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ACUTE EFFECTS OF ORAL SODIUM BICARBONATE ON BLOOD MARKER LEVELS IN ELITE JUDO ATHLETES

AKUTNI EFEKTI UPOTREBE NATRIJUM-BIKARBONATA NA NIVO MARKERA KRVI KOD ELITNIH DŽUDISTA

Goran DANKOVIĆ[1, 2], Tomislav STANTIĆ[3], Nenad STOJILJKOVIĆ[4], Ivana ALEKSIĆ[5], Vladimir ŽIVKOVIĆ[1] and Vladimir JAKOVLJEVIĆ[1]

Summary

Introduction. The aim of this study was to establish if sodium bicarbonate affects the blood marker levels after a Special Judo Fitness Test in elite judo athletes. **Material and Methods.** Ten male judo athletes (age 20 ± 2.1 years; body height 180.18 ± 8.11 cm; body mass 85.24 ± 23.17 kg; body mass index 25.2 ± 3.4 kg/m^2), judo masters (black belt holders) with at least 10 years of training and competition experience, agreed to participate in the current research. **Results.** The results showed a significant main effect of time ($p < 0.05$) for the following variables: uric acid, aspartate aminotransferase, alanine transaminase, creatine kinase, lactate dehydrogenase, phosphate, magnesium, calcium, sodium, potassium, and chloride. We found that creatine kinase, C-reactive protein, sodium and chloride were significantly different ($p < 0.05$) in the sodium bicarbonate group compared to placebo group after the Special Judo Fitness Test. **Conclusion.** The main finding of the present study was that sodium bicarbonate (0.3 g/kg) improved recovery compared to placebo in elite judokas. Therefore, coaches should consider sodium bicarbonate to improve athlete recovery during combat.

Key words: Sodium Bicarbonate; Blood; Exercise Test; Martial Arts; Athletic Performance; Recovery of Function

Sažetak

Uvod. Cilj ove studije bio je da se utvrdi da li natrijum-bikarbonat utiče na nivo markera krvi nakon specifičnog džudo-testa kod vrhunskih džudista. **Materijal i metode.** Deset muških džudista (uzrast 20 ± 2,1 godina; telesna visina 180,18 ± 8,11 cm; telesna masa 85,24 ± 23,17 kg; indeks telesne mase 25,2 ± 3,4 kg/m^2) koji su majstori džudoa (nosioci crnog pojasa) sa najmanje 10 godina obuke i takmičarskog iskustva, pristali su da učestvuju u tekućem istraživanju. **Rezultati.** Rezultati ukazuju na to da postoji glavni vremenski efekat za sledeće varijable: urea, aspartat aminotransferaza, alanin aminotransferaza, kreatin kinaza, laktat dehidrogenaza, fosfat, magnezijum, kalcijum, natrijum, kalijum i hlor. Otkrili smo da su kreatin kinaza, visoko senzitivni C-reaktivni protein, natrijum i hlor bili značajno različiti u grupi sa natrijum bikarbonatom u poređenju sa placebo grupom nakon *Special Judo Fitness Test.* **Zaključak.** Glavni nalaz ove studije bio je da je natrijum bikarbonat (0,3 g kg−**1**) poboljšao oporavak u poređenju sa placebom kod vrhunskih džudista. Zbog toga bi treneri trebalo da razmotre uzimanje natrijum bikarbonata kako bi poboljšali oporavak sportista tokom borbe.

Ključne reči: natrijum bikarbonat; krv; fizički test; borilačke veštine; atletske performanse; oporavak funkcije

Introduction

Competitive judo is a sport of high-intensity where athletes repeatedly push and pull each other in order to perform different techniques (throws, arm bars, chokes, pins…) [1, 2]. It has been acknowledged that judo is a difficult sport that requires a variety of unique traits in order to compete at a high level [3]. Strength and endurance of upper and lower body, anaerobic power, speed and trunk muscle functions are the most important factors for success in judo [4, 5]. Furthermore, core stability may improve judo performance because it will make it easier for the lower body to transmit forces to the upper body [6] during judo techniques and it can also improve balance control [7] which is essential for dealing with disturbances brought on by the opponent [1, 2].

Recovery of the organism is important due to the appearance of fatigue [8]. Fatigue can be compensated by recovery and leads to the restoration of allostatic balance of the organism by establishing resources on the psychological and physiological level

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Abbreviations

ALT – alanine transaminase
AST – aspartate aminotransferase
Ca – calcium
Cl – chloride
CK – creatine kinase
hsCRP – high-sensitivity C-reactive protein
K – potassium
LDH – lactate dehydrogenase
Mg – magnesium
$NaHCO_3$ – sodium bicarbonate
Na – sodium
SJFT – Special Judo Fitness Test
HR – heart rate

[9]. It is very important to monitor the training load, recovery and changes in psychological status in judo, in order to improve performance and avoid non-functional overload [10, 11]. In addition, it is documented that high-intensity physical exercises may lead to localized muscle damage and a significant increase in the levels of creatine kinase (CK), lactate dehydrogenase (LDH) and myoglobin build-up after combat [12]. Also, significant increase in LDH and CK levels after strength training with a multiple series protocol is also present [13, 14]. Rapid weight loss is another issue that has a negative impact on muscle damage in judo athletes leading to a significant decline in performance during competition [15]. Therefore, it is crucial to monitor the recovery of athletes in order to reduce these indicators of muscle damage in order to avoid them [12].

To enhance recovery during training and competition, judo athletes use various types of products, chocolate milk [16], beta-alanine supplementation [17, 18], caffeine-containing energy drinks [19], caffeine [20, 21], and creatine [22]. The usage of sodium bicarbonate ($NaHCO_3$) for recovery improves judo-related performance and blood lactate concentration [23, 24]. On the other hand, Šančić et al. showed that active recovery was better compared to $NaHCO_3$ intake when lactic acid levels were used to determine the recovery levels in judokas [25]. Although the mentioned studies have shown the positive effects on several markers of recovery in judo, to the best of the authors' knowledge there were no studies that included blood markers. Therefore, the aim of this study was to determine whether $NaHCO_3$ affects blood markers after a specific judo test in elite judokas.

Material and Methods

Ten male judokas, aged 20.1 ± 2.8 years, judo masters (black belt holders) with at least 10 years of training and competition experience, agreed to participate in the current research **(Table 1)**. The inclusion criteria were male gender, age from 18 to 25 years, judo masters (black belt holders) with at least 10 years of training and competition experience, absence of diseases and injuries, and using no supplementation 2 months before the start of this study. The protocol of the study was approved by the Ethics Committee of the Faculty of Sport and Physical Education, University of Niš (04-1847/2; November 26, 2020), in accordance with the International Ethical Guidelines. In addition, all participants were informed about the protocol and gave their written consent to participate in the study.

The study was a double-blind crossover trial with the order of treatments being randomly assigned. The washout period was 72 hours. All subjects received a dose of $NaHCO_3$ (0.3 g/kg body weight) [24] or a placebo (Ringer's solution) 120 minutes before the fatigue caused by the Special Judo Fitness Test (SJFT) which was validated in high-level judokas [26].

Venous blood samples were taken before starting the training protocol, in the morning between 7 and 8 a.m., and after an overnight 10-hour fasting. In the second phase of the experimental treatment, the acute effects of $NaCO_3$ supplementation were investigated. At this stage, experimental group (N = 5) were supplemented with $NaCO_3$, while the control group (N = 5) received placebo. After supplementation, the participants had a "washout" period lasting 72 hours, after which the identical protocol was repeated in the same participants after they switched groups. The second blood sampling was done 5 minutes after the end of the SJFT, while the last blood collection was performed 30 minutes after the second one.

The SJFT was performed in the following order: two subjects (Uke) of the same weight category and similar height were positioned at 6 meters from each other, while the tested subject (Tori) was standing in the middle. At the timekeeper's signal, the tested participant runs to one Uke, performs a throw and then does the same with the other Uke. The test consists of three parts: the first part lasts 15 seconds of throwing and 10 seconds of rest. The second part lasts 30 seconds of throwing and 10 seconds of rest. The third part lasts 30 seconds of throwing.

Immediately after the end of the third part, the heart rate (HR) was measured with a HR monitor (Polar Team System, Polar, Kempele, Finland) (after exercise) as well as after 60 seconds of rest (after recovery). The index was calculated by summing the results of the HR after the test and the HR after 60 seconds of recovery, which is related to the total number of throws (n).

Index = HR after the test + HR 1 min after the test/n

Measurements of anthropometric parameters (body height, body weight) were measured by an anthropometer and the bioelectrical impedance method (InBody 770) before testing. Blood analysis was per-

Table 1. Basic descriptive characteristics of the sample (mean ± SD)
Tabela 1. *Bazična deskriptivna statistika uzorka (aritmetička sredina ± standardna devijacija*

Age (years) *Starost (godine)*	Training background (years) *Godine treniranja (godine)*	Body height (cm) *Telesna visina (cm)*	Body mass (kg) *Telesna težina (kg)*	Body fat (%) *Procenat masti (%)*	Fat mass (kg) *Masti (kg)*
20.1 ± 2.8	10.3 ± 1.2	180.2 ± 8.1	85.2 ± 23.1	12.8 ± 5.3	11.8 ± 8.6

Table 2. Blood marker levels following $NaHCO_3$ or placebo
Tabela 2. *Markeri krvi nakon $NaHCO_3$ ili placeba*

Variables/*Varijable*	Group/*Grupa*	1	2	3
Uric acid (mmol/L) *Mokraćna kiselina*	$NaHCO_3$ Placebo	352.18 ± 53.94	347.78 ± 50.09* 345.82 ± 44.73*	448.75 ± 52.07* 444.07 ± 42.35*
AST (U/L)	$NaHCO_3$ Placebo	23.55 ± 5.97	31.12 ± 6.51* 28.64 ± 3.50*	30.75 ± 11.41 28.60 ± 6.27
ALT (IJ/l)	$NaHCO_3$ Placebo	15.82 ± 6.19	25.12 ± 10.95 21.27 ± 10.58	18.62 ± 10.10 19.30 ± 8.08
CK (U/L)†	$NaHCO_3$ Placebo	245.73 ± 107.84	338.37 ± 135.84* 395.00 ± 163. 19	271.80 ± 114.61 289.64 ± 105.19
LDH (U/L)	$NaHCO_3$ Placebo	369.18 ± 42.78	445.78 ± 52.10* 438.45 ± 55.46*	415.87 ± 106.76 435.70 ± 78.40
hsCRP (mg/L) †	$NaHCO_3$ Placebo	1.36 ± 1.48	1.60 ± 2.47 1.52 ± 2.56	0.48 ± 0.30* 0.75 ± 0.55*
Phosphate/*Fosfat* (mmol/1)	$NaHCO_3$ Placebo	1.21 ± 0.15	1.46 ± 0.26* 1.51 ± 0.20*	0.89 ± 0.19* 1.15 ± 0.24*
Mg (mmol/1)	$NaHCO_3$ Placebo	0.77 ± 0.04	0.83 ± 0.06* 0.81 ± 0.05*	0.72 ± 0.08* 0.75 ± 0.05*
Ca (mmol/1)	$NaHCO_3$ Placebo	2.46 ± 0.08	2.64 ± 0.18* 2.65 ± 0.06*	2.42 ± 0.12* 2.61 ± 0.05*
Na (mmol/1)†	$NaHCO_3$ Placebo	138.82 ± 4.12	149.78 ± 8.00* 142.00 ± 3.19	141.25 ± 4.59* 142.50 ± 0.97
K (mmol/1)	$NaHCO_3$ Placebo	4.06 ± 0.21	3.54 ± 0.32* 3.66 ± 0.28*	3.85 ± 0.44 4.10 ± 0.25*
Cl (mmol/1)†	$NaHCO_3$ Placebo	100.27 ± 2.97	106.00 ± 5.36* 101.55 ± 2.62	99.12 ± 3.44* 102.30 ± 1.34
Myoglobin/*Mioglobin* (mcg/l)	$NaHCO_3$ Placebo	84.43 ± 42.35	81.63 ± 22.85 74.77 ± 50.04	94.11 ± 24.14 92.07 ± 56.82

Legend: * - statistically significant differences within groups ($p < 0.05$); † - group x time interaction ($p < 0.05$); 1 - baseline; 2 - after SJFT (5 min.); 3 - after SJFT (30 min.); $NaHCO_3$ – sodium-bicarbonate; AST - aspartate aminotransferase; ALT - alanine transaminase; CK - creatine kinase; LDH - lactate dehydrogenase; hsCRP - high-sensitivity C-reactive protein; Mg – magnesium; Ca – calcium; Na – sodium; K – potassium; Cl – chloride
*Legenda: * - statistički značajna razlika unutar grupa ($p<0.05$); † - grupa x vreme interakcija ($p<0.05$); 1 - inicijalno; 2 - nakon SJFT (5 min.); 3 - nakon SJFT (30 min.); $NaHCO_3$ – natrijum bikarbonat; AST - aspartat aminotransferaza; ALT - alanin aminotransferaza; CK - kreatin kinaza; LDH - laktat dehidrogenaza; hsCRP – visoko senzitivni C-reaktivni protein; Mg – magnezijum; Ca – kalcijum; Na – natrijum; K – kalijum; Cl – hlorid*

formed before SJFT and two times after SFJT. During every time point, all subjects rated the perceived exertion on Borg's scale.

Biochemical parameters were determined at the Faculty of Medical Science in Niš using standard routines and methods. Serum was used for biochemical analyses, and the blood count with the leukocyte formula was determined from whole blood. Test tubes with K2 EDTA anticoagulant were used for blood sampling to determine the blood count, and for fibrinogen test tubes with citrate as an anticoagulant. Biochemical analyses were performed on a Beckman Coulter AU680 (Beckman Coulter, Brea, CA) biochemical analyzer, blood count on a Cell-Dyn Ruby hematology analyzer, and fibrinogen on a Thrombostat coagulometer (Thrombostat I, Behnk Elektronik GmbH & Co, Germany). The following blood markers were taken for further analysis: uric acid, myoglobin, CK, LDH, aspartate-aminotransferase (AST), high-sensitivity C-reactive protein (hsCRP), sodium (Na), magnesium (Mg) calcium (Ca), potassium (K), chloride (Cl), phosphate.

To test the normality of the data, we applied the Shapiro-Wilk test. Additionally, the data were tested for homogeneity using Levene's test. After that, a two-way analysis of variance with repeated measurements was used with supplementation and time point as factors (supplementation × round). When necessary, a post hoc test was used to identify possible differences between conditions and time. For analysis of variance results, effect sizes were calculated using eta squared (η^2), classified according to Cohen. The level of statistical significance was set at $p < 0.05$. Statistical data processing was carried out in the statistical package IBM SPSS 24.

Results

Table 2 presents the results of uric acid, AST, alanine transaminase (ALT), CK, LDH, phosphate, hsCRP, Mg, Ca, Na, K and Cl measured in different periods of time. The results showed a significant main effect of time for the following variables: uric acid ($F = 44.7$; $p = 0.001$; $\eta^2 = 0.87$), AST ($F = 8.5$; $p = 0.004$; $\eta^2 = 0.55$), ALT ($F = 9.01$; $p = 0.003$; $\eta^2 = 0.56$), CK ($F = 8.4$; $p = 0.004$; $\eta^2 = 0.55$), LDH ($F = 10.0$; $p = 0.002$; $\eta^2 = 0.59$), hsCRP ($F = 21.7$; $p = 0.01$; $\eta^2 = 0.55$); phosphate ($F = 49.1$; $p = 0.001$;

$\eta^2 = 0.86$), Mg ($F = 8.7$; $p = 0.004$; $\eta^2 = 0.55$), Ca ($F = 12.4$; $p = 0.001$; $\eta^2 = 0.64$), Na ($F = 7.8$; $p = 0.005$; $\eta^2 = 0.53$), K ($F = 9.2$; $p = 0.003$; $\eta^2 = 0.57$) and Cl ($F = 4.23$; $p = 0.036$; $\eta^2 = 0.38$). Additionally, group x time interactions were found for CK ($F = 5.2$; $p = 0.02$; $\eta^2 = 0.43$), hsCRP ($F = 3.9$; $p = 0.04$; $\eta^2 = 0.64$), Na ($F = 5.3$; $p = 0.02$; $\eta^2 = 0.43$) and Cl ($F = 6.3$; $p = 0.01$; $\eta^2 = 0.47$).

Discussion

The purpose of the present study was to investigate the effects of $NaHCO_3$ ingestion on selected blood markers during SJFT. The main finding was that $NaHCO_3$ (0.3 g/kg) improved recovery compared to placebo in elite judokas. We found that CK, hsCRP, Na and Cl were significantly different in $NaHCO_3$ group compared to placebo group after SJFT.

It is well known that quick recovery after intense physical activity has many benefits for athletes, such as improved performance and reduced possibility of overtraining [27]. Faster recovery is of crucial importance in judo as well as in other high-intensity combat sports [28, 29]. It is also known that high-intensity activities can have impact on acid-base balance, while further exercise-induced acidosis can negatively affect performance and athlete's recovery [30]. In order to regulate exercise-induced metabolic acidosis, athletes often use various nutritional and pharmacological agents that affect pH values in blood and muscles [23]. Mueller et al. [31] found that $NaHCO_3$ supplementation is useful in reducing acidosis as well as improving sports performance. Several studies [23–25, 32] were conducted in order to determine if using $NaHCO_3$ helps in recovery of judokas. Artioli et al. [24] tried to determine the acute effects of $NaHCO_3$, and found no improvements following the first two matches, while an improvement was noted in matches 3 and 4. There is a lack of studies dealing with blood markers and $NaHCO_3$ supplementation in judokas, which would provide direct comparison and some significant conclusions. One research aimed to determine the effects of caffeine and $NaHCO_3$ supplementation as well as the separate effects on recovery in judokas [32]. However, regarding biochemical markers, plasma lactates were the only ones sampled, showing that the combination of supplements had the greatest impact on recovery. Potential stronger effects with combinations of supplements were confirmed by a recent review [33] showing a significantly greater ergogenic effect when combining $NaHCO_3$ and beta-alanine compared to isolated intake of beta-alanine (Cohen's $d = 0.43$ versus 0.24).

It is believed that 3 successive judo matches may induce an increase in muscle damage markers, especially, serum CK and LDH [34]. Therefore, it is of great importance that in the current study CK was significantly different in $NaHCO_3$ group compared to placebo group after the SJFT. Moreover, it is also important to mention that serum CK and LDH reach their peak 24 - 96 hours after the exercise [35]. We evaluated the recovery 30 minutes following the SFJT. Accordingly, it can be assumed that the difference may be even higher in the current study regarding CK levels. Therefore, future studies should include additional testing the day after SFJT.

