various demonstrations, conditions for preventive measures disappeared. Even more expressed mortality occurs in Zagreb in the second half of November and the first half of December, which is certainly related to the termination of all kinds of public health activities, more intensive contacts among people. Croatian sources indicate that a significant number of Serbian soldiers died of the Spanish Flu in this city. „Obzor“ dated November 9, reported that entire houses were left empty in Bosnia [14].

Dr. Aleksandar Radosavljević remembers his arrival in Sarajevo:

„When we arrived in Sarajevo with our medical corps unit of the Timok Division of the first call-up, we started immediately working in the Sarajevo hospital. Only there were we able to see that the Spanish Flu epidemic had spread largely. There were many ill soldiers and civilians in the Sarajevo hospital. I even saw, among the ills, my acquain-

tance, Dr. Jefto Dedijer, a university assistant professor, who was on his way back to his family from Switzerland. Dr. Jefto Dedijer, the father of Vladimir Dedijer, was hurrying home, but fell ill in Sarajevo. I talked to him, thinking that I would see him again the next day, but unfortunately, he died that very day" [11].

It is not easy to get the precise data about the number of the dead in the different environments. Documents were not kept with great precision, the demographic picture of the different environments changed significantly in the war period. Still, it is possible to say with great certainty, based on the existing data, that people died everywhere of the Spanish Flu in large numbers, that it was really a matter of a „terrible epidemic".

A new cemetery was opened in the village Tovariševo in Bačka in the course of the pandemic. A total of 55 people of Orthodox religion mainly very young, died in the village from September 15, 1918 until November 28, 1918. The village had a population of a little over 2,500 Orthodox followers in this period, however the number of soldiers from the village who succumbed to the flu, is not known. Dr. Živojin Gavrilović, who studied the consequences of the Spanish Flu pandemic in 15 villages in south-eastern Bačka, found that 369 people died of it in them [34].

It is possible to find information that 775 people died of the Spanish Flu in the Zlatibor canton and that some houses were completely devastated [35].

There were many Serbian victims of the Spanish Flu, one should also bear in mind that the Serbian population was also densely settled outside of Serbia at that time, on the very territories which were to be united with Serbia. The Spanish Flu took thousands of Serbian lives. The pandemic was ignored during its course, because of war goals, thus it has remained a mysterious, forgotten disease to date. To die of it, meant practically to get killed in the war. That is probably the reason why it was neglected. However, the disease could certainly not have been ignored in that war time by families who lost their dearest ones. The Spanish Flu took young men and girls, children and adults at the peak of their vitality, leaving orphans everywhere, dooming children to a miserable childhood, without one or both parents, bringing pain to elderly people, bringing them suffering for the rest of their life.

A text appeared in „The Serbian Newspaper" dated November 10/23, 1918, about lung auscultation, as a protest because of the concealing of the tragic consequences of the pandemic:

„It is not sad when you listen to lungs, and nothing is heard in them. It is sad when even desperate consciousness is not heard, which is screaming, imploring, begging us to get rid of magician and secret moves and significantly wrinkled eyebrows and meaningless expectoration of the many „hm!" and continuous annoying positioning of pince-nez, which is not slipping anywhere and pretences to ourselves and to the world. Medicine is not acting" [36].

This bitterness related to doctors, of whom there were not many anyway, is not strange. Little were they able to do anyway, despite everything.

Finally, it is possible to say, that Serbian doctors noticed after the pandemic, in many people, who had survived the Spanish Flu, neurological and psychiatric consequences. While speaking of the patients with the Spanish Flu sequelae, Dr. Aleksandar Radosavljević, indicates:

„Almost all the beds were occupied in the Neurological Department at the Belgrade hospital, by the diseased with indicated severe symptoms. These patients left a very sad and dismal impression and fast death was often the consequence of this disease. These patients were coming to the Belgrade hospital until the end of 1927. We do not know how many diseased there were, how many came and how many did not come to the hospital" [11].

There were also other consequences. The Spanish Flu „transformed" into tuberculosis in the never determined, but certainly not small number of cases. Following the recovery from the Spanish Flu, the impaired lungs by virus, were probably not efficient in fighting against the tuberculosis bacillus.