The most recently published review article [36] showed that acute or chronic $NaHCO_3$ supplementation is effective in improving certain variables of physical performance in combat sports. The authors also claimed that the positive effects are most often visible following the onset of fatigue. We found that $NaHCO_3$ intake was significantly more effective than placebo for CK, hsCRP, Na and Cl recovery. However, no effects were observed for any other outcomes in the current study. The reason for this may be the training protocol or doses of $NaHCO_3$ in this study. Although all judokas were high level athletes and trained at least ten years, variations among individuals with regard to the blood marker levels may be a possible explanation for these results.

The current study has some limitations. The main limitation is that some markers of muscle damage were not sampled 12 and 24 hours after muscle damage. It could be speculated that $NaHCO_3$ supplementation would show significant effects compared to the placebo group. Moreover, the results should be applied only to male judokas since the study included only male athletes. The sample size was small. However, it is hard to find a larger sample size at this level of sport. In addition, official combats should be used to evaluate $NaHCO_3$ effects on blood markers. Nevertheless, this kind of studies are of great importance in judo as a predominantly anaerobic sport [37] having in mind that excessive physical load may lead to oxidative stress in athletes.

Conclusion

The current study showed that sodium bicarbonate may lead to better recovery after a Special Judo Fitness Test or combat simulation. This supports the fact that sodium bicarbonate ingestion is important to increase glycolytic energy production and performance during a simulated judo combat. Therefore, coaches should consider sodium bicarbonate ingestion to improve athlete recovery during combat.

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EFFECTS OF MECHANICAL VENTILATION DURING CARDIOPULMONARY BYPASS ON POSTOPERATIVE PULMONARY COMPLICATIONS

UTICAJ MEHANIČKE VENTILACIJE U TOKU EKSTRAKORPORALNE CIRKULACIJE NA POSTOPERATIVNE PLUĆNE KOMPLIKACIJE

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Summary

Introduction. It is common practice in on-pump cardiac surgery to stop mechanical ventilation when extracorporeal circulation is started or to continue with low tidal volumes. The aim of this study was to investigate whether patients ventilated with low tidal volumes had a lower percentage of postoperative pulmonary complications compared to patients who were not ventilated during cardiopulmonary bypass. **Material and Methods.** This retrospective study included patients who underwent coronary artery bypass graft surgery over a period of 14 months. Patients with lung diseases and those with an ejection fraction < 30% were excluded from the study. **Results.** A total of 499 patients were included in the study. Of these, 398 were ventilated with low tidal volumes, while 101 patients were not ventilated during extracorporeal circulation. The groups did not differ in baseline characteristics, comorbidities, and intraoperative data. Pulmonary complications were equally prevalent in both groups (ventilated 16%, not ventilated 17.8%). The most frequent were the need for prolonged mechanical ventilation (ventilated 5.8%, not ventilated 5.9%), and pleural effusions (ventilated 4.8%, not ventilated 5.9%). The incidence of pneumonia was identical in both groups (2%). Other complications were less frequent. Duration of mechanical ventilation after surgery, stay in the intensive care unit, and in-hospital mortality did not differ significantly between the groups. **Conclusion.** Pulmonary complications after cardiac surgery are still common. The experience at our clinic showed that the choice of mechanical ventilation strategy during cardiopulmonary bypass does not affect postoperative pulmonary complications.

Key words: Cardiac Surgical Procedures; Cardiopulmonary Bypass; Respiration, Artificial; Lung; Risk Factors; Postoperative Complications; Treatment Outcome

Sažetak

Uvod. Uobičajena praksa kod *on-pump* kardiohirurških operacija jeste da se mehanička ventilacija pluća obustavlja kada se započne ekstrakorporalna cirkulacija ili se nastavlja niskim disajnim volumenom. Cilj ove studije bio je da ispita da li su pacijenti ventilirani niskim disajnim volumenom imali manji procenat postoperativnih plućnih komplikacija u odnosu na pacijente koji nisu ventilirani u toku ekstrakorporalne cirkulacije. **Materijal i metode.** Retrospektivna studija kardiohirurških pacijenata operisanih u periodu od 14 meseci. U studiju su uključeni samo pacijenti sa hirurškom revaskularizacijom miokarda. Iz studije su isključeni pacijenti sa plućnim bolestima i oni sa ejekcionom frakcijom < 30%. **Rezultati.** U studiju je uključeno ukupno 499 pacijenata. Od toga, 398 je ventilirano niskim disajnim volumenom dok 101 pacijent nije ventiliran u toku ekstrakorporalne cirkulacije. Grupe se nisu razlikovale po osnovnim karakteristikama, komorbiditetima i intraoperativnim podacima. Plućne komplikacije su bile podjednako zastupljene (ventilirani 16%, neventilirani 17,8%). Najučestalije su bile potreba za produženom mehaničkom ventilacijom pluća (ventilirani 5,8%, neventilirani 5,9%) i pleuralni izlivi (ventilirani 4,8%, neventilirani 5,9%). Učestalost pneumonije je bila identična u obe grupe (2%). Ostale komplikacije su bile manje učestalosti. Trajanje mehaničke ventilacije pluća nakon operacije, boravak u jedinici intenzivnog lečenja i intrahospitalni mortalitet nisu se značajno razlikovali po grupama. **Zaključak.** Plućne komplikacije nakon kardiohirurških operacija su i dalje česte. Iskustvo na našoj klinici je pokazalo da izbor strategije mehaničke ventilacije pluća u toku ekstrakorporalne cirkulacije ne utiče na plućne komplikacije.

Ključne reči: Kardiohirurške procedure; kardiopulmonalni bajpas; mehanička ventilacija; pluća; faktori rizika; postoperativne komplikacije; ishod lečenja

Introduction

About 1.5 million cardiac surgeries are performed annually around the world [1]. Despite great progress in surgical technique and perioperative anesthetic management, cardiac surgeries are accompanied by numerous postoperative complications, caused both by the surgical procedure itself, and by numerous unfavorable characteristics of the patients (age, comorbidities) [2]. After cardiovascular complications, postoperative pulmonary complications (PPCs) are the most common complications in cardiac surgery, occurring in up to 40% of patients [3]. They are associated with prolonged stay

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Abbreviations

PPCs – postoperative pulmonary complications
ICU – intensive care unit
MV – mechanical ventilation
TV – tidal volume
PEEP – positive end-expiratory pressure
CPB – cardiopulmonary bypass
PaO_2 – arterial oxygen partial pressure
FiO_2 – fractional inspired oxygen
$PaCO_2$ – partial pressure of carbon dioxide
CABG – coronary artery bypass graft
IQR – interquartile range

in the intensive care unit (ICU), prolonged hospitalization, and increased mortality [3–7].

Mechanical ventilation (MV) is an integral part of cardiac surgery. It is certainly a risk for the development of PPCs. In the last two decades, introduction of lung protective ventilation, which includes low tidal volume (TV), low plateau and driving pressure, recruitment maneuvers, and adequate positive end-expiratory pressure (PEEP), has contributed to the reduction of pulmonary complications in surgery patients [8, 9]. However, on-pump cardiac surgery is performed in conditions of cardiopulmonary bypass (CPB), which is responsible for systemic inflammatory response and oxidative stress, leading to pulmonary ischemia-reperfusion injury [4, 10, 11]. Other factors also contribute to the development of complications, including the patient's respiratory function, type of surgery, pain after sternotomy, anesthesia protocol, and use of blood and blood products [4, 12]. The CPB completely takes over the role of the heart and lungs and enables smooth surgical work, so the question arises whether MV is necessary during that period. International guidelines for CPB management recommend the use of PEEP (recommendation class IIa), as well as ventilation during CPB (recommendation class IIb), due to lung protection [13]. However, these are low-grade recommendations, mainly due to different study results. In practice, the dilemma of applying the MV during CPB still remains. The usual practice is not to ventilate the lungs or to ventilate with low TV. A study that included 69 cardiac surgery centers in Italy showed that in as many as 75% of centers, ventilation stops during CPB [14].

The results of some studies showed that CPB without MV is associated with decrease in the arterial oxygen partial pressure (PaO_2) to fractional inspired oxygen (FiO_2) ratio, arterial blood pH, static pulmonary compliance, as well as increase in partial pressure of carbon dioxide ($PaCO_2$), pulmonary shunt, and alveolar-arterial oxygen gradient [15]. One meta-analysis showed that MV during CPB may improve post-CPB oxygenation and gas exchange in patients undergoing cardiac surgery, altough long-term outcomes are unknown [16]. On the other hand, some randomized studies and meta-analyses showed that maintaining a low TV did not reduce the incidence of PPCs compared to a strategy in which no ventilation was performed during CPB [5, 6, 17–19].

The aim of this study was to investigate whether patients ventilated with low TV with the use of PEEP after coronary artery bypass graft (CABG) surgery have a lower percentage of PPCs compared to patients who were not ventilated during CPB.

Material and Methods

The retrospective study was conducted at the Clinic of Cardiovascular Surgery of the Institute of Cardiovascular Diseases of Vojvodina in Sremska Kamenica in the period from October 1, 2021 to December 1, 2022. The study was approved by the Ethics Committee of the Institute of Cardiovascular Diseases of Vojvodina (No. 2115-1/4). The study included patients who were admitted for CABG surgery. Only patients undergoing elective surgery were included in the study. Patients with chronic lung diseases and patients with an ejection fraction < 30% were excluded from the study. The first group (group V) included patients who were ventilated during CPB (TV 3 ml/kg predicted body weight, PEEP 5 cm H_2O, respiratory rate 10 - 12/min, FiO_2 0.6 - 0.7). The second group (group NV) included patients who were not ventilated during CPB.

All patients underwent surgery under general endotracheal anesthesia. As premedication, they received midazolam 3.75 - 7.5 mg orally. Midazolam, sufentanil, propofol, and rocuronium bromide were used to induce anesthesia. After intubation, the lungs were mechanically ventilated with a 50/50 oxygen/air mixture. Anesthesia was maintained with sevoflurane, analgesia with continuous infusion of sufentanil, while neuromuscular relaxation was maintained with intermittent administration of rocuronium bromide. The following monitoring was used perioperatively: electrocardiography, pulse oximetry, continuous arterial pressure, arterial gas analysis, central venous pressure, body temperature, and diuresis. Medial sternotomy approach was used in all patients. After surgery, patients were transferred to the ICU, where sedation with propofol continued, until the conditions for extubation were met.

The following parameters were also examined in all patients: demographic data (age and sex), height, weight, body mass index (BMI), comorbidities (arterial hypertension, previous myocardial infarction, cerebrovascular accident, smoking, dyslipidemia, diabetes, chronic kidney disease), ejection fraction before surgery, and European System for Cardiac Operative Risk Evaluation (EuroScore II). Intraoperative variables included: cross-clamp time and CPB time. Postoperatively, the duration of MV and the number of days in the ICU were recorded. Of particular importance was the monitoring of PPCs: prolonged MV (≥ 24 h), pleural effusion, pneumonia, pneumothorax, respiratory failure, reintubation, and bronchospasm. We also compared in-hospital mortality between groups.

We used descriptive statistical measures: arithmetic mean, standard deviation, median, quartiles, frequency, and percentile. The t-test for independent samples and the Mann-Whitney U test were used to

Table 1. Baseline patient characteristics and intraoperative data
Tabela 1. *Osnovne karakteristike pacijenata i intraoperativni podaci*

	Group V *Grupa V*	Group NV *Grupa NV*	p *p*
Patients No./*Pacijenti Br.*	398	101	
Male No. (%)/*Muškarci Br. (%)* Female No. (%)/*Žene Br. (%)*	292 (73.4) 106 (26.6)	81 (80.2) 20 (19.8)	0.199
Age (years) mean ± SD/*Starost (godine) srednja vrednost ± SD*	65.5 ± 7.8	66.6 ± 8.3	0.238
Weight (kg) median (IQR)/*Težina (kg) medijana (IQR)*	80 (72 - 90)	82 (72 - 92)	0.494
Height (cm) median (IQR)/*Visina (cm) medijana (IQR)*	171 (163 - 176)	171 (165 - 176)	0.548
Body mass index (kg/m^2) median (IQR) *Indeks telesne mase (kg/m^2) medijana (IQR)*	27.6 (25.4 - 30.8)	27.8 (25.6 - 30.4)	0.823
Ejection fraction (%) mean ± SD *Ejekciona frakcija (%) srednja vrednost ± SD*	53 (46 - 59)	53 (44 - 58)	0.667
Hypertension No. (%)/*Hipertenzija Br. (%)*	339 (85.2)	87 (86.1)	0.876
Hyperlipoproteinemia No. (%)/*Hiperlipoproteinemija Br. (%)*	250 (62.8)	65 (64.4)	0.818
History of myocardial infarction No. (%)/*Infarkt miokarda u istoriji Br. (%)*	161 (40.4)	37 (36.6)	0.497
History of cerebrovascular accident No. (%)/*Cerebrovaskularni događaj u istoriji Br. (%)*	26 (6.5)	9 (8.9)	0.388
Diabetes mellitus No. (%)/*Dijabetes melitus Br. (%)*	140 (35.2)	39 (38.6)	0.562
Chronic kidney disease No. (%)/*Hronična bubrežna insuficijencija Br. (%)*	36 (9.0)	8 (7.9)	0.845
Smokers No. (%)/*Pušači Br. (%)*	200 (50.2)	52 (51.5)	0.911
EuroScore II/*EuroSkor II*	1.15 (0.8-1.9)	1.27 (0.85-1.92)	0.432
Intraoperative data/*Intraoperativni podaci*			
Aortic cross-clamp time (min) mean ± SD *Trajanje aortne kleme (min) srednja vrednost ± SD*	54.7 ± 20.0	54.8 ± 14.1	0.935
Cardiopulmonary bypass time (min) mean ±SD *Trajanje ekstrakorporalne cirkulacije (min) srednja vrednost ± SD*	62.0 ± 21.7	63.3 ± 24.4	0.618

Legend: EuroScore II - The European System for Cardiac Operative Risk Evaluation; IQR - interquartile range; Group V - patients ventilateds during CPB; Group NV - patients not ventilated during CPB
Legenda: EuroScore II – Evropski sistem za procenu operativnog rizika u kardiohirurgiji; IQR – interkvartalni raspon; Grupa V – pacijenti ventilirani niskim disajnim volumenom; Grupa NV – pacijenti koji nisu ventilirani u toku ekstrakarpalne cirkulacije; SD – standardna devijacija

compare the mean values of two variables. The association of categorical variables was examined using the χ^2 test for contingency tables and Fisher's exact test. A value of $p < 0.05$ was taken as statistically significant. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 19.0 (IBM Corp., Armonk, NY, USA).

Results

In the above-mentioned period, a total of 551 on-pump CABG surgeries were performed. Fifty-two patients were excluded from the study due to an ejection fraction < 30% or chronic lung disease. A total of 499 patients were included in the study. **Table 1** shows that during CPB, 398 patients were ventilated with low TV (group V), while there were 101 patients in the group without MV (group NV).

The groups did not differ significantly in basic demographic and anthropometric characteristics, comorbidities, ejection fraction, and EuroScore II. Both groups included mostly male patients. The average age in group V was 65.5 years, while in group NV it was 66.6 years. The average value of the ejection fraction was identical in both groups (53%). The leading comorbidity was hypertension, which was present in 85.2% of group V and 86.1% of group NV. The second most frequent comorbidity was hyperlipoproteinemia (group V 62.8%, group NV 64.4%). Diabetes mellitus and previous myocardial infarction were present in a significant percentage. Smokers accounted for half of the patients in both groups. Other comorbidities were present in a smaller percentage.

Intraoperative data were not significantly different between the two groups. The duration of the aortic clamp was 54.7 minutes in the group of ventilated patients and 54.8 minutes in patients without MV. The average duration of CPB was 62 minutes in group V and 63.3 minutes in group NV.

The primary outcomes and PPCs are shown in **Table 2**. They did not differ significantly between the groups. The most frequent were the need for prolonged MV (V 5.8%, NV 5.9%), and pleural effusions (V 4.8%, NV 5.9%). The frequency of pneumonia was identical in both groups (2%). Pneumothorax occurred in 1.8% of patients in group V and in 2% of patients in group NV. Other PPCs occurred in a smaller percentage.

Table 3 shows that patients in both groups were ventilated for an average of 10 hours after surgery

Table 2. Primary outcomes
Tabela 2. *Primarni ishodi*

	Group V *Grupa V*	Group NV *Grupa NV*	p *p*
Prolonged mechanical ventilation No. (%)/*Produžena mehanička ventilacija Br. (%)*	23 (5.8)	6 (5.9)	1.000
Pleural effusion No. (%)/*Pleuralni izliv Br. (%)*	19 (4.8)	6 (5.9)	0.613
Pneumonia No. (%)/*Pneumonija Br. (%)*	8 (2.0)	2 (2.0)	1.000
Pneumothorax No. (%)/*Pneumotoraks Br. (%)*	7 (1.8)	2 (2.0)	1.000
Respiratory failure/*Respiratorna insuficijencija Br. (%)*	3 (0.8)	2 (2.0)	0.267
Reintubation No. (%)/*Reintubacija Br. (%)*	3 (0.8)	0	0.877
Bronchospasm No. (%)/*Bronhospazam Br. (%)*	0	0	–

Legend: EuroScore II - **The European System for Cardiac Operative Risk Evaluation; IQR - interquartile range; Group V - patients ventilateds during CPB; Group NV - patients not ventilated during CPB**
Legenda: EuroScore II – Evropski sistem za procenu operativnog rizika u kardiohirurgiji; IQR - interkvartalni raspon; Grupa V - pacijenti ventilirani niskim disajnim volumenom; Grupa NV – pacijenti koji nisu ventilirani u toku ekstrakarpalne cirkulacije; SD – standardna devijacija

Table 3. Secondary outcomes
Tabela 3. *Sekundarni ishodi*

	Group V *Grupa V*	Group NV *Grupa NV*	p *p*
ICU intubation time (h) median (IQR) *Trajanje mehaničke ventilacije pluća u JIL (h) medijana (IQR)*	10 (8 - 12)	10 (8 - 12)	0.896
ICU length of stay (days) median (IQR)/*Boravak u JIL (dani) medijana (IQR)*	1 (0.9 - 1.1)	1 (0.9 - 1.1)	0.405
In-hospital mortality No. (%)/*Intrahospitalni mortalitet Br. (%)*	11 (2.8)	1 (1.0)	0.474

Legend: ICU – intensive care unit; IQR - interquartile range; Group V - patients ventilateds during CPB; Group NV - patients not ventilated during CPB
Legenda: *JIL – jedinica intenzivnog lečenja; IQR – interkvartilni raspon, Grupa V – pacijenti ventilirani niskim disajnim volumenom; Grupa NV – pacijenti koji nisu ventilirani u toku ekstrakarpalne cirkulacije*

which they spent in the ICU. In the ventilated group, 11 patients died (2.8%), and in the group of patients without MV, 1 patient died (1%).

Discussion

Pulmonary complications are very common after cardiac surgery. Most of these complications are not severe, but when a severe complication does occur, patients' lives may be in significant danger [20]. The aim of this study was to investigate whether MV with a low TV leads to a lower incidence of PPCs compared to the non-ventilated group during CPB. The study showed that there were no statistically significant differences in postoperative outcomes between the ventilated and non-ventilated groups. In the group that was ventilated with a low TV, pulmonary complications occurred in 16% of patients, and in the non-ventilated group in 17.8% of patients. The need for prolonged MV, pleural effusions, and pneumonia were the most common pulmonary complications in both groups.

John and Ervine used TV 5 ml/kg in their randomized, controlled study [21]. Their patients were exclusively non-smokers, while we included this group of patients in the research. They concluded that the time spent on MV was significantly reduced in the ventilated group, which indicates potential benefits of ventilation during CPB. However, their research included a total of 23 patients divided into 2 groups, which significantly decreased the power of the study. Davoudi et al. concluded that the group ventilated with continuous low TV (3 ml/kg, respiratory rate 12/min, PEEP 5 cmH_2O, and FiO_2 1.0) had better oxygenation after CPB, as well as better pulmonary function, which caused a reduction in the time at MV [22].

Recent studies have not found a significant difference between different MV strategies. A large, randomized study (MECANO study) included 1501 patients [5] who required valvular surgery, patients with chronic lung diseases and patients with heart failure, while our research excluded this category of patients due to the associated factors. In subjects who were ventilated with TV 3 ml/kg, frequency 5/min, and PEEP 5 cmH_2O, no reduction in PPCs was observed compared to the group of non-ventilated patients. The most frequent PPCs were pneumonia, need for respiratory support after 2 days, and reintubation. However, a post-hoc analysis of the same study, but in patients who underwent isolated CABG surgery, showed a lower percentage of PPCs in the group of patients in whom MV with a low TV was used, which may support the hypothesis that CABG procedures benefit more from ventilation strategy than other types of cardiac procedures [3].

The VENICE International Cohort Study, conducted in 9 countries, analyzed 676 patients and showed that PPCs were equally present in the group ventilated with low TV as in the group without MV

[4]. The same result was ontained by a meta-analysis conducted by Chi et al. [15]. An observational study examined the impact of continuing MV during CPB on functional residual lung capacity and it did not show a difference compared to the group of patients in whom ventilation was discontinued [23].

A comparative study from 2019 attempted to find out whether ventilation during CPB has an effect on postoperative pulmonary dysfunction [24]. The research included 66 patients divided into 3 groups: a group with pressure-controlled ventilation, a group with volume-controlled ventilation, and a control group of non-ventilated patients. The study showed that there were no significant differences in the PaO_2, $PaCO_2$, and PaO_2/FiO_2 ratios, nor were there significant differences observed on the chest X-rays among these three groups. In their study, Zhang et al. concluded that maintaining a low TV during CPB has no significant advantage in reducing the incidence of PPCs compared to a non-MV strategy among a non-ventilated group and two ventilated groups, with one group being ventilated with TV 3 - 4 ml/kg, respiratory frequency 10 - 12/min, PEEP 5 - 8 cm H_2O, and FiO_2 0.3, and the second group having the same ventilation parameters with FiO_2 0.8 [6]. Unlike our study, which included only patients who were admitted for CABG surgery, this study included predominantly patients who required valvular surgery (> 80%). The leading three PPCs were pleural effusion, atelectasis, and respiratory infection. The duration of MV in ICU was longer in all three groups compared to our study (non-ventilated 14.5 hours; ventilated FiO_2 0.3 15.5 hours; ventilated FiO_2 0.8 16 hours), while the length of stay in ICU was 3 days. Hospital mortality was similar to our results.

Conclusion

Pulmonary complications after cardiac surgery are still common. Experience at our clinic showed that the choice of mechanical ventilation strategy during cardiopulmonary bypass does not affect postoperative complications. Despite several studies done in the last decade, we still have no clear ventilation strategy for patients during cardiopulmonary bypass. Randomized, well-designed, and large multicenter studies with different tidal volumes, fractional inspired oxygen, and positive end-expiratory pressure are needed to provide stong recommendations.

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INDICATORS OF COGNITIVE DECLINE IN PERSONS WITH PRESBYCUSIS

INDIKATORI PADA KOGNITIVNE FUNKCIJE KOD OSOBA SA PREZBIAKUZIJOM

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Summary

Introduction. Presbycusis or age-related hearing loss is a physiological elevation of hearing threshold and is one of the leading chronic health problems. A growing number of studies show a correlation between hearing loss in old age and decline in cognitive function. **Material and Methods**. The Serbian version of the Montreal Cognitive Assessment test was used, and the study included 56 subjects with a confirmed diagnosis of presbycusis of which 29 (51.8%) were hearing aid users. **Results.** The score of cognitive function in the respondents was lower compared to the results of previous research (mean = 19.07; standard deviation = 5.03). Also, there were significant differences between the scores of cognitive function in persons who used amplification and persons who did not. There was no significant correlation between gender, employment status, and the degree of hearing impairment, while the correlation was significant between the level of education, age, the length of hearing aid use, and the number of hours per day a person used a hearing aid. Regression analysis showed that about 88% of the variance of the dependent variable could be explained by four variables: age, level of education, length of hearing aid use, and daily level of hearing aid use. **Conclusion.** Persons with presbycusis from the territory of the Autonomous Province of Vojvodina showed poor performance scores on the cognitive ability test compared to the results of other researchers. The results showed that the length of hearing aid use and the daily level of hearing aid use significantly affect the cognitive functions in persons with presbycusis.

Keywords: Cognition; Presbycusis; Cognitive Dysfunction; Persons With Hearing Impairments; Surveys and Questionnaires; Hearing Aids

Sažetak

Uvod. Staračka nagluvost podrazumeva fiziološko povećanje praga sluha i jedan je od vodećih hroničnih zdravstvenih problema. Sve veći broj istraživanja pokazuje međusobnu povezanost gubitka sluha u starosti i pada kognitivne funkcije. **Materijal i metode.** Korišćena je srpska verzija Montrealske procene kognicije, a studija je obuhvatila 56 ispitanika sa potvrđenom dijagnozom prezbiakuzije, od čega je 29 (51,8%) korisnika slušnih aparata. **Rezultati.** Skor kognitivnog funkcionisanja ispitanika bio je niži u odnosu na rezultate prethodnih istraživanja (srednja vrednost = 19,07; standradna devijacija = 5,03). Postoje značajne razlike između skora kognitivnog funkcionisanja osoba koje koriste amplifikaciju i osoba koje je ne koriste. Nema značajne korelacije sa polom i statusom zaposlenja, kao ni stepenom oštećenja sluha. Korelacija je značajna sa stepenom obrazovanja, starošću, dužinom korišćenja slušnog aparata, kao i brojem sati u danu u kom osoba koristi slušni aparat. Regresionom analizom utvrđeno je da oko 88% varijanse zavisne promenljive objašnjavaju četiri varijable – starost, stepen obrazovanja, dužina korišćenja i dnevni nivo korišćenja slušnog aparata. **Zaključak.** Osobe sa prezbiakuzijom sa teritorije Autonomne Pokrajne Vojvodine pokazale su prosečno niže postignuće na testu kognitivnih sposobnosti u odnosu na rezultate drugih istraživača. Rezultati su pokazali da dužina korišćenja slušnog aparata, ali i korišćenja slušnog aparata na dnevnom nivou, značajno utiču na kognitivne funkcije osoba sa prezbiakuzijom.

Ključne reči: kognicija; presbiakuzija; kognitivna disfunkcija; osobe sa oštećenjem sluha; ankete i istraživanja; slušna pomagala

Introduction

Presbycusis is a physiological process that leads to a gradual loss of hearing. Presbycusis is a progressive, bilateral, permanent hearing impairment that occurs as a result of degenerative changes in the structures of the inner ear and/or auditory nerve [1]. According to the World Health Organization [2] presbycusis affects every third person over the age of 65, half of the adults over the age of 75, the majority of adults over the age of 80, and almost all people over the age of 90. The latest report [3] estimates that globally more than 1.2 billion people live with some degree of hearing loss. The World Health Organization points out that if appropriate measures of prevention and care for hearing health are not taken by 2050, the number of people with hearing impairment will double and more than 700 million will require some kind of hearing intervention.

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Abbreviations

HA – hearing aid
SD – standard deviation
MoCA – Montreal Cognitive Assessment

The decline in cognitive function is another health challenge that globally affects the elderly population and includes a wide range of conditions, from mild impairment of cognitive function to severe dementia [4]. The increasing incidence of these conditions in adulthood and the devastating impact they may have on the quality of life of individuals, their families and society, have made the prevention and treatment of cognitive function decline a public health priority [5]. The most common domains of cognitive functions affected by aging are the speed of information processing, memory, and attention. The number of people suffering from dementia has rapidly increased, and it is expected that the number will increase to 152 million by 2050 [5–7]. A growing number of studies show the connection between hearing loss in older people and various forms of decline in cognitive function such as dementia, Alzheimer's disease etc. [8, 9]. Hearing impairment causes a load at the level of cortical auditory processing and the available cognitive resources are diverted to auditory processing [4, 10]. Other theories suggest that hearing loss in old age leads to social isolation and then to a decline in cognitive functions [11] or that the reason for the connection lies in the (common) cause of both conditions, i.e. that hearing loss is an early manifestation of cognitive pathology [12]. Thomson et al. [13] claim that the link between the decline in cognitive functions and hearing loss was confirmed in all analyzed studies, which supports the hypothesis that hearing loss is one of the risk factors for the decline in cognitive function.

Timely diagnosis of hearing impairment and auditory rehabilitation of persons with presbycusis can reduce the impact of hearing impairment on cognitive deterioration, thus reducing healthcare costs, increasing the quality of life and facilitating daily functioning of these persons [14]. Timely diagnosis of hearing loss should insure adequate amplification, which implies the use of hearing aids (HAs) for minor hearing impairments or the use of cochlear implants for severe and profound hearing impairments [9]. The research aimed to determine the indicators of cognitive function decline in persons with confirmed presbycusis in the territory of Vojvodina. The research also examined the impact of hearing-aid amplification on the cognitive status of persons with presbycusis.

Material and Methods

The research was conducted from March to July 2022, in the territory of the Autonomous Province of Vojvodina, Republic of Serbia. The research sample included 56 persons with presbycusis, patients of the Clinic of Otorhinolaryngology and Head and Neck Surgery of the Clinical Center of Vojvodina. The questionnaire was anonymous. Out of the total number of respondents, there were 26 (46.4%) males and 30 (53.6%) females, of which 29 (51.8%) used a HA. The average age was 73.41 years with a standard deviation (SD) of 8.07; 11 subjects (19.6%) had a moderately severe hearing loss (56 – 70 decibels - dB), 29 subjects (51.8%) had severe (71 – 90 dB), and 16 subjects (28.6%) had a profound hearing loss (over 90 dB). The mean length of use of HA was 5.65 years (SD = 5.12). On average, the respondents used the HA 8.97 hours per day (SD = 3.96). There were more unemployed respondents (34; 60.7%). The approval of the Ethics Committee of the Clinical Center of Vojvodina (decision number 00-57) was obtained for conducting the research. For this research, the Serbian version of the Montreal Cognitive Assessment (MoCA) [15] was used. The consent to use this instrument was obtained by the author, and the research was conducted by a certified researcher. The MoCA [16] is a test for rapid assessment of cognition, which includes seven domains in 11 tasks: visuospatial and executive function, naming, memory, attention, language, abstraction, delayed recall, and orientation. The MoCA is a 30-point scale, with a result of 26 or more points being considered good, and it takes about 10 minutes.

The dependent variable was the cognitive status of persons with presbycusis, evaluated by the Serbian version of the MoCA test. This variable is numerical, discontinuous and quantitative according to the way its value is expressed, and according to the possibility of being influenced by other variables, it is defined as endogenous. Independent variables were defined through two larger groups: variables related to sociodemographic factors and variables related to hearing impairment. Variables related to hearing impairment included the degree of hearing impairment defined as a quantitative indicator of a person's hearing status, divided into three categories (moderately severe hearing impairment: 56 – 70 dB, severe hearing impairment: 71 – 90 dB, and profound hearing impairment: over 90 dB). The length of hearing aid use was defined as a quantitative, numerical, discontinuous indicator of experience in the use of auditory amplification, expressed in months. The third variable related to the length of hearing aid use during one day was defined as a quantitative, numerical, discontinuous indicator of actual hearing aid use expressed through the number of hours during the day. Variables related to sociodemographic factors included age, defined as a numerical, discontinuous and quantitative indicator, the level of employment, defined as a qualitative indicator of the person's current working ability, consisting of two categories - employed and unemployed, and finally the level of education, as a quantitative indicator of the level of acquired education, divided into four categories (primary education, secondary school, high school, and university).

Data processing was performed using the Statistical Package for the Social Sciences version 20.0. Descriptive statistics methods were frequencies, percentages, contingency coefficient, measures of central tendency and dispersion measures, as well as appropriate inferential statistics methods (Student's t-test, Pearson's correlation analysis, multiple linear regression analysis). Using the Kolmogorov-Smirnov test, we examined the normality of the distribution of scores and the results showed there is no statistically significant deviation (Z

Table 1. Descriptive values of cognitive function scores of persons with presbycusis (No. = 56)
Tabela 1. *Deskriptivne vrednosti procene skora kognitivnog funkcionisanja osoba sa presbiakuzijom* (*Br.* = 56)

Cognitive function *Kognitivna funkcija* (Max)	Min *Min*	Max *Maks.*	M *M*	Mdn *Mdn*	SD *SD*	IQR *IQR*	SEM *SEM*	95% Confidence interval *Interval poverenja* 95%
Visuospatial, executive *Vizuoprostorne, egzekutivne f.* (5)	1	5	3.59	4	1.35	2	0.18	3.23 - 3.95
Naming/*Imenovanje* (3)	2	3	2.88	3	0.33	0	0.05	2.79 - 2.96
Attention/*Pažnja* (6)	0	6	3.54	3.50	1.44	1	0.19	3.15 - 3.92
Language/*Jezik* (3)	0	3	1.45	1.50	0.93	1	0.12	1.20 - 1.70
Abstraction/*Apstrakcija* (2)	0	2	0.93	1	0.71	1	0.09	0.74 - 1.12
Delayed recall/*Odgođeno prisećanje* (5)	0	3	0.84	0	1.06	1	0.14	0.56 - 1.12
Orientation/*Orijentacija* (6)	3	6	5.82	6	0.60	0	0.08	5.66 - 5.98
Total score/*Ukupan skor* (30)	6	28	19.07	19	5.03	5	0.67	17.55 - 20.13

Legend: Min - minimum score; Max - maximum score; M - mean; Mdn - median; SD - standard deviation; IQR - interquartile range; SEM - standard error
Legenda: min – minimum rezultata; max – maksimum rezultata; M – aritmetička sredina; Mdn – medijana; SD – standardna devijacija; IQR – interkvartalni raspon; SEM – standardna greška

Table 2. Descriptive measures of cognitive achievement, differences between the group of subjects using HA and the group not using HA
Tabela 2. *Deskriptivne mere kognitivnog postignuća ispitanika, razlike između grupe ispitanika koja koristi slušni aparat i koja ga ne koristi*

Cognitive function *Kognitivna funkcija* (Max)	Using HA/*Koristi SA*				Not using HA/*Ne koristi SA*				
	Min *Min*	Max *Maks.*	M (SD) *M (SD)*	Mdn *Mdn*	Min *Min*	Max *Maks.*	M (SD) *M (SD)*	Mdn *Mdn*	t-test *t-test*
Visuospatial, executive *Vizuoprostorne, egzekutivne f.* (5)	2	5	4.07 (0.99)	4	1	5	3.07 (1.49)	3	-2.95**
Naming/*Imenovanje* (3)	2	3	2.93 (0.26)	3	2	3	2.81 (0.40)	3	-1.31
Attention/*Pažnja* (6)	2	6	4.24 (1.27)	4	0	5	2.78 (1.22)	3	-4.39**
Language/*Jezik* (3)	1	3	1.93 (0.75)	2	0	2	0.93 (0.83)	1	-4.75**
Abstraction/*Apstrakcija* (2)	0	2	1.00 (0.76)	1	0	2	0.85 (0.66)	1	-0.77
Delayed recall/*Odgođeno prisećanje* (5)	0	3	1.28 (1.25)	1	0	1	0.37 (0.49)	0	-3.51**
Orientation/*Orijentacija* (6)	6	6	6 (0)	6	3	6	5.63 (0.84)	6	-2.38*
Total score/*Ukupan skor* (30)	14	28	21.52(4.38)	21	6	23	16.44 (4.34)	17	-4.34**

Legend: HA - hearing aid; Min - minimum score; Max - maximum score; M - mean; Mdn - median; SD - standard deviation;
Legenda: SA – slušni aparat; - min – minimum rezultata; max – maksimum rezultata; M – aritmetička sredina; Mdn – medijana; SD – standardna devijacija; * $p \leq .05$; ** $p \leq .01$ *Perit officiu reicillanda et perest, corporepres essi volupta spelige nimpost, ent.*

= 0.095, p = .20). The internal consistency of the MoCA test was checked by calculating Cronbach's alpha coefficient, the reliability at the level of the overall scale was high (α = 0.85).

Results

The analysis of results showed that the arithmetic mean was lower than the cut-off score determined by the authors **(Table 1)**. Only eight respondents (14.24%) scored 26 points or more.

Descriptive measures of the subjects' cognitive performance on the MoCA test, as well as the values of the Student's t-test were used to test the difference between the group of subjects who used HA and subjects who did not **(Table 2)**.