The third wave

The third wave of the Spanish Flu appeared in January 1919. Although the war had already ended, there was not much data even about this last pandemic incursion. One gets the impression that the disease did not appear everywhere in the third wave, but that it was present only in some places, and that it took fewer lives in comparison with its second wave. However, people were still dying of the Spanish disease.

The third pandemic wave lasted in Spain from January to June 1919. It was found that the disease appeared mostly in the parts of the country which were struck by the first wave of the disease, whereas the parts which had suffered from the second wave, were mainly spared. The number of the dead of the flu in Spain reached about 147,000 in 1918, whereas the number of the dead in 1919 was a little over 21,000 [1].

The third wave was also present on the territory of the present Serbia. Unfortunately, the data are scarce. Dr. Živojin Gavrilović indicated a total of 12 death cases in the villages Kać and Gospođinci for 1919 [34]. Two people died of the Spanish Flu in the village Tovariševo at the beginning of 1919. Influenza cases were registered in the hospital in Vranje in the first four months of 1919 [28].

The disease reached also Australia at the beginning of 1919. However, it is not possible to talk about the third pandemic wave in this case, as its second wave was not present at all on this continent, due to the strict quarantine. The influenza pandemic virus was significantly less deadly at the beginning of 1919 than in the autumn of 1918, probably due to certain genetic, i.e. antigenic changes of the virus. Still, the disease took also thousands of lives in Australia [4].

Over 2,600 people died of influenza and pneumonia in Paris in February 1919. [4]. This information is particularly significant, if we know that a peace conference was open in Paris on January 18, 1919 for signing of the peace treaty between the Allies and the defeated Central Powers. Maybe

it was here that influenza had, for the second time, an impact on the outcome and consequences of World War I. In the first case, it is said that it is possible that the Spanish Flu slowed down the strong German offensive at the crucial moment, preventing thus the Central Powers to win the war. In the second case, influenza disabled, probably the most important figure of the peace conference, the American president Thomas Woodrow Wilson, (1856–1924), at the very important moment of the peace negotiations. Wilson fell ill on April 3, and the cough paroxysms appeared so suddenly that Wilson's personal doctor thought that it was a question of an assassination attempt by poisoning. The first signs of recovery appeared on the fourth day, following a very severe course of the disease [4].

Before the beginning of the disease, Wilson had insisted on the peace treaty being acceptable for both sides. He was so persistent in this, that he even threatened to leave the peace conference, unless his principles were respected. Very soon after his disease, Wilson continued negotiations, but the people close to him noticed a change in his conduct. The American president had become forgetful, he concentrated with difficulty. His personality had somehow changed, and this was manifested in his refraining from the political principles, he had advocated before his disease. Then Wilson accepted easily the requests made by the French prime minister, Georges Benjamin Clemenceau, (1841–1929) which entailed extremely humiliating terms for the defeated Germany. Before influenza, Wilson threatened to abort negotiations because of the same requests made by Georges Clemenceau. Finally, the humiliating peace terms were imposed on Germany, in which many historians see the causes of the next world war. It is possible that the neurological complications of the Spanish Flu caused the change in Wilson's conduct [4].

Many authors indicate 1920 instead of 1919, as the final year of the Spanish Flu pandemic. The disease appeared also after the first half of 1919, but sporadically. The renowned Canadian doctor, Sir William Osler, (1849–1919) fell ill with the Spanish Flu on September 29, 1919. He was working at the Oxford University in England at that time. Influenza was present in that part of England to such an extent, that considerations were made about postponing the beginning of the lectures at Oxford. Following a short recovery, Dr. William Osler got pneumonia, of which he died on December 29, 1919, despite long, intensive treatment [4].

There is an indication of numerous death cases caused by influenza and its consequences in New York and Chicago at the beginning of 1920 [4].

There were also death cases in Serbia in 1920. Dr. Gavrilović indicated a total of 8 in Kać, Budisava and Gospođinci [34].