More than one-third of the respondents (37.93%) who used HAs had good results (score ≥ 26), while in the group of persons who did not use HAs there were no respondents with good results. The t-test for independent samples showed a statistically significant difference between the test groups in almost all domains, as well as in the total score. The mutual correlations of the predictor variables are shown in **Table 3**.

Socio-demographic variables did not show a significant correlation between the MoCA scores and gender and employment status, while the correlation between the level of education was positive and significant. The age of the subjects significantly and negatively correlated with the MoCA scores, showing that young respondents had better cognitive functions compared to the older subjects. A positive correlation was established between the length of HA use and the number of hours a day a person used a HA and the MoCA score, but there was no significant connection between the degree of hearing impairment, as expected.

Table 3. Intercorrelations of predictor variables of cognitive status
Tabela 3. *Međusobne korelacije prediktorskih varijabli kognitivnog statusa*

	1.	2.	3.	4.	5.	6.	7.	8.
1. Gender/*Pol*	1							
2. Employment status/*Status zaposlenja*	-.02	1						
3. Age/*Starost*	.11	.49**	1					
4. Education level/*Stepen obrazovanja*	-.12	.03	.06	1				
5. Degree of impairment/*Stepen oštećenja*	.12	.20	.08	-.16	1			
6. Length of HA use/*Dužina korišćenja SA*	-.14	.16	-.07	.33*	.42**	1		
7. Use of HA per day/Korišćenje SA na dan	-.17	-.02	-.25	.36	.74**	.74**	1	
8. MoCA score/*MoCA skor*	-.12	-.23	-0.72**	0.40**	-.05	.56**	.70**	1

Legend: * p ≤ .05; ** p ≤ .01; HA - hearing aid; MoCA score - Montreal Cognitive Assessment
*Legenda: * p ≤ .05; ** p ≤ .01; SA – slušni aparat; MoCA skor – skala Montrealska procena kognicije*

Table 4. Characteristics of the total score indicators on the MoCA scale in a linear model
Tabela 4. *Karakteristike indikatora ukupnog skora na skali Montrealska procena kognicije po linearnom modelu*

	B	SE	β	T	p/*p*
Constant/*Konstanta*	-40,61	2.08		19.51	.000
Age/*Starost*	-.36	0.03	-.65	13.20	.000
Education level/*Stepen obrazovanja*	1.29	0.25	.26	5.25	.000
Length of HA use/*Dužina korišćenja SA*	.23	0.08	.21	2.99	.004
Use of HA per day/*Korišćenje SA na dan*	.28	0.07	.29	3.94	.000

Legend: HA - hearing aid; MoCA score - Montreal Cognitive Assessment
Legenda: SA – slušni aparat; MoCA skor – skala Montrealska procena kognicije

Correlations from 0.3 to 0.7, as well as those close to the value of 0.3, justified the application of regression analysis [17]. The Bonferroni adjustment was used to avoid errors. The alpha value was reduced in the four factor model and it was adjusted to 0.0125. Again, we gained significant correlations and a model was proposed to test the contributions of selected features for predicting the cognitive status of persons with presbycusis.

The analysis of variance, which is a test of the null hypothesis, according to which the coefficient of determination is equal to zero, gave a high F-coefficient ($F = 104.83$, $p < .001$), which showed that the regression analysis was justified and that we could expect an approximate F value in the future samples of the same size or larger samples with the same characteristics [17]. **Table 4** presents the linear regression coefficients between the cognitive status of persons with presbycusis and the previously mentioned factors.

The results showed that the four factor model had an acceptable fit to the data and represented a statistically significant proportion of the variance ($R2 = 0.88$, $p < .000$), which means that about 88% of the variance of the dependent variable is explained by four variables - age, level of education, length of HA use, and the number of hours per day in which a person uses HA.

Discussion

This research aimed to determine the indicators of cognitive function decline in persons with presbycusis. The results showed lower average MoCA scores in the subjects included in this study than in subjects from other studies that included people with presbycusis: in Italy (M = 21.8) [18], Canada (M = 24.4) [19] and China (M = 25) [20]. In the study by Urqueta et al. [21], over 50% of people with hearing loss had good MoCA scores. In a 2013 study [22], the authors concluded that people with hearing loss experience 30% to 40% faster cognitive decline. On average, a person with hearing loss would need 7.7 years for a five-point decline on cognitive tests compared to 10.9 years in people without hearing loss [22].

The analysis of the results of this study indicate significant differences in the cognitive function of persons who use amplification and persons who do not, which speaks in favor of the protective effect of amplification on the decline of cognitive functions. The difference in the MoCA scores regarding the cognitive function between these two groups was five points in favour of persons using amplification ($M_{amp} = 21.52$; $M_{non\text{-}amp} = 16.44$). Similar results were obtained by authors from Italy, whose subjects using amplification achieved a score of 23.71 points compared to the non-amplified group who scored 19.89 points [18]. In our research, people using amplification were significantly more successful in most individual test domains (Visuospatial and executive functions, Attention, Language, Delayed recall, Orientation), as well as in the total score, which is in line with the results of other research [23, 24]. The greatest differences between the two groups of subjects were in the following

domains: Language, Attention, as well as in the total score, while persons with amplification were more successful in the domains of Naming and Abstract thinking, but the difference between the groups was not significant. Several tasks from the two domains of the MoCA test rely on listening, i.e. a correct answer first requires a correctly perceived stimulus. These tasks are from the domain of Language and Attention, which could be the cause of the greatest differences between the two groups of respondents (amplified/non-amplified) precisely due to poor auditory perception and processing in the group of people who do not use amplification.

Correlation analyses show that there is no correlation between hearing loss and the cognitive function score, which contradicts with some earlier research that concluded that hearing loss is associated with accelerated cognitive decline and incident cognitive impairment in older adults [22, 25]. Results also showed that there is a negative correlation between the cognitive function score and age, which also coincides with earlier research on this topic [22, 25], that is, the older the person, the lower the cognitive ability. The authors [25] claim that people with a higher degree of education willingly accept various aids, including a HA, and this fact could be the reason for better cognitive functions in people with higher degree of education.

The length of HA use showed a statistically significant positive correlation with the cognitive function test score, which indicates that people who use HA for a greater number of years have higher cognitive function scores. The correlation between cognitive function test scores and the number of hours of HA use daily was also positive and statistically significant, that is, people who use their HA for a longer time during the day have higher scores on the cognitive function test. Through further regression analyses, it was established that about 88% of the variance of the dependent variable is explained by four variables - age, level of education, length of use of a HA, and the number of hours per day in which a person uses a HA. The results are in accordance with the research results of Brewster [26] who concluded that after 12 weeks of using amplification for a minimum of nine hours a day, a significant shift in hearing function, reduction of depressive symptoms, and the cognitive function score was achieved in persons with presbycusis. Naylor G. et al. [27] concluded that the use of a hearing aid reduces the risk of dementia and that better cognitive function is associated with longer use of the device; they also emphasized the importance of the availability and use of hearing aids, regardless of current cognitive status or age.

Conclusion

People with presbycusis from the territory of the Autonomous Province of Vojvodina showed a lower mean achievement on the cognitive ability test compared to the results of other researchers which indicates the need for better care of elderly people with presbycusis in the region of Vojvodina in order to prevent deterioration of their cognitive functions. The results of this research showed that the length of hearing aid use, in terms of the listening experience with amplification and the use of a hearing aid daily, significantly affects the preservation of the cognitive function of people with presbycusis. Age, level of education, length of use, and the number of hours a day in which a person uses a hearing aid showed a significant correlation with the cognitive function scores and it is recommended to establish more precise relationships between the mentioned factors on a larger sample of respondents through further research. This research is particularly significant, considering that it is the first research dealing with this topic in the territory of Vojvodina, and it may be the first step towards a better understanding of the indicators of cognitive function decline and understanding the importance of timely diagnosis and amplification in elderly people with impaired hearing.

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QUALITY OF COMMUNICATION AND QUALITY OF LIFE OF PEOPLE WITH APHASIA AND DYSARTHRIA AFTER STROKE

KVALITET KOMUNIKACIJE I KVALITET ŽIVOTA OSOBA SA AFAZIJOM I DIZARTRIJOM USLED MOŽDANOG UDARA

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Summary

Introduction. Aphasia and dysarthria are permanent consequences of stroke in many patients. These disorders significantly disrupt the person's functioning in everyday life. The aim of this paper is to examine the quality of communication and quality of life in patients with aphasia and dysarthria. **Material and Methods**. The clinical group included 25 patients with aphasia and 20 patients with dysarthria due to stroke. The control group included 15 post-stroke people without speech and language disorders and 15 neurologically healthy subjects. The Quality of Communication Life Scale was used to assess the quality of communication. This scale provides information about the impact of speech and language disorders on individuals' ability to communicate and quality of life in general. The scale consists of 18 items scored from 1 to 5. **Results.** Patients with aphasia and dysarthria have a significantly lower quality of communication compared to stroke survivors with preserved speech and language functions and neurologically healthy subjects. The severity of the language and speech disorder proved to be a significant factor in determining the quality of communication. Namely, patients with more severe forms of aphasia and dysarthria scored significantly lower on the Quality of Communication Life Scale compared to the patients with milder forms. It was also shown that patients with flaccid dysarthria have the worst quality of communication compared to the patients with other types of dysarthria. **Conclusion.** Aphasia and dysarthria following a stroke significantly impair the quality of communication and quality of life of the affected persons.

Key words: Aphasia; Dysarthria; Communication; Quality of Life; Stroke

Sažetak

Uvod. Afazija i dizartrija ostaju kao trajne posledice moždanog udara kod mnogih pacijenata. Ovi poremećaji značajno remete funkcionisanje osobe u svakodnevnom životu. Cilj ovog rada je utvrđivanje kvaliteta komunikacije i kvaliteta života kod pacijenata sa afazijom i dizartrijom. **Materijal i metode**. Kliničku grupu činilo je 25 ispitanika sa afazijom i 20 ispitanika sa dizartrijom usled moždanog udara. U kontrolnu grupu uključeno je 15 ispitanika sa moždanim udarom bez poremećaja govora i jezika i 15 neurološki zdravih govornika. Za procenu kvaliteta komunikacije primenjena je *Skala kvaliteta komunikacionog života.* Primenom ove skale dobijaju se informacije o uticaju govornih i jezičkih poremećaja na sposobnost komunikacije pojedinca i kvalitet života uopšte. Skala se sastoji od osamnaest tvrdnji koje ispitanici vrednuju ocenom od jedan do pet. **Rezultati.** Ispitanici sa afazijom i dizartrijom imaju značajno niži kvalitet komunikacije u poređenju sa osobama sa moždanim udarom očuvanih govornih i jezičkih funkcija i neurološki zdravim govornicima. Težina jezičkog i govornog poremećaja se pokazala značajnim faktorom u određivanju kvaliteta komunikacije. Utvrđeno je da pacijenti sa težim formama afazije i dizartrije imaju značajno niži skor na *Skali kvaliteta komunikativnog života* u odnosu na pacijente sa lakšim formama. Takođe je pokazano da pacijenti sa flacidnom dizartrijom imaju najlošiji kvalitet komunikacije u grupi ispitanika sa dizartrijom. **Zaključak.** Afazija i dizartrija nakon moždanog udara znatno narušavaju kvalitet komunikacije i kvalitet života pogođenih osoba.

Ključne reči: afazija; disartrija; komunikacija; kvalitet života; moždani udar

Introduction

Stroke is the most common vascular brain disorder causing impairments in the domain of motor skills, vision, swallowing, language, speech, etc. Language and speech disorders mainly manifest as aphasia and dysarthria.

Aphasia occurs as a result of damage to the dominant (mainly left) hemisphere of the brain. It manifests with impaired production and comprehension of spoken and written language. Due to its tendency to a chronic course, aphasia is one of the most severe disorders of psychological functions caused by stroke. Of all disorders of higher mental function that are caused by stroke, aphasia impoverishes personality the most [1]. Furthermore, aphasia significantly limits communication and impairs the individual to such an extent that some affected people

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BDAE – Boston Diagnostic Aphasia Examination
TSA – transcortical sensory aphasia
QCL – Quality of Communication Life Scale

remain debilitated for the rest of their lives [2]. Many empirical data show that aphasia negatively affects communication abilities, social relations, and activities of these people [3–6]. It has also been shown that patients with aphasia develop negative emotions, such as low mood (depression), frustration, anxiety, alienation, and low self-esteem [7]. Finally, findings show that people with aphasia are socially isolated and generally have a poor quality of life [8, 9].

Dysarthria is caused by damage to the central and/or peripheral nervous system. It is a motor speech disorder caused by paralysis, slowness, weakness, inaccuracy and uncoordinated movements of the speech musculature. Dysarthria manifests as impaired speech production: phonation, resonance, articulation and prosody. Often, the most noticeable deficits are in the domain of articulation, which significantly impairs the intelligibility of speech [10].

Although it has been previously shown that examination of the quality of life of people with aphasia contributes to a better understanding of the nature of the disorder and better assessment of outcomes and treatment planning, this topic remains under-researched [11]. In particular, there is a lack of papers dealing with self-perception of the quality of communication and quality of life in relation to the type and severity of aphasic syndrome.

Unlike with aphasia, there is very little data on the quality of communication and quality of life of people with dysarthria. There are practically no papers that examine the self-perception of one's own communication ability and quality of life in patients with different types and severity of acquired dysarthria. Finally, as far as we are aware, there are no studies that compare the self-perception of one's own communication ability among people with aphasia and dysarthria.

In this paper, we investigated the self-perception of the quality of communication and the quality of life of people with aphasia and dysarthria due to stroke, in comparison with people without speech and language disorders. Also, our aim was to examine whether there are differences in the quality of communication and quality of life between the respondents with aphasia and dysarthria, as well as whether the type and severity of aphasia and dysarthria affect the self-perception of communication abilities and quality of life.

Material and Methods

The clinical group included 25 subjects with aphasia and 20 subjects with dysarthria due to stroke in the left hemisphere. The control group included 15 subjects with a stroke in the right hemisphere, without speech and language disorders, and 15 neurologically healthy subjects. Exclusion criteria for post-stroke patients were: apraxia of speech, severe reading disorder, dementia, visual neglect, and psychiatric disorders. All participants were from 34 to 81 years of age, with 8 to 16 years of education. They were all native Serbian speakers.

The groups were matched according to age: no statistically significant differences in age were found between subjects with aphasia and dysarthria ($t = 0.74$, $df = 43$, $p = .46$), or between these groups and neurologically healthy subjects ($t = 0.48$, $df = 28$, $p = .64$). Also, no statistically significant differences were found between subjects with aphasia and dysarthria and post-stroke patients without speech and language disorders ($t = 1.03$, $df = 73$, $p = .31$).

There were no statistically significant differences in the level of education between respondents with aphasia and dysarthria ($t = 0.05$, $df = 43$, $p = .96$), subjects with aphasia and post-stroke patients without speech and language disorders ($t = 0.39$, $df = 38$, $p = .70$), subjects with aphasia and neurologically healthy subjects ($t = -0.45$, $df = 38$, $p = .65$), subjects with dysarthria and post-stroke patients without speech and language disorders ($t = 0.34$, $df = 33$, $p = . 73$), patients with dysarthria and neurologically healthy subjects ($t = 0.49$, $df = 33$, $p = .63$), and between subjects with stroke without speech and language impairments and neurologically healthy subjects ($t = 0.76$, $df = 28$, $p = .46$). Finally, the groups were also matched in gender ($\chi^2 = 0.12$, $df = 1$, $p = .73$).

The Serbian Aphasia Screening Test [12] and the Boston Diagnostic Aphasia Examination (BDAE) [13] were used in order to determine presence and type of aphasia. The patients were then classified into the following types of aphasia: Broca's aphasia, Wernicke's aphasia, conduction, anomic, and transcortical sensory aphasia (TSA). The severity of aphasia was determined by the BDAE Aphasia Severity Rating Scale and based on the scores the subjects were divided into three groups: mild, moderate and severe aphasia. Mild aphasia includes patients with non-fluent speech, without any significant limitations in expressing ideas and formulation of spoken language, and without any deficits in auditory comprehension. Moderate aphasia includes subjects with a reduced ability to speak spontaneously and/or understand, but who can converse on almost all topics from everyday life, with a little help of the interlocutor. Patients with a severe aphasia are often unable to clearly communicate ideas; they can discuss familiar topics, but with a significant help of the interlocutor [2].

The Screening Dysarthria Assessment was used in order to detect the presence of dysarthria, and we identified flaccid, spastic, ataxic, and hypokinetic dysarthria [10]. Based on the perceptual analysis of speech, carried out by two speech therapists, patients with dysarthria were divided into three groups: mild dysarthria, moderate dysarthria, and severe dysarthria.

The Quality of Communication Life Scale (QCL) [14], which was translated and adapted for Serbian language [1], was used to assess the quality of communication and quality of life. The QCL is intend-

ed for adults with acquired aphasia, dysarthria or communication disorders following traumatic brain injury. Using this scale, information are obtained about the impact of speech and language disorders on the ability to communicate, relationships with others, participation in various everyday activities and quality of life in general. The scale consists of 18 items scored from 1 to 5. Score 1 means that the respondent does not agree with the statement at all, and score 5 means that he/she completely agrees with it. The total raw score is obtained by adding up the scores for statements 1 to 17, and then calculating the average score. Statement number 18 "On the whole, my quality of life is good" represents a measure of quality of life, and is evaluated separately [1, 14].

The research was carried out at the Rehabilitation Clinic "Dr. Miroslav Zotović" in Belgrade from July to November 2022. All respondents gave their consent to participate in the research, which was approved by the Ethics Committee of the Clinic (N. 03-3475/1).

Statistical data processing was performed using a program for statistical data processing (IBM SPSS 26 Statistics for Windows). Descriptive statistical measures were frequency, mean, standard deviation, median, minimum, maximum and interquartile range. The χ^2 test and T-test were used to compare groups according to gender, age and years of education, while Kruskal-Wallis and Mann-Whitney U test were used to compare the results between the groups. The threshold for statistical significance was $p < 0.05$. The obtained results are shown in tables.

Results

First we examined the quality of communication and then the quality of life.

The results of the Kruskal-Wallis test showed that there were statistically significant differences in the average score of the communication quality between the tested groups ($H = 38.36$, $df = 3$, $p < .001$). Furthermore, the results of Mann-Whitney U test revealed statistically significant differences between the scores of patients with aphasia and neurologically healthy subjects ($U = 17.50$, $p < .001$) as well as between patients with aphasia and post-stroke patients without speech and language disorders ($U = 28.00$, $p < .001$). Differences were also found between patients with dysarthria and neurologically healthy subjects ($U = 27.00$, $p < .001$) and patients with dysarthria and post-stroke patients without speech and language disorders ($U = 31.50$, $p < .001$). No statistically significant differences were found between patients with aphasia and dysarthria ($U = 236.00$, $p = .749$), or between post-stroke patients without speech and language disorders and neurologically healthy subjects ($U = 94.500$, $p = .454$) **(Table 1)**.

The results of the Kruskal-Wallis test showed that there were statistically significant differences between the groups related to the quality of life ($H = 25.91$, $df = 3$, $p < .001$). Furthermore, the results of Mann-Whitney U test revealed that in terms of quality of life there were statistically significant differences between patients with aphasia and neurologically healthy subjects ($U = 50.00$, $p < .001$), patients with aphasia and post-stroke patients without speech and language disorders ($U = 89.00$, $p < .01$), patients with dysarthria and neurologically healthy subjects ($U = 40.00$, $p < .001$), and patients with dysarthria and post-stroke patients without speech and language disorders ($U = 67.00$, $p < .01$). No statistically significant differences were found between patients with aphasia and dysarthria ($U =$

Table 1. Distribution of groups of respondents related to the quality of communication
Tabela 1. *Distribucija grupa ispitanika prema kvalitetu komunikacije*

Group/*Grupa*	No./*Br.*	M/*M*	SD/*SD*	Min/*Min*	Max/*Maks*	Mdn/*Mdn*	IQR/*IQR*
Aphasia/*Afazija*	25	3.51	0.71	2.00	4.35	3.76	0.80
Dysarthria/*Dizartrija*	20	3.38	0.84	2.21	4.76	3.53	1.63
Post-stroke patients without speech and language disorders *Osobe sa moždanim udarom očuvanih govornih i jezičkih funkcija*	15	4.40	0.40	3.11	4.82	4.53	0.36
Neurologically healthy subjects/*Neurološki zdravi govornici*	15	4.53	0.34	3.88	5.00	4.55	0.41

Legend: M – mean; SD - Standard deviation; Mdn – Median; IQR - Interquartile range
Legenda: M – Srednja vrednost; SD – Standardna devijacija; Mdn – Medijana; IQR – Interkvartilni raspon

Table 2. Distribution of groups of respondents related to the quality of life
Tabela 2. *Distribucija grupa ispitanika prema kvalitetu života*

Group/*Grupa*	No./*Br.*	M/*M*	SD/*SD*	Min/*Min*	Max/*Maks*	Mdn/*Mdn*	IQR/*IQR*
Aphasia/*Afazija*	25	3.60	0.71	2	5	4.00	1.00
Dysarthria/*Dizartrija*	20	3.40	0.94	2	5	3.50	1.00
Post-stroke patients without speech and language disorders *Osobe sa moždanim udarom očuvanih govornih i jezičkih funkcija*	15	4.33	0.62	3	5	4.00	1.00
Neurologically healthy subjects/*Neurološki zdravi govornici*	15	4.67	0.49	4	5	5.00	1.00

Legend: M – mean; SD - Standard deviation; Mdn – Median; IQR - Interquartile range
Legenda: M – Srednja vrednost; SD – Standardna devijacija; Mdn – Medijana; IQR – Interkvartilni raspon

222.00, p = .492), post-stroke patients without speech and language disorders and neurologically healthy subjects (U = 80.00, p = .124) **(Table 2)**.

The results of the Kruskal-Wallis test showed that there was no statistically significant difference in the quality of communication between patients with different types of aphasia (H = 9.04, df = 4, p = .060). On the other hand, there was a statistically significant difference in the quality of communication of patients with different degrees of aphasia severity (H = 14.50, df = 2, p = .001), with the highest average value of respondents with mild aphasia **(Table 3)**.

The results of the Kruskal-Wallis test showed a statistically significant difference between patients with different types (H = 6.89, df = 3, p = .075) and severity of dysarthria (H = 12.26, df = 2, p < .005). The patients with spastic dysarthria and those with mild dysarthria had the highest average scores **(Table 4)**.

The results of the Kruskal-Wallis test showed no statistically significant difference between patients with different types of aphasia related to the perception of their quality of life (H = 4.55, p = .337), but significant differences were found between patients with different severity of aphasia (H = 8.65, p = .01).

Table 3. Distribution of subjects with different types and severity of aphasia related to the quality of communication
Tabela 3. *Distribucija ispitanika različitih tipova i težina afazije prema kvalitetu komunikacije*

		No./*Br.*	M/*M*	SD/*SD*	Min/*Min*	Max/*Maks*	Mdn/*Mdn*	IQR/*IQR*
Types of aphasia *Tipovi afazije*	Broca's/*Brokina*	5	3.64	0.29	3.17	3.88	3.76	0.47
	Wernicke's/*Vernikeova*	5	3.28	0.83	2.24	3.94	3.76	1.56
	Conduction/*Konduktivna*	5	3.41	0.85	2.00	4.29	3.59	1.21
	TSA	5	3.07	0.83	2.06	3.94	3.11	1.64
	Anomic/*Anomička*	5	4.08	0.20	3.88	4.35	4.12	0.38
Severity of aphasia *Težina afazije*	Mild/*Blaga*	8	4.13	0.21	3.82	4.35	4.06	0.41
	Moderate/*Umerena*	8	3.68	0.25	3.17	3.94	3.70	0.32
	Severe/*Teška*	9	2.84	0.75	2.00	3.94	2.53	1.49

Legend: M – mean; SD - Standard deviation; Mdn – Median; IQR - Interquartile range; TSA - Transcortical sensory aphasia
Legenda: M – Srednja vrednost; SD – Standardna devijacija; Mdn – Medijana; IQR – Interkvartilni raspon; TSA – Transkortikalna senzorna afazija

Table 4. Distribution of subjects with different types and severity of dysarthria related to the quality of communication
Tabela 4. *Distribucija ispitanika različitih tipova i težine dizartrije prema kvalitetu komunikacije*

		No./*Br.*	M/*M*	SD/*SD*	Min/*Min*	Max/*Maks*	Mdn/*Mdn*	IQR/*IQR*
Types of dysarthria *Tipovi dizartrije*	Flaccid/*Flacidna*	6	2.30	0.79	2.23	4.17	2.91	1.37
	Spastic/*Spastična*	5	4.18	0.41	3.76	4.76	4.23	0.76
	Ataxic/*Ataksična*	5	3.19	0.75	2.35	4.11	3.41	1.44
	Hypokinetic/*Hipokinetička*	4	3.19	0.99	2.12	4.06	3.29	1.81
Severity of dysarthria *Težina dizartrije*	Mild/*Blaga*	6	4.17	0.44	3.41	4.76	4.20	0.52
	Moderate/*Umerena*	7	3.52	0.47	2.59	4.06	3.59	0.47
	Severe/*Teška*	7	2.56	0.65	2.12	4.00	2.35	0.24

Legend: M – mean; SD - Standard deviation; Mdn – Median; IQR - Interquartile range
Legenda: M – Srednja vrednost; SD – Standardna devijacija; Mdn – Medijana; IQR – Interkvartilni raspon

Table 5. Distribution of subjects with different types and severity of aphasia related to their self-assessed quality of life
Tabela 5. *Distribucija subjekata različitih tipova i težine afazije prema oceni kvaliteta života*

		No./*Br.*	M/*M*	SD/*SD*	Min/*Min*	Max/*Maks*	Mdn/*Mdn*	IQR/*IQR*
Type of aphasia *Tipovi afazije*	Broca's/*Brokina*	5	3.60	0.55	3	4	4.00	1.00
	Wernicke's/*Vernikeova*	5	3.60	0.55	3	4	4.00	1.00
	Conduction/*Konduktivna*	5	3.20	0.84	2	4	3.00	1.50
	TSA	5	3.40	0.55	3	4	3.00	1.00
	Anomic/*Anomička*	5	4.20	0.84	3	5	4.00	1.50
Severity of aphasia *Težina afazije*	Mild/*Blaga*	8	4.13	0.64	3	5	4.00	0.75
	Moderate/*Umerena*	8	3.63	0.52	3	4	4.00	1.00
	Severe/*Teška*	9	3.11	0.60	2	4	3.00	0.50

Legend: M – mean; SD - Standard deviation; Mdn – Median; IQR - Interquartile range; TSA - Transcortical sensory aphasia
Legenda: M – Srednja vrednost; SD - Standardna devijacija; Mdn – Medijana; IQR - Interkvartilni raspon; TSA - Transkortikalna senzorna afazija

Table 6. Distribution of subjects with different types and severity of dysarthria related to their self-assessed quality of life
Tabela 6. *Distribucija ispitanika različitog tipa i težine dizartrije prema proceni kvaliteta života*

		No./*Br.*	M/*M*	SD/*SD*	Min/*Min*	Max/*Maks*	Mdn/*Mdn*	IQR/*IQR*
Types of dysarthria *Tipovi dizartrije*	Flaccid/*Flacidna*	6	2.83	0.98	2	4	2.50	2.00
	Spastic/*Spastična*	5	4.00	0.71	3	5	4.00	1.00
	Ataxic/*Ataksična*	5	3.20	0.84	2	4	3.00	1.50
	Hypokinetic/*Hipokinetička*	4	3.75	0.96	3	5	3.50	1.75
Severity of dysarthria *Težina dizartrije*	Mild/*Blaga*	6	3.67	1.03	2	5	4.00	1.50
	Moderate/*Umerena*	7	3.57	0.89	2	4	4.00	1.00
	Severe/*Teška*	7	3.00	1.00	2	5	3.00	1.00

Legend: M – mean; SD - Standard deviation; Mdn – Median; IQR - Interquartile range
Legenda: M – Srednja vrednost; SD - Standardna devijacija; Mdn – Medijana; IQR - Interkvartilni raspon

Namely, patients with mild aphasia had significantly higher scores compared to patients with severe aphasia ($U = 10.00$, $p < .01$), as well as patients with moderate aphasia compared to those with severe aphasia ($U = 20.00$, $p = .082$). The differences between subjects with mild and moderate aphasia were not statistically significant ($U = 19.00$, $p = .113$) **(Table 5)**.

The results of the Kruskal-Wallis test showed no statistically significant difference in the quality of life between subjects with different types of dysarthria ($H = 4.57$, $p = .206$) or between subjects with different severity of dysarthria ($H = 2.53$, $p =. 283$) **(Table 6)**.

Discussion

This study examined patients with aphasia and dysarthria due to stroke. Our aim was to investigate their quality of communication and quality of life by comparing them with control groups including post-stroke patients without speech and language disorders and neurologically healthy subjects.

The results of our study showed that subjects with aphasia and dysarthria had significantly lower scores related to their quality of communication and quality of life compared to the control groups. Additional analysis showed that there was no statistically significant difference in the quality of communication between patients with different types of aphasia. However, the results showed a tendency for patients with Wernicke's aphasia and TSA to rate their communication abilities lower compared to patients with other types of aphasia, which indicates a possible influence of the type of aphasia on the quality of communication. Given that the type of aphasia may affect the quality of communication, as shown in some earlier studies [5, 6, 15], the question of the relationship between the type of aphasia and the self-assessment of the quality of communication remains open. In order to get a valid answer to this question, it is necessary to include a larger number of respondents for each type of aphasia and to equalize them according to the severity of the language disorder.

The results of research also showed that people with aphasia have a poor quality of communication. For example, Pallavi et al. found that patients with Broca's aphasia had significantly lower scores on the QCL compared to the control group of neurologically healthy subjects [15]. Similar findings were reported by Vuković, who determined a significantly worse quality of communication in patients with Broca's and conduction aphasia compared to neurologically healthy subjects [5].

The current research further showed that the quality of communication depends on the severity of aphasia. The lowest self-assessment scores of communicative abilities were observed in patients with severe aphasia, while the highest scores were observed in patients with mild aphasia. The results obtained by comparison within the same type of aphasic syndrome in another study [5] also lend support to the influence of the severity of aphasia on the quality of communication. Specifically, that study found that people with a severe form of conduction aphasia have significantly worse scores on the QCL Scale compared to people with a milder form [5].

Concerning the assessment of quality of life, the present study shows that patients with aphasia, regardless of its type, rate their quality of life significantly lower compared to subjects without speech and language disorders. It also shows that subjects with a more severe degree of aphasia rate their quality of life lower compared to those with milder aphasic disorders.

The analysis of the results of subjects with dysarthria also revealed a lower quality of communication compared to neurologically healthy subjects and post-stroke patients without speech and language disorders. The type of dysarthria proved to be a significant factor in determining the quality of communication. Namely, subjects with flaccid dysarthria had the lowest scores on the QCL, while the highest scores were found in the group of subjects with spastic dysarthria**.** Since the most noticeable signs of flaccid dysarthria are difficulty in pronouncing consonants and hypernasality [10, 16], it is to be assumed that these deficits in speech contribute most to the poor quality of communication. In addition to the type, it was found that the severity of dysarthria also significantly impacts the quality of communication of people with dysarthria. People with a severe degree of dysarthria were the least satisfied with their quality of communication, while people with mild dysarthria rated their communication abilities the highest.

Regarding self-perception of the quality of life, our results show that patients with dysarthria, regardless of type and severity, rate it significantly lower compared to subjects without speech and language disorders.

Finally, our results showed that people with aphasia and dysarthria included in this research rated their communication quality equally poorly. However, bearing in mind that the study did not include persons with very severe aphasia (global aphasia, transcortical mixed aphasia, severe forms of Wernicke's or Broca's aphasia), we cannot say with certainty that aphasia and dysarthria impair the QCL to the same extent. In order to get a valid answer to this question, it is necessary to develop and apply scales adapted to people with very severe aphasic disorders.

Conclusion

People with aphasia and dysarthria have a significantly impaired quality of communication and quality of life compared to people without speech and language disorders. The severity of aphasia was identified as an important factor in determining the quality of communication and quality of life. Patients with severe aphasia have significantly worse quality of communication and quality of life compared to those with moderate or mild aphasia. The quality of communication of patients with dysarthria is affected by the severity and type of dysarthria. Patients with flaccid dysarthria and severe form of dysarthria have the worst quality of communication. Judging from our results, we strongly believe that, as a part of speech-language therapy, patients with aphasia and dysarthria should be encouraged to communicate, regardless of the severity of disorder.

One of the limitations of this study is the small number of respondents within different types of aphasia and dysarthria. In addition, communication assessment scales adapted to patients with very severe forms of aphasia should be applied in future research.

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PROFESSIONAL ARTICLES
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EVALUATION OF KNOWLEDGE ON INDUCED PLURIPOTENT STEM CELLS AMONG THE GENERAL POPULATION AND MEDICAL PROFESSIONALS

ISPITIVANJE ZNANJA PRIPADNIKA OPŠTE POPULACIJE I POPULACIJE MEDICINSKIH RADNIKA O INDUKOVANIM PLURIPOTENTNIM MATIČNIM ĆELIJAMA

Sanja RAŠČANIN[1], Mirjana JOVANOVIĆ[1, 2] and Nemanja RANČIĆ[3, 4]

Summary

Introduction. Induced pluripotent stem cells are ethically much more acceptable than embryonic stem cells. The aim of this paper is to evaluate the knowledge on these cells among the general population and medical professionals, because this may influence further research. **Material and Methods**. We conducted a survey to assess knowledge on induced pluripotent stem cells among the general population and medical workers. The inclusion criteria were age over 18 years and the ability to read and write in Serbian. The survey was conducted via email and printed materials using a validated questionnaire for evaluation of awareness, knowledge, and attitudes towards donation, storage, and application of induced pluripotent stem cells. The collected data were entered into an Excel database, and complete statistical analysis was performed using the Statistical Package for the Social Sciences version 26.0. **Results**. The rate of correct answers among health workers ranged from 17.5% to 67.1%, and among the general population from 16.4% to 49.4%. The average number of correct answers per respondent in the population of health workers was 6, while in the general population it was 4, which is statistically significantly lower. **Conclusion**. The research results showed that healthcare workers have a higher level of knowledge on induced pluripotent stem cells than members of the general population, but the level of knowledge can be influenced by the level of education, availability of information, socioeconomic status, ideology, and conservative attitudes.

Key words: knowledge, induced pluripotent stem cells, general population, medical workers

Sažetak

Uvod. Indukovane pluripotentne matične ćelije su etički mnogo prihvatljivije od embrionalnih matičnih ćelija. Cilj ovog rada je da se ispita znanje pripadnika opšte populacije i populacije medicinskih radnika o ovim ćelijama jer to može uticati na dalja istraživanja. **Materijal i metode.** Sproveli smo anketiranje kako bismo procenili znanje između opšte populacije i populacije medicinskih radnika. Kriterijumi za uključivanje u studiju bili su da su ispitanici osobe starije od 18 godina i da imaju sposobnost čitanja i pisanja na srpskom jeziku. Istraživanje je sprovedeno korišćenjem validiranog Upitnika za procenu informisanosti, znanja i stavova o donaciji, skladištenju i primeni indukovanih pluripotentnih matičnih ćelija putem e-pošte i korišćenjem štampanih materijala. Prikupljeni podaci su prezentovani u *Excel* bazi podataka, a kompletna statistička analiza podataka izvršena je korišćenjem *IBM SPSS* softverskog paketa verzije 26.0. **Rezultati.** Stopa tačnih odgovora među zdravstvenim radnicima kretala se od 17,5% do 67,1%, a među pripadnicima opšte populacije od 16,4% do 49,4%. Prosečan broj tačnih odgovora po ispitaniku u populaciji zdravstvenih radnika bio je 6, dok je u grupi pripadnika opšte populacije bio 4, što je statistički značajno manje. **Zaključak.** Rezultati istraživanja pokazali su da zdravstveni radnici imaju viši nivo znanja od pripadnika opšte populacije, ali na nivo znanja mogu uticati stepen obrazovanja, dostupnost informacija, socioekonomski status, ideologija i konzervativni stavovi.

Ključne reči: znanje, indukovane pluripotentne matične ćelije, opšta populacija, medicinski radnici

Introduction

Induced pluripotent stem cells (iPSCs) have become one of the most common topics in recent years, both among members of the general population and in the scientific community. The question is how much we actually know about iPSCs?