Many who had recovered from the Spanish Flu, felt the consequences for long. Cases similar to the ones which were treated in the Neurological Department of the Belgrade Hospital following the Spanish Flu pandemic, were reported throughout the world for years after the Spanish Flu. Dr. Aleksandar Radosavljević described the appearance of these patients:

„... one of the main symptoms was a lethargic condition, with a numb facial expression, so that the face of the diseased had the expression of a statue – or a mask" [11]. This disease, which was believed to be the consequence of the Spanish Flu, was called „encephalitis lethargica".

Conclusion

The Spanish Flu is a disease which claimed millions of lives in 1918 and 1919. It appeared at the end of the bloody World War I, thus it is perceived in some way as an inevitable part of the war reality. Namely, it is a known fact throughout history that war happenings are, by rule, followed by a significant number of victims of infectious diseases. Yet, the disease took in this case five times as many lives as the whole World War I. That speaks enough about its significance.

The Spanish Flu was a disease which caused an enormous number of family tragedies, we could say that an ocean of tears has been shed because of this disease. Numerous young lives, millions of them, became victims of the pandemic. Those who could have offered most, those from whom most was expected, the strongest ones, those were the ones who ended their lives in terrible agony, cyanotic, fighting for air. Their dearest ones, who survived, were left with suffering for life. The significance of the Spanish Flu is exactly in this and this is the very reason why we should not allow it to be forgotten. Millions of those who died of the Spanish Flu oblige us to remember this and to strive by means of our knowledge of this pandemic to prevent any similar future mass tragedy.

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LETTER TO THE EDITOR / PISMO UREDNIKU

The Spanish Flu
(A coment on the article: Radusin M. The Spanich Flu – Part I: the first wave. Vojnosanit Pregl 2012; 69(9): 812–7)

Španska groznica
(Komentar o članku: Radusin M. Španska groznica – I deo: prvi talas. Vojnosanit Pregl 2012; 69(9): 812–7)

Dr. Milorad Radusin [1] in his article payed extremely high attention to diagnostic difficulties, especially during the first wave of the Spanish flu epidemic and particularly with respect to the distinction between the Spanish flu and pneumonia, which frequently led, as a complication, to fatal outcomes, having a further reflection also on hospital records of the diseased and dead.

Here are some more details which confirm this very connection.

In the report of the hospital Griton and Newnham Unit, which was situated in Thessaloniki within the Scottish Women's Hospitals (SWH) from 1915 to 1918 the following was mentioned, too [2]: "122 patients were treated in the Ward from October 1 till December 31, 1918; 74 of the latter were admitted with influenza, mainly French. There were no fatal cases; 16 were admitted with lung complications, 7 died. Of the surgical cases, 24 got the influenza, five of which developed pneumonia. All got well. 8 cases occurred among Serbian orderlies (working under the supervision of nurses). There were no complications, they all got well. This points out to the significance of nursing in the case of influenza, having a fatal outcome only when it is complicated by pneumonia."

In the 6-month report of SWH, the hospital "America", situated in Vranje (1918/19) (end of October 1918 – May 1919) it was indicated that 334 cases were registered as suffering from influenza, wheras 500 diseased were at the same time recorded as suffering from pneumonia, bronchitis, TBC, although a certain number of pneumonia cases were quite certainly complications of the Spanish flu. In the 3-month report for May, June and July 1919, a distinction had been made between pneumonia and bronchitis (total of 84 cases) on one hand and tuberculosis (87) on the other, whereas influenza was still recorded separately (10 cases). However, already in the 6-month report on mortality, the Spanish flu and pneumonia were classified together: Influenza & pneumonia = 80, with the same occurring in the following 3-month report: Influenza & pneumonia = 2 [3].

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ERRATUM

Nataša Perković Vukčević, Gordaba Babić, Zoran Šegrt, Goerdabna vukiović Ercegović, Snežana Janković, Ljubomir Aćimović. Severe acute caffeine poisoning due to intradermal injections: meso-therapy hazard. **Vojnosanit Pregl 2012; 69(8): 707–13**.

In the article cited above, on the page 711, in the right column, line 7 and 12 from above, the word **hyperkalemia** should be replaced by the word **hypokalemia**.

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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.

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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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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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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.

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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. 413-28.

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.

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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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