The iPSCs are a type of pluripotent stem cells that can be obtained by reprogramming adult somatic cells into a pluripotent state in vitro by inducing a forced expression of four transcription factors that are important for the maintenance of pluripotency [1–8]. Although these cells show a number of similarities with embryonic stem cells (ESCs), there are

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Abbreviations

iPSCs – induced pluripotent stem cells
ESCs – embryonic stem cells
SPSS – Statistical Package for the Social Sciences
OR – odds ratio

also significant differences between these two types of cells; in addition to morphological and functional differences, the one that stands out from the aspect of research and potential application is ethical acceptability, where iPSCs are significantly more acceptable than ESCs [8–11]. They offer opportunities for potential treatment of diseases and injuries, restoring functions, and drug testing [12–23]. Also, it should be noted that potential application of stem cells is associated with a risk of tumorigenesis [8, 23–26].

The aim of this paper is to examine the knowledge about iPSCs among the general population and medical professionals. Similar studies were performed and showed that the general public was familiar with the terms of stem cells, as well as that respondents showed a certain level of knowledge [27–37]. We also expected our respondents to show a certain level of knowledge, whereby we expected that health professionals would show a higher level of knowledge compared to the respondents from the general population. Due to the interest in this topic, it is very important to assess the knowledge of both members of the general population and the population of medical workers, because awareness and knowledge can influence the formation of positive attitudes and support for further research.

Material and Methods

The study was conducted in the period from September 1, 2021 to January 1, 2022, and it was designed as a survey-based cohort study which examined the general population and the population of health workers using a validated Questionnaire for Evaluation of Awareness, Knowledge, and Attitudes towards Donation, Storage, and Application of iPSCs [38] via e-mail and directly using printed material. The obtained data were entered into an Excel database, followed by statistical analysis of data and summarized research results.

The research was conducted in a Serbian-speaking area, in the territory of Kragujevac and Belgrade. The inclusion criteria were age over 18 years and the ability to read and write in Serbian. The sampling was random; the independent variables were gender, age, religion, ideology, socioeconomic status, level of education, and the dependent variables were awareness and the level of knowledge about iPSCs. The study surveyed a total of 1,047 respondents, 46.5% of men and 53.5% of women. Respondents were mostly aged 31 to 60 years (85.4%).

Complete statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 26.0. Data were presented in the form of numbers (percentage). Statistical significance was tested by the Chi-square test for variables in the form of frequencies of individual categories. Continuous variables were presented as mean with standard deviation (SD) or median with interquartile range (according to the data distribution tested by the Kolmogorov-Smirnov test). The significance of the difference in continuous variables was tested by the Student T-test for independent causes or Mann-Whitney test; Kruskal-Wallis test was also used for variables that had three or more categories. The correlation was tasted by Spearman correlation, and the correlation strength was assessed as very strong ($r > 0.5$), strong (r 0.3 - 0.49) or weak ($r < 0.29$). In the prediction of the dependent variables with the help of independent variables, univariate and multivariate logistic regression was performed, and the results were presented as an odds ratio (OR) or cross OR with a 95% confidence interval. The statistical significance was set at $p < 0.05$.

Results

Respondents employed in health care system in relation to respondents from the general population

Of all respondents, 35.4% were health workers, while significantly more were respondents from the general population, 64.6%. Among health care workers, there were significantly more males compared to the general population (53.9% vs. 42.5%), in which there were more females ($p < 0.001$). In the group of health workers, most were aged from 31 to 50 years (79.8%), while in the general population most were aged from 31 to 60 years (80.2%). In terms of education and socioeconomic status, in both examined groups, most had a higher education, i.e. a university degree, but there were significantly more persons with a doctoral degree among the health care workers compared to members of the general population (37.5% vs. 5.6%); also, health workers mostly had incomes over 100,000 dinars, while members of the general population mostly had 50,000 to 75,000 dinars. When asked whether their religion affected their decisions, 32.6% of health workers partially agreed with it, 25.1% disagreed, while 17.3% said that they absolutely agreed with it. On the other hand, in the general population, 25% partially agreed with it, 24.3% disagreed, and 16% did not agree with it at all (Chi-Square test; $p <0.001$). The majority of respondents in both groups stated that they had highly or partially liberal ideological views (health workers: 64.7% vs. general population: 60.6%) (Chi-Square test; $p = 0.007$). All health workers responded that they were informed about stem cells online, while members of the general population were informed predominantly online (77.4%), but also through newspapers and television. Both groups of respondents believe that this topic is given insufficient, little or very little attention in the media and only 8% of health workers believe that it is paid enough attention ($p < 0.001$).

There was a statistically significant difference in the distribution of answers between health workers and the general population. A higher percentage of health professionals have heard about iPSCs com-

pared to the general population (82.5% vs. 65.7%). Also, compared to the general population, health workers statistically more often believe that these cells can be used in the treatment of diabetes (57.4% vs. 38.8%). An interesting thing is that both groups are most likely to consent to treatment with these cells (> 50% in both groups). Both groups mostly believe that there are risks in the use of these cells, but 10% of the general population answered this question with ''I do not know''. Both groups believe (56%) that these cells can be used as a cure. Health workers are significantly more likely to believe that treatment with these cells is both ethically and morally justified (80.9%), while the general population has the same view in only 57.4% of cases; they also answered that they would store iPSCs in Serbia, while the general population answered that they would also store these cells in Serbia, but almost 30% of respondents would store these cells abroad. Healthcare professionals are significantly more likely to donate these cells compared to the general population (70.4% vs. 54.6%), and more likely to support research with these cells compared to the general population (54.7% vs. 40.2%). Healthcare workers are significantly more likely to agree with research related to cloning of human tissues and organs compared to the general population (69.6% vs. 62.3%), and they are significantly more often interested in learning about these cells compared to the general population (86.3% vs. 55%).

We found that there is a statistically significant difference in the distribution of answers to most questions between health workers and the general population. The rate of correct answers among health workers ranged from 17.5% to 67.1%. The rate of correct answers among health workers ranged from 17.5% to 67.1%, and the least correct answers were given about the characteristics of pluripotent stem cells: self-renewal, potency and differentiation. In the general population, the rate of correct answers ranged from 16.4% to 49.4%, and the least correct answers were given about the transcription factors included in Thomson's modification: Oct4, Sox2, Nanog, and Lin28. Interestingly, the rate of correct answers in the general population did not exceed 50% to any question, while more than 50% of correct answers were given by health professionals to 5 out of 12 questions. The general population had a higher rate of correct answers: IPSCs can differentiate only into the bone, cartilage, and fatty tissue cells; Characteristics of pluripotent stem cells are self-renewal, potency and differentiation; and Reprogramming of somatic cells to IPSCs is done using only the non-integrative method with micro-ribonucleic acid.

Our results showed that the average number of correct answers per respondent from the group of health workers was 6 (3 - 7) (data presented as median with interquartile range: 25 – 75), while in the group of the general population it was statistically significantly lower 4 (1.25 - 7) (Mann-Whitney test; $p < 0.001$). In regard to the minimum and maximum number of answers per respondent, we see that in the group of health workers there were none giving 10 correct answers, while in the general population this range was from zero to all 12 affected. It is important to note that the number of respondents with no correct answers was significantly higher in the general population compared to health workers (16.3% vs. 1.1%), and it is similar with one correct answer (8.7 % vs. 0.5%). However, there were 2.4% or 16 respondents, out of a total of 676, from the general population group with eleven or all twelve correct answers, while there were no such respondents among health professionals. From two to ten correct answers in almost all categories, there were more respondents among health workers compared to the general population.

Correlation between the respondents' knowledge and other variables

If a correlation is made between the overall knowledge score in the group of health professionals or in the general population, a statistically significant correlation is established (Spearman's rho = -0.191; $p < 0.001$). This shows that the score increases in the group of health workers, while it is lower in the general population. Although this is statistically significantly related, the correlation coefficient shows that this is still a weak correlation, so this significance should be observed with caution. There is also a significant correlation between age and level of education, so the overall score gets higher with age and higher level of education.

The correlation between the overall knowledge score regarding awareness of health professionals shows that there is a statistically significant association with some variables. On the other hand, all questions on awareness of the general population are statistically significantly related to the overall knowledge score.

Regarding the connection of awareness of health workers and socioeconomic status, religion, ideology and media attention in relation to iPSCs, it can be noticed that there is a strong connection between certain characteristics. Socioeconomic status and the question on the level of awareness are strongly related, which means that respondents with higher financial incomes stated that they would rather leave their cells abroad than in Serbia ($r = 0.479$). Respondents with more conservative attitudes are less likely to give a positive answer regarding the donation of iPSCs for the purpose of treatment ($r = 0.489$). There is also a strong correlation between the level of awareness and ideological attitudes, i.e. respondents with more conservative attitudes are less likely to be interested in learning more about iPSCs ($r = 0.393$). There is also a strong correlation between the level of awareness and media attention given to iPSCs, i.e. more health professionals stated that the more attention is paid to these cells, the less they agreed with research related to cloning human tissues and organs ($r = 0.388$).

In regard to the connection between the level of awareness of the general population with socioeco-

nomic status, religion, ideology and media attention to iPSCs, there is a strong connection between certain characteristics. Ideology and the level of awareness are strongly connected, i.e. respondents with more conservative attitudes are less likely to give a positive answer regarding the donation of these cells for the purpose of treatment ($r = 0.334$).

Regarding the correlation between knowledge and socioeconomic status, religion, ideology and media attention related to iPSCs, although there is a statistically significant correlation between individual variables, no strong correlation between examined variables was established in both groups of examinees.

Predictors of respondents' knowledge

If the total sum of correct answers is presented in a histogram, specifically for health workers, specifically for the general population, it is noticed that 5 correct answers represent the mean value and it is viewed as limited value. The total sum of 5 answers plus 5 below is unsatisfactory, while 6 or more correct answers are satisfactory. If we first cross the OR for the whole group, where the dependent variable is whether the respondents had 5 correct answers below or above, and the independent variable is the affiliation to health care group or the general population, we see that a significant value is obtained (Univariate logistic regression: OR = 0.573 (0.443 - 0.740); $p < 0.001$). That is, health workers were 1.74 times more likely to be in the group with a total knowledge score over 5 correct answers. Therefore, we looked at all predictions separately for these two subgroups of respondents.

A multivariate regression analysis shows predictiors regarding the knowledge of health workers, including ideologies, attention paid to this topic in the media, and issues of their awareness (Do you think iPSCs can be used to treat diabetes? Do you think there are risks when using iPSCs for treatment? Would you keep your iPSCs in the state cell bank in Serbia or abroad? Do you agree with the research on cloning human tissues and organs? This shows that the more conservative attitudes the respondents have, and the less attention is paid to this topic in the media, the better the knowledge expressed in the overall score. Awareness also shows that if respondents think that these cells can be used to treat diabetes, there are risks in using these cells for therapeutic purposes, and if they leave these cells for storage in Serbia, they have higher scores. It has also been shown that those who agreed with tests related to cloning of human cells and tissues are more likely to have a score above 5.

On the other hand, a prediction for the general population was made and it was shown by multivariate regression analysis that significant predictors are age, religiosity, how much attention is paid to this topic in the media and how someone is informed about this topic. For example: Have you heard about induced pluripotent stem cells so-called iPSCs? Do you think iPSCs can be used to treat diabetes? Would you agree to be treated by iPSCs? Do you think there are risks when using iPSCs for treatment? Would you keep your iPSCs in the state cell bank in Serbia or abroad? Do you support research with iPSCs? Do you agree with the research on cloning human tissues and organs? Are you interested in learning more about iPSCs? Older respondents, the less religious he is; more respondents are informed through newspapers and television and not through the Internet, and the less attention is paid to this topic in the media, they have better knowledge expressed by the overall score. Awareness shows that if respondents have heard of iPSCs, they have higher scores on the scale of knowledge. If respondents think that iPSCs can be used to treat diabetes, there are risks in using these cells for therapeutic purposes, and if they would agree to treatment using these cells, they are more likely to have a score above 5. If they left iPSCs abroad, respondents showed higher scores. It has also been shown that those who agree with trials related to human cell and tissue cloning, they would support research on these cells, and those who would be interested in learning more about these cells are more likely to have a score above 5.

Discussion

Awareness and knowledge of iPSCs can significantly influence the formation of attitudes among the general population and health professionals, which can later be reflected in the course of further research in this area. That is why it is important to examine awareness and knowledge, because it has been shown that respondents who were better informed and have greater knowledge have more positive attitudes towards research in the field of stem cells.

Similar studies conducted in Japan over several years aimed to survey public opinion on iPSCs; the results of the study showed that the general population in Japan is well informed about iPSCs and that it supports further research with these cells [27–31].

A survey conducted in Malaysia in 2015 included 88 randomly selected nurses, showed that 92% of nurses in their final year of study had moderate knowledge of stem cells, and 8% had a high knowledge of stem cells [32]. A similar study was conducted in Saudi Arabia in 2015 and it included 53 nurses. The assessment of knowledge before testing showed poor knowledge in 30.2%, average knowledge in 62.3% and good knowledge in 7.5%. After testing, a noticeable improvement in knowledge was observed, with 80.8% of respondents showing good knowledge and 19.2% average knowledge [34]. In a study conducted by McCaughey et al., 91.5% of respondents believed they understood what was meant by "stem cells", and only 16.1% knew that their sample could be maintained indefinitely, 51.8% of respondents knew that they could differentiate into any other adult body cell [33]. Abouzeid MI et al., conducted a study in Egypt (2017 – 2018) including a sample of 42 nursing students. The study showed that the respondents had a satisfactory knowledge in the pre-test, and after the of the educational program the subsequent test showed an improvement of up to 90.5% [35]. The results of a study conducted in Iran (2019 – 2020) showed that the

knowledge of medical students from different years of study depended on the year of study, practice and period of externship periods. It is interesting that the participants showed the best knowledge of the use of stem cells, especially students who had close relatives with degenerative neurological diseases [36]. A study conducted in Saudi Arabia in 2021 included students of medicine and dentistry; 72.4% of respondents showed average knowledge of stem cells, and 23% showed a high level of knowledge, with a significant positive correlation between attitudes and knowledge [37].

In our study, if the total sum of correct answers is presented in a histogram for both populations, a limit value of 5 is obtained (below 5 - unsatisfactory, 6 and more correct answers - satisfactory value); in this regard, the rate of correct answers among health workers ranged from 17.5% to 67.1%, and among members of the general population it ranged from 16.4% to 49.4%. Our results showed that the average number of correct answers per respondent in the population of health workers was 6, while in the group of members of the general population it was 4, which is statistically significantly lower. The following predictors have been shown to influence the knowledge of health professionals: ideology, stem cell representation as a current topic in the media and information, i.e. if the media pay less attention to this topic, respondents with more conservative attitudes have better knowledge; in addition, if respondents think that these cells can be used for potential treatment of diabetes, there are risks associated with using these cells, and if they would leave their stem cells for storage in Serbia, then they have higher scores; also respondents who support research related to cloning of human tissues and organs may have a higher score.

The hypothesis that healthcare professionals have a higher level of knowledge about iPSCs compared to members of the general population was confirmed. However, this knowledge should be at an even higher level, given that professional literature is available to them, so future healthcare workers should be educated in more detail about these cells. In order to improve knowledge of the members of the general population about stem cells, especially about iPSCs, the level of information should be raised to a higher level, so it is necessary to inform the public better through social networks, video animations on potential applications and risks, organize educational programs that should be mandatory for members of medical profession, and which can be led by volunteers, final year students of medical and related universities.

Conclusion

Based on the results of our research, we can conclude that health workers showed a higher level of awareness and knowledge about induced pluripotent stem cells compared to members of the general population, although awareness and knowledge, as shown by the results of our study, can be influenced by other factors such as ideology, conservative attitudes, availability of information, level of education and socioeconomic status.

Many researchers dealt with different topics, but had similar approaches to the problem by investigating the attitudes, awareness and knowledge of the public, which shows that the opinion of the public should not be ignored; the common conclusion is that it is necessary to enhance informative and educational strategies.

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SAPHENOUS NERVE INJURY AFTER ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION

POVREDA SAFENUS NERVA TOKOM REKONSTRUKCIJE PREDNJEG UKRŠTENOG LIGAMENTA

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Summary

Introduction. Iatrogenic injury to the infrapatellar branch of the saphenous nerve is the most common complication after anterior cruciate ligament reconstruction. The aim of the study is to present the incidence, analyze risk factors, and possibilities of prevention. **Material and Methods**. One year after bone-patellar tendon-bone surgery, we surveyed 787 patients, 78.3% males, with mean age 27.7 years (14 - 59), mean height 180.6 cm (154 - 207), and mean weight 81.8 kg (46 - 145). We monitored the incidence of anterolateral skin numbness below the operated knee joint. **Results and Discussion**. Of the total number of examinees, 71.8% had a feeling of numbness, while 27.3% reported constant numbness. In the group of patients with a higher body mass, the feeling of numbness occurred significantly less often compared to the group with lower body mass, as was the case in the tallest patients, who reported numbness significantly less often compared to the shortest ($p < 0.001$). The incidence of anterolateral skin numbness was lowest among basketball players (64.5%) and highest among skiers (84.8%). Numbness was not significantly affected by age, laterality, and body mass index, level of sports activity, competition ranking or time until surgery. The horizontal surgical incision, intraoperative identification of the nerve, minimally invasive surgery, and the choice of bone graft harvesting sites, can reduce the complication rate. **Conclusion**. One year after the anterior cruciate ligament reconstruction, every fourth patient felt constant anterolateral skin numbness of the operated knee. Although this did not significantly affect the quality of life, it can be prevented by the surgeon who is obliged to warn every candidate for surgery about the possibility of complications, especially short and slim persons.

Key words: Anterior Cruciate Ligament Reconstruction; Peripheral Nerve Injuries; Intraoperative Complications; Iatrogenic Disease; Risk Factors; Hypesthesia; Accident Prevention

Sažetak

Uvod. Jatrogena povreda podčašične grane predstavlja najčešću komplikaciju rekonstrukcije prednjeg ukrštenog ligamenta, pa cilj studije predstavlja prikaz njene učestalosti, analizu faktora rizika i mogućnosti prevencije. **Materijal i metode.** Godinu dana nakon operacije kost-čašična veza-kost tehnikom, anketirali smo 787 pacijenata, 78,3% muškog pola, prosečne: starosti 27,7 godina (14−59), visine 180,6 cm (154−207) i telesne mase 81,8 kg (46−145). Pratili smo učestalost utrnulosti kože sa spoljašnje strane ispod operisanog kolenog zgloba. **Rezultati i diskusija.** Osećaj utrnulosti imalo je 71,8% ispitanika, konstantnu 27,3%. U grupi pacijenata sa većom telesnom masom osećaj utrnulosti se značajno ređe javljao u poređenju sa grupama mršavijih pacijenata, kao što je bio slučaj i kod najviših pacijenata koji su ga značajno ređe imali u poređenju sa najnižim ($p < 0,001$). Komplikacija se najređe javljala među košarkašima (u 64,5% slučajeva), a najčešće među skijašima (84,8%). Na utrnulost nisu značajno uticali: starost, lateralnost, indeks telesne mase, nivo sportske aktivnosti, rang takmičenja i vreme proteklo do operacije. Horizontalni položaj hirurškog reza, intraoperativna identifikacija živca, minimalno invazivna hirurgija i izbor mesta uzimanja kalema, mogu je smanjiti. **Zaključak.** Godinu dana nakon rekonstrukcije prednjeg ukrštenog ligamenta konstantnu utrnulost oseća svaki četvrti pacijent. Iako komplikacija ne ostavlja značajne posledice na kvalitet života, hirurg može da prevenira njenu učestalost i dužan je da svakog kandidata za operaciju upozori, posebno niže i mršavije osobe.

Ključne reči: rekonstrukcija prednjeg ukrštenog ligamenta; povrede perifernih nerava; intraoperativne komplikacije; jatrogene povrede; faktori rizika; hipoestezija; prevencija povreda

Introduction

Saphenous nerve divides into two subcutaneous branches above the hamstring tendon junction on the tibial pes anserinus. One of them passes over the patellar ligament [1, 2]. This infrapatellar branch is purely sensory, without a motor component and innervates the antero-lateral region below the knee [2]. Anatomical position is important due to its vulnerability during surgical approaches to the knee, especially graft harvesting for anterior cruciate ligament (ACL) reconstruction [1, 3]. There is no absolutely safe incision that would avoid it, due to numerous variations in the path of its propagation

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Abbreviations

ACL – anterior cruciate ligament
BMI – body mass index
BPTB – bone-patellar tendon-bone
HT – hamstring tendon

[2]. The recovery prognosis is also uncertain, so spontaneous regeneration may take a few months, but irreversible damage may also be done [1].

Until the last twenty years, surgeons considered saphenous nerve injury inevitable and unimportant [2, 3]. The preventive measures to avoid injury started mainly with studies that identified this injury as a complication of knee surgery, including ultrasonography, blunt nerve isolation, grafting procedure with the knee in 90 degrees of flexion, and localization of safer surgical incision sites [4–24].

Iatrogenic injury to the infrapatellar branch of the saphenous nerve is the most common complication after anterior cruciate ligament reconstruction, but a completely safe operative technique to avoid it has not yet been found [4–24]. The aim of the study is to present the incidence, analyze risk factors, and possibilities of prevention.

Material and Methods

The research was carried out at the Clinic of Orthopedic Surgery and Traumatology of the Clinical Center of Vojvodina, with the prior approval of the Ethics Committee. This retrospective study included 787 respondents who filled out the survey: Response to quality of life [25].

All patients underwent the same operative bone-patellar tendon-bone (BPTB) technique [21] and were monitored for at least 12 months after ACL reconstruction. The following data were recorded and analyzed: gender, age, height, weight, cause of injury, level of sports activity, competition ranking, side of the injured limb, time from injury to diagnosis, time from injury to surgery, feeling of skin numbness below the knee and potential dissatisfactions with the surgery due to this complication.

The survey included 616 males (78.27%) and 171 females (21.73%). The average age was 27.71 years (28.32 years in males and 25.49 years in females). The youngest respondent was 14 years old, the oldest 59. They were divided into seven groups according to age. There were 134 patients under the age of 20 (17.03%); 205 between 20 and 25 years (26.05%); 171 from 25 - 30 years (21.73%); 102 from 30 - 35 years (12.96%); 91 from 35 - 40 years (11.56%); 46 from 40 - 45 years (5.84%), and 38 over the age of 45 years (4.83%). Thus, young athletes (20 - 25 years) made up the largest part of the sample, and the fewest respondents were in the group over the age of 45 years.

The average height was 180.65 cm. The shortest respondent was 154 cm and the highest 207 cm high. The largest part of the sample was between 180 and 190 cm high, and the least respondents were shorter than 160 cm **(Table 1)**.

The average body weight was 81.82 kg; the lowest weight was 46 kg and the highest 145 kg. The sample was divided into six groups: 50 respondents weighed up to 60 kg (6.35%), 99 60 - 70 kg (12.58%), 178 70 - 80 kg (22.62%), 217 80 - 90 kg (27.57%), 163 90 - 100 kg (20.71%), and 80 of them weighed over 100 kg (10.17%). The largest group weighed between 80 and 90 kg, and the smallest weighed less than 60 kg.

In the total sample, 409 had ACL reconstruction of the right knee, 355 of the left, while 23 had an injury of both knees.

According to sports activity, the respondents were divided into: 282 professional athletes (22.19%), 463 recreational athletes (58.06%) and 42 inactive in sports (4.7%). Among the active athletes, 82 compete at an international level, 140 at national, and 176 at regional level.

During the first month after the injury, the diagnosis of ACL rupture was made in 461 cases (58.58%), in the second month in 72 cases, in the third in 42, in the fourth in 27, in the fifth in 15, in the sixth month in 38, and more than half a year after injury the correct diagnosis was made in 132 respondents (16.77%). Seven subjects waited up to 15 days for surgery (0.89%), 18 waited 15 - 30 days, 79 30 - 45 days, 20 45 - 60 days, and 663 waited for over 60 days (84.24%).

The descriptive statistics included the mean value, standard deviation, minimum and maximum, analysis of variance and F-test. In comparative statistics, T-test was used for independent samples, with statistical significance set at $p < 0.001$. The results were compared, analyzed and presented in a table and graphs.

The study excluded 312 subjects who did not want to fill out the form voluntarily or filled it incompletely, as well as those who had other surgeries on the same knee joint, polyneuropathy or spinal nerve root damage.

Results

In the whole sample, 71.8% of the respondents (565) felt skin numbness on the anterolateral side of the operated knee. Numbness did not occur in 28.2% of cases (222), and it was always present in 27.3% (215). Persistent numbness was reported in 13.6% (107), occasional in 16.7% (131), rare in 14.2% i.e. 112 respondents.

Laterality did not significantly affect the sensation of numbness, which never occurred in 116 subjects with an injury of the right knee (28.3%), 100 with an injury of the left (28.2%) and 6 with an injury of both knees (26.1%). It was always present in 109 subjects with right knee injury (26.7%), 98 with left knee injury (27.6%) and 8 with both knee injuries (34.8%). Persistent numbness was the least reported, in 53 with an injury of the right knee (13%) and 56 with an injury of the left knee (15.8%). The subgroup with bilateral knee injuries included the fewest respondents who sometimes experienced numbness.

Table. 1. Incidence of numbness in groups classified according to height
Tabela 1. *Učestalost utrnutosti u grupama telesne visine*

Hight/*Visina*	No./*Br.*	Always/*Uvek*	Never/*Nikad*
< 160 cm	6	50%	16.7%
160 - 169 cm	73	38.4%	21.9%
170 - 179 cm	255	28.2%	20%
180 - 189 cm	321	25.6%	29.3%
190 - 199 cm	124	23.4%	38.7%
> 200 cm	8	12.5%	62.5%

In the youngest group (up to 20 years) including 134 respondents, 43 (32.1%) felt numbness all the time, and 42 (31.3%) never felt numbness. In the oldest group (over 45 years) out of 38 respondents, 8 (21.1%) always felt numbness and 9 (23.7%) never. The feeling of numbness never appeared in 69 out of 205 subjects (33.7%) aged between 20 and 25 years, but in the same age group there were most of those who always felt numbness (51 cases). Between the ages of 25 and 30, numbness rarely occurred in 31 respondents, often in 25, and the same age group had the largest number of those who sometimes experienced it, so there was no significant correlation (p = 0.05).

According to the gender distribution, 30 females (17.5%) and 192 males (31.2%) never felt numbness, while 69 females (40.4%) and 146 males (23.7%) always felt it. In 18 female respondents, numbness occurred sometimes (10.5%), while in 76 males it occurred least often (12.3%).

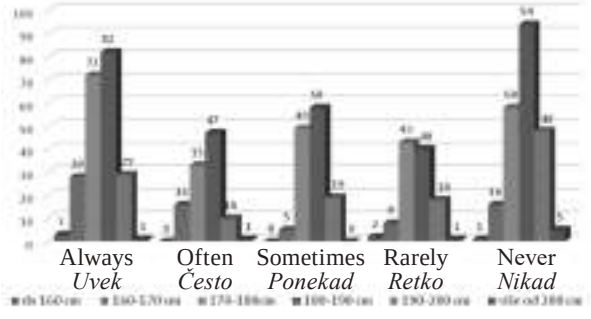
Shorter respondents reported this complication significantly more often than taller ones **(Table 1)**. Among the six subjects up to 160 cm high, there were three cases of permanent numbness (50%), compared to eight subjects over two-meters tall, where only one always felt numbness (12.5%). We can conclude that the increase in body height is associated with lower incidence of the feeling of numbness, so in the tallest respondents it occurred least often, while in the shortest, it occurred most often, especially in 83.3% of the respondents in the shortest group. There is a statistically significant difference (p < 0.001) in the correlation between this complication and the height of the examinees **(Graph 1)**.

In the slimmest group of 50 subjects weighing up to 60 kg, 19 (38%) always felt numbness and 9 (18%) never. In the group with the highest body weight over 100 kg, among 80 subjects, 16 (20%) always had this complication and 29 (36.2%) never **(Graph 2)**. We found that subjects with a higher body mass least often had the feeling of numbness (never), while those with a lower body mass often had this complication (always) (p = 0.001).

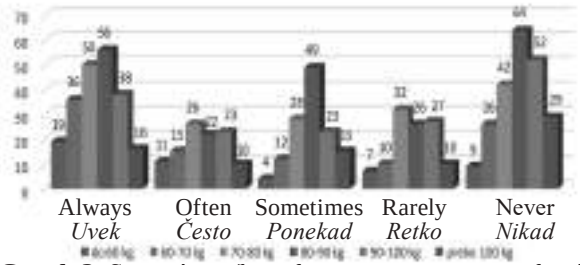
Analyzing the relationship between the body mass index (BMI) and the feeling of numbness, we may conclude that in subjects with higher BMI, the feeling of numbness "never" occurred, while in those with lower BMI it occurred "always", but the BMI does not statistically significantly correlate with this complication (p = 0.102).

In regard to sports activity, numbness was never reported in 126 subjects who were recreational athletes, i.e. in 89 subjects who were professional athletes and 7 non-athletes. However, numbness always occurred in 116 recreational athletes (25.1%), 87 professional athletes (30.9%) and 12 non-athletes (28.6%). The complication occurred least often in recreational and professional athletes and sometimes in non-athletes. There is no statistically significant correlation (p = 0.167) between numbness and the level of sports activities.

The feeling of numbness never appeared in 44 competitors at the national level, 52 at the regional level and in 94 recreational athletes, 26 respondents



Graph. 1. Sensation of numbness among groups classified according to height (always, often, sometimes, rarely, never)
Grafikon 1*. Osećaj stepena utrnutosti među grupama po visini (uvek, često, ponekad, retko, nikad)*



Graph 2. Sensation of numbness among groups classified according to body weight (always, often, sometimes, rarely, never)
Grafikon 2*. Osećaj stepena utrnutosti među grupama po telesnoj masi (uvek, često, ponekad, retko, nikad)*

at the international level and 6 non-athletes. It rarely occurred in 8 non-athletes, 60 recreational athletes, and 13 respondents at the national level, 19 at the regional level and 12 at the international level of competition. There is no statistically significant correlation ($p = 0.134$) between the feeling of numbness and the rank of competition.

The statistical analysis showed that there is no statistically significant difference ($p = 0.529$) in the occurrence of the feeling of numbness in relation to the time that passed from the moment of the injury to surgery.

Returning to sports activities one year after surgery was reported by 575 respondents (73.1%). Among the other 212 (26.9%) who did not return to sports, not a single respondent reported numbness of the antero-lateral side below the knee as the cause of dissatisfaction with the surgery outcome.

Discussion

Although it is the most common postoperative complication of ACL reconstruction [1, 4, 5, 26], certainly the most common neurological complication, studies have intensively monitored only the iatrogenic injury of the infrapatellar branch of the saphenous nerve in the last 20 years. This was contributed to unclear causes of anterior knee pain after numerous surgical procedures [22, 24, 27], such as prosthetic knee replacement, osteosynthesis of the proximal part of the tibia, reconstruction of the patellar ligament [28] and especially after harvesting a graft for ACL reconstruction, both BPTB [4, 13–17] and hamstring tendons (HT) [5–12, 26]. This complication can also occur during the incision of the antero-medial portal for arthroscopy, as well as by drilling a tunnel in the tibia [6, 7]. Injury to this sensory branch may have consequences in the form of symptoms of saphenous neuralgia, which, especially immediately postoperatively, can manifest as intense burning pain, increased local sensitivity during palpation, and later as a feeling of numbness below the antero-lateral side of the knee [1, 3]. In such cases, application of local therapy is suggested: 1.5 ml of anesthetic (0.5% bupivacaine), with or without depo corticosteroids [3]. At the end of the surgery, patients also receive a local anesthetic. More serious symptoms due to painful neuroma and sympathetic algodystrophy have also been described [5], resulting in anterior knee pain and discomfort during kneeling, sometimes with a negative impact on the patient's quality of life and satisfaction with surgery [5].

There are no clear guidelines for the diagnosis of this complication. Certain studies claim that ultrasonography provides the best information about nerve projections [29]. If an injury to the infrapatellar branch is suspected, the following methods are available: clinical examination, inspection of the scar site, type of pain, loss of sensitivity, positive Tinel sign, and electrodiagnostic procedures [3, 12]. Palpation and percussion are limited by the differential diagnosis of this region, and the complication may be misdiagnosed by the pathology associated with other nerves and anatomical structures (e.g. medial collateral ligament injury) [29]. Electrodiagnostic tests are technically challenging and usually useless in routine practice. Nevertheless, a group of Chilean authors, managed to detect 68% of these cases using an electrophysiological method, out of 77% of patients with numbness [12].

The incidence of saphenous nerve injury during classic HT harvesting ranges from 21 to even 88% [5–12, 26]. In an American study, 70% of patients felt numbness 6 weeks after surgery. Six months later, only 17% had a spontaneous recovery, 73% noticed an improvement after a year, and 14% had no complaints [10]. There are studies that prove that spontaneous recovery until returning to sports occurs only in every fourth patient, and every twentieth regretted having the surgery at all [13]. When we add that a Norwegian received insurance compensation of €605,100 due to permanent saphenous nerve deficit after ACL reconstruction [30], as well as that every fourth of our operated patients has a permanent feeling of numbness after one year, everything points to the importance of the problem and its prevention.

A group of Iranian authors significantly reduced the incidence of this iatrogenic injury ($p < 0.001$) when harvesting HT through a horizontal and oblique incisions, parallel to the extension of the nerve branch ($p < 0.001$) [5]. On cadavers, the oblique incision at a 45 degree angle proved to be the best, because the vertical one caused 65%, the horizontal 50%, and the oblique only 28% of injuries [9]. A group of Greek authors also reduced the incidence of complication just by changing the position of the incision from 40% in vertical to only 15% in horizontal [11]. Successful techniques for harvesting HT using two smaller incisions have also been described [31]. However, there are also studies that show that the incidence of complications is not affected by the position of the incision [5, 7]. While some authors believe that the length of the surgical incision does not have a significant effect [12], others have proven that a smaller incision reduces the risk [7] and that inadequate manipulation of the stripper for taking HT can cause saphenous nerve injury [6, 7].

The exploration of this nerve would be ideal for prevention, but the sensory branch of saphenous nerve is small and difficult to identify. Nevertheless, a group of Iranian authors prolonged the surgery by five minutes to find and explore it with a classic incision of 3 cm in length. During 98 surgeries, the nerve was not located 54 times, but found in 44 cases and protected with a rubber band. Postoperatively, only 20% of patients had a sensory deficit, in contrast to 72% where it was not found and protected [8]. There is also evidence that the incidence of nerve injury can be reduced by 13% only by following the surgical approach during the harvesting of a graft [17]. The posterior approach to HT harvesting can preserve the sensory branches [32]. Some authors believe that, due to the frequency of neurological complications, a completely different graft should be chosen instead of the usual ones [1]. For example, the quadriceps tendon graft does not endanger the path of propagation of the nerve branches or an al-

lograft should be used [10]. Comparing the quadriceps tendon and HT groups, the quadriceps tendon group had only 17% paresthesia versus 76% among HT [1]. The above may suggest that the cause does not lie solely in the choice of the graft, because if it were so, the nerve would never have been damaged in the quadriceps tendon autograft and allograft groups. The cause of some paresthesia probably lies in the coincidence of the path of nerve propagation with the place where the tunnel is drilled in the tibia, the arthroscopic portal, postoperative swelling that compresses it, or other reasons [7].

Prevention does not depend on the choice of one of the two most commonly used grafts, because no significant difference in the incidence of saphenous nerve injury was found by comparing BPTB and HT groups [10, 12]. Previously, it was thought that the main disadvantage of HT autograft harvesting was damage to the infrapatellar branch [17, 26], but it has been proven that this complication may also occur in as many as 90% of cases using traditional harvesting of BPTB (with vertical incision) [4, 15, 16]. Formerly, it was believed that the main disadvantage of the classic BPTB technique was anterior knee pain and extension deficit [17], but these complications can occur with both operative methods [4, 10, 12, 15, 16, 21, 22]. The advantages of the BPTB technique lie primarily in the firmer fixation of the graft and its faster biological incorporation [24, 33]. The potential disadvantages are patellofemoral pain, damage to the extensor apparatus of the knee, calcification of the patellar tendon, and patellar fracture [22, 27]. Also, a common complication, especially in female patients, is the weakness of the quadriceps muscle, which can last for two years after surgery [4].

Therefore, even with the BPTB technique, which was used in our patients, this nerve is not safe. A group of Israeli authors also registered numbness among 77% of patients, 19% with a complete spontaneous recovery after 8 months, while two years after surgery as many as 58% had a permanent loss of sensation below the knee. These authors, like us, prefer the BPTB technique in young active athletes, although by the time they return to sports, after 8 months, they have recorded complete nerve recovery in less than a quarter of cases, only in 24% undergoing BPTB and 23% in the HT group [13]. In order to prevent saphenous nerve injury, a group of Japanese authors [14] changed the traditional vertical incision for harvesting BPTB with two horizontal, and managed to reduce the complication rate to only 17%. French authors [4, 15] used a similar minimally invasive technique, using two 2 cm long vertical incisions (proximal that does not exceed the apex of patella and the distal in the area of the tibial tubercle), managed to significantly reduce the nerve damage. A new minimally invasive technique for harvesting BPTB graft uses only one patellar incision introducing a special instrument. In a group of 18 patients undergoing a classic method, there were 16 cases of numbness, and in minimally invasive there was only one [16].

Although there are no absolutely safe operative techniques, it is comforting that the majority of surveys confirmed that none of the subjects with damage to this nerve had impairment in daily activities attributable to sensory changes, nor delayed their rehabilitation due to this problem [12, 13, 19]. In another study, only one out of 60 respondents complained that the sensory change significantly affected his daily life [34]. It is similar in our sample, so after infrapatellar branch injury, no specific treatment is required [12, 13, 29, 34].

Most studies have proven that age, gender, BMI, as well as additional meniscus injuries, and the timing of ACL reconstruction, have no significant impact on the incidence of this neurological complication [1, 5, 7]. This is consistent with our results, with the exception of body height and body mass. We also noted that the complication was more frequent in females (82%) than in males (69%). The cause of this difference has not yet been established, since cadaveric studies indicate that there is no difference in skin innervation between the sexes [35]. Swedish researchers also found that there is no statistically significant difference between the occurrence of numbness in relation to gender, age, and the time from injury to surgery, but that there is a significant difference in relation to the level of activity before the injury, which was not the case in our study [36]. Most of our respondents were operated on in the first three months after the injury. On average, they waited for surgery 20 months and 14 days. In an Iranian study [5], in which the average time from injury to surgery was similar (22 months), this complication was observed in 83% of patients [5]. In another study, with a shorter elapsed period to surgery (11.2 months), slight numbness of the skin was reported by 42% of respondents, moderate by 13%, and severe by only 1% [33].

We found a statistically significant correlation between the appearance of numbness and the height of the examinees. The average height of our respondents was 180.65 cm (154 cm to 207 cm). The tallest (over two meters) stated that numbness generally never occurred, while the shortest (below 160 cm) experienced it very often (83%). The tallest subject who always feels numbness below the knee is 202 cm tall and plays basketball. An anatomical study showed that the average distance between the apex of patella and the infrapatellar branch of the saphenous nerve is 21.9 mm (15 - 30 mm), and between the branch and the top of the tibial tubercle it is 16.2 mm (0 - 27 mm) [6]. However, there are no data on the height of cadavers, so we cannot say with certainty whether the height of a person has a role in the anatomical variation of nerve path. Nevertheless, from the aspect of sports our respondents were engaged in, the highest incidence of numbness was found among skiers. Among 33 skiers, the complication occurred in 85% with an average height of 177 cm. Numbness occurred most rarely among respondents who play basketball, because out of 124 basketball players, 80 (65%) had this complication. The basketball players were on average 8.42 cm taller than the skiers, with an average height of 185.78 cm. The heaviest examinee that experienced numbness weighed 145 kg and was also injured during skiing.

The main advantage of this research is based on the fact that most other studies followed the saphenous nerve injury on a smaller sample, and were not able to compare the incidence among the lowest, highest, heaviest and thinnest respondents [37]. The limitations of this retrospective study lie in the fact that the area of the affected skin was not measured, nor were data collected at multiple time intervals. Therefore, we were unable to monitor whether the numbing sensation and numbing area decreased over time. In future research, it would be desirable to provide an objective answer as to whether the propagation path of infrapatellar branch differs between high and short i.e. obese and malnourished cadavers.

Conclusion

Injury to the infrapatellar branch of the saphenous nerve during the anterior cruciate ligament reconstruction is not a rare complication. It occurred in 72% of our operated patients, of which 27% felt constant numbness below the antero-lateral side of the knee one year after surgery. This complication is significantly more frequent in persons with lower body height and weight. There is no statistically significant difference in the occurrence of skin numbness according to age, body mass index, side of the injured knee, time of surgery, level of sports activity and competition ranking. Currently, there is no absolutely safe surgical procedure that prevents damage to this nerve, but there are techniques that involve its identification, or minimally invasive procedures which significantly reduce the frequency of this iatrogenic complication. Surgeons should warn all candidates for this procedure, especially those who are shorter and thinner, that there is a significant risk of numbness, which is unlikely to affect their knee function and quality of life.

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MECHANISMS OF ANTERIOR CRUCIATE LIGAMENT INJURY

MEHANIZAM POVREDE PREDNJEG UKRŠTENOG LIGAMENTA

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Summary

Introduction. The goal of this study is to analyze the mechanisms of injury of patients diagnosed with anterior cruciate ligament injury and their correlation with risk factors in our clinical material. **Material and Methods.** The study included 1,471 patients, 1192 male and 279 female, with a diagnosed anterior cruciate ligament injury, that were surgically treated in the period between the end of January 2012 and the middle of June 2018. **Results.** Of the total number of women, around 51% sustained the injury when changing direction, 35% during landing, and 12% during a collision. Among men, 46% sustained injuries during a change of direction, 30% during landing, while the percentage of injuries sustained during a collision was higher than among women, amounting to 23%. The impact of gender on the type of injury mechanism and on the injury mechanism is statistically significant. The incidence of left knee injuries is higher in non-contact injuries, while right knee injuries are more common in contact injuries. The level of sports activity showed no statistically significant impact on the type of the mechanism of injury, but its impact on the category of mechanism of injury proved to be statistically significant. The impact of sport on the type of the mechanism of injury, as well as on the mechanism of injury categories was statistically significant. Non-contact injuries commonly occurred during the warm-up, beginning and end of a training session, while collisions mostly occurred halfway through the activity. Contact injuries were most often sustained on grass and training mats, while non-contact injuries occurred more often on other surfaces. **Conclusion.** Most participants sustained injury through non-contact mechanisms and the most frequent non-contact mechanism is change of direction.

Key words: anterior cruciate ligament, injury mechanism of anterior cruciate ligament, sex characteristics, sport

Sažetak

Uvod. Cilj istraživanja je analiza mehanizma povrede pacijenta sa dijagnostikovanom povredom prednjeg ukrštenog ligamenta kolena i njihova povezanost sa faktorima rizika na našem kliničkom materijalu. **Materijal i metode.** Ispitivanje je obuhvatilo 1.471 pacijenta, 1.192 muškarada i 279 žena sa dijagnostikovanom povredom prednjeg ukrštenog ligamenta kolena, koji su operativno lečeni u periodu od kraja januara 2012. godine do sredine juna 2018. godine. **Rezultati.** Od ukupnog broja žena, oko 51% povredilo se prilikom izmene pravca, 35% prilikom doskoka, a 12% prilikom sudara. Kod muškaraca povrede su nastale prilikom izmene pravca (46%) i doskoka (30%), dok je udeo povreda nastalih prilikom sudara veći nego kod žena i iznosi 23%. Uticaj pola na vrstu mehanizma povrede i na mehanizam povrede je statistički značajan. Udeo povreda levog kolena veći je kod nekontaktnih, dok su povrede desnog kolena češće kod kontaktnih povreda. Uticaj nivoa sportske aktivnosti na vrstu mehanizma povrede nije se pokazao statistički značajnim, dok se njegov uticaj na kategorije mehanizma povrede pokazao kao statistički značajan. Uticaj sporta na vrstu mehanizma povrede, kao i na pojedinačne kategorije mehanizma povrede, pokazao se statistički značajnim. Do nekontaktnih povreda je dolazilo na zagrevanju, početku i kraju treninga, dok je do sudara najčešće dolazilo sredinom treninga. Do kontaktnih povreda najčešće je dolazilo na travi i strunjači, dok su nekontaktne češće nastajale na ostalim podlogama. **Zaključak.** Najveći broj ispitanika povredio se nekontaktnim mehanizmom, a najučestaliji nekontaktni mehanizam je izmena pravca.

Ključne reči: prednji ukršteni ligament, mehanizam povrede prednjeg ukrštenog ligament, polne karakteristike, sport.

Introduction

Anterior cruciate ligament (ACL) is the central stabilizing ligament of the knee that has a key role in physical activity [1, 2]. It prevents anterior tibial translation relative to the femur, thus facilitating normal function of the knee, and it also contributes to transverse and rotational stability of the joint [3, 4]. Damage to the ACL is the most common injury of the knee joint sustained as a result of sports activities [5, 6]. It represents a complex trauma resulting in mechanical and functional instability, usually combined with limited range of motion, muscular weakness and irregular movement patterns, all of which resulting in rare return to pre-injury levels of activity [7].

The ACL injuries are sustained as a result of contact or non-contact mechanisms. About 70% of ACL injuries are sustained through non-contact and 30% via a contact mechanism [8]. Olsen et al. defined non-contact ACL injuries as injuries which occurred without a contact with other players, and divided contact injuries into direct and indirect. Direct injuries are

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Abbreviations
ACL – anterior cruciate ligament
BMI – body mass index

caused by an impact on a lower extremity (thigh, knee or shin), while indirect injury is caused through contact on another body part that indirectly causes damage to ACL (for example posture, players pushing, and so on) [9]. In indirect injuries, damage to ACL happens when internal loads exceed the elastic properties of the ligament, while in contact injuries the knee is subjected to external loads applied by another person or object [10]. The causes of non-contact ACL injuries include rapid change of direction combined with deceleration, landing with the knee in or near the state of full extension, and turning with the knee in extension and the foot firmly planted [11]. Usually, ACL injury is the consequence of increased valgus load on the knee combined with outward rotation of the tibia, or hyperextension combined with inward rotation of the tibia [12, 13].

While the problem of ACL injury itself is well documented, mechanisms and risk factors causing it are still not fully understood, and their identification will play a key role in developing effective means of prevention [14, 15]. The goal of this study is to analyze the mechanisms of injury in patients diagnosed with ACL injury of the knee and their correlation with risk factors in our clinical material.

Material and Methods

A retrospective study was carried out at the Clinic of Orthopedic Surgery and Traumatology in Novi Sad, with the approval of the Ethics Committee of the Clinical Center of Vojvodina. It included 1,471 patients diagnosed with ACL injury who underwent surgical treatment between the end of January of 2012 and the middle of June 2018. Data were collected from patients' medical records and the following parameters were included in the analysis: age and sex distribution, body weight, body height, body side of the injury, activity during which the injury was sustained, level of sports activity, type of sport, location of injury, mechanism of injury, time of injury, and type of surface **(Table 1)**.

The collected data were statistically processed using the Microsoft Office 2016 (Word, Access and Excel) and IBM SPSS v. 23. The measure of central tendency of numerical indicators is shown as arithmetic mean, dispersion is shown as standard deviation, minimum and maximum. Attributive indicators are shown in absolute and relative frequency. Proportional differences were examined using the Fisher's exact and χ^2 tests, significance level set at 5%. Results are shown in tables and graphs.

Results

Of the total number of women, around 51% sustained the injury when changing direction, 35% during landing, and 12% during collision. In men, there were somewhat fewer injuries sustained when changing direction (46%) and landing (30%), while the percentage of injuries sustained during collision exceeds that found in women, amounting to 23% **(Table 2)**.

Based on the Fisher's test ($p = 0.000 < 0.05$) it can be concluded that gender has a statistically significant impact on the type of injury mechanism. The proportion of non-contact injuries is much higher in women, while the proportion of contact injuries is much higher in men.

According to age, the participants were divided into three groups of approximately similar size **(Table 2)**. The impact of age on injury mechanisms was examined using the χ^2 test and showed no statistical significance.

With regards to body mass index (BMI), since there was a total of 25 malnourished, obese or grossly obese patients across all three groups, these three weight groups were excluded from analysis. The BMI showed no impact on the type of injury mechanism.

Table 1. Demographic data
Tabela 1. *Demografski podaci*

Gender/*Pol*	Age (years)/*Uzrast (godine)*	Weight/*Težina*	Height/*Visina*	BMI/*BMI*
Male/*Muški* 1192 (81%)	13 - 21 (39.20%)	Min. 47 kg	Min. 147	Min. 17.31
Female/*Ženski* 279 (19%)	22 - 27 (27.80%)	Max. 190 kg	Max. 212	Max. 68.03
∑ 1471	Over 27/*Stariji od 27* (33%)	80.96 ± 14.61	180.75 ± 8.54	24.68 ± 3.75

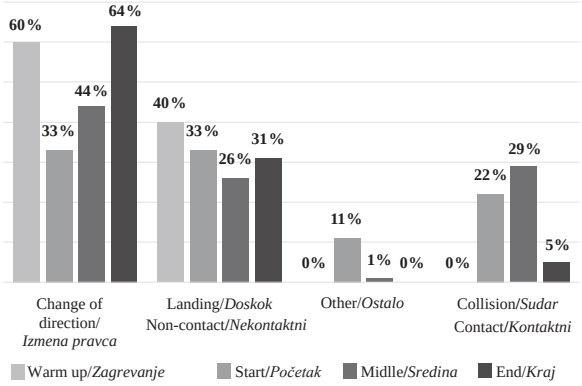
Legend: BMI - body mass index
Legenda: BMI - indeks telesne mase

Table 2. The impact of gender and age on injury mechanisms
Tabela 2. *Uticaj pola i starosti na mehanizam povrede*

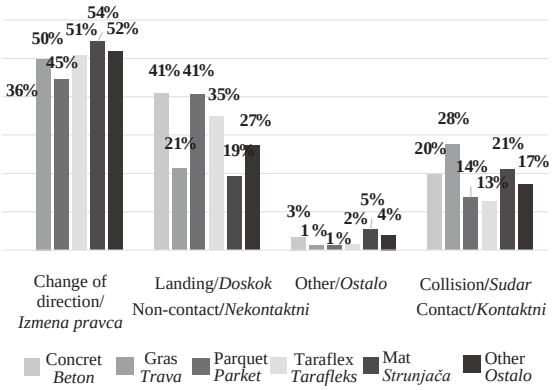
Injury mechanism *Mehanizam povrede*	Male *Muškarci*	Female *Žene*	Age/*Uzrast* < 21	Age/*Uzrast* 21 - 27	Age/*Uzrast* > 27
Change of direction/*Izmena pravca*	46.2%	50.7%	43.5%	49.4%	49.3%
Landing/*Doskok*	29.2%	34.8%	33.5%	28.5%	28.5%
Other/*Ostalo*	1.7%	3%	2.7%	0.5%	2.8%
Collision/*Sudar*	22.6%	11.5%	20.4%	21.6%	19.5%

Table 3. The impact of side and level of sports activity on the injury mechanisms
Tabela 3. *Uticaj strane i nivoa sportske aktivnosti na mehanizam povrede*

Injury mechanism *Mehanizam povrede*	Left knee *Levo koleno*	Right knee *Desno koleno*	Non-athlete *Nesportista*	Recreationalist *Rekreativac*	Professional athlete *Profesionalni sportista*
Change of direction/*Izmena pravca*	48.5%	45.1%	33%	51%	43%
Landing/*Doskok*	33.1%	28.7%	42%	29%	32%
Other/*Ostalo*	1.8%	2.4%	6%	2%	2%
Collision/*Sudar*	16.6%	23.8%	19%	19%	22%



Graph 1. The impact of the stage of a training session on the injury mechanisms
Grafikon 1. *Uticaj dela treninga na mehanizam povrede*



Graph 2. The impact of surface on the injury mechanisms
Grafikon 2. *Uticaj vrste podloge na mehanizam povrede*

The analysis of the body side of the injury showed higher incidence of injury in the right knee during collision (Fisher's test p = 0.000.). The impact of the body side of the injury was examined using the χ^2 test and showed a statistically significant difference χ^2 **(Table 3)**.

Change of direction is the most common injury mechanism in skiers (65%), hokey players (55%), football players (51%), martial artists (48%), basketball players (45%), and handball players (43%). Landing is the most common mechanism of injury in volleyball players (72%), but also among handball players (43%), basketball players (38%) and football players (22%). Collision is the most frequent mechanism of injury in rugby players (46%).

Injuries during warm-up were caused by a change of direction in 60% of cases, and in 40% during landing **(Graph 1)**. At the beginning of a training session, 33% of injuries were sustained during a change of direction, 33% during landing, and 22% during a collision. Halfway through a training session, 44% of injuries were sustained during a change of direction, 26% during landing, and 29% during a collision. Towards the end of a training session, 64% of injuries happened during a change of direction, 31% during landing, and only 5% during a collision. The impact of the stage of a training session on the type of injury mechanism was shown to be statistically significant.

During warm-up, 58% of injuries were sustained during landing and 42% during a change of direction. At the beginning of the game, change of direction was the cause of injury in 42% of cases, landing in 32%, and a collision in 24%. Halfway through the game, change of direction was the cause of injury in 43% of cases, landing in 29%, and a collision in 27%. At the end of the game, change of direction was the cause of injury in 46% of cases, landing in 30%, and a collision in 21%. The impact of the stage of the game was not shown to be statistically significant.

Contact injuries were more frequently sustained on grass and training mats, while non-contact injuries were more frequent on other surfaces. The impact of surface on the category of injury mechanism was also shown to be statistically significant **(Graph 2)**.

Discussion

Potential risk factors leading to ACL injury are divided into intrinsic and extrinsic. Extrinsic factors include level of competition, level of personal skills, type of footwear, friction coefficient of the floor, and preventative use of orthoses, while intrinsic factors include sex, age, BMI, previous injuries, muscle strength, balance issues, and postural stability [13].

Almost 70% of ACL injuries occur during sports activities; the highest injury rates in Serbia are in football, basketball and handball [13]. Of the 1,471 patients included in our study, most sustained injury playing football (48.2%), basketball (15.4%) and handball (10%). The fact that a large number of injuries happened while participating in these sports indicates their popularity in our country. This is further confirmed by the fact that in Vojvodina, 37 - 50% of patients sustained injuries playing football [16]. In Scandinavian countries the most popular and the most risky sports are handball and skiing, and in the United States of America these are rugby and basketball [14]. Authors from Japan consider basketball and gymnastics the highest risk sports with regards to sustaining ACL injuries [16].

The ACL injuries happen as a result of contact or non-contact mechanisms. The percentage of left knee injuries is higher in non-contact, while right knee injuries are more common in contact sports. Non-contact injury is mostly the result of abrupt deceleration and change of direction, while the foot is firmly planted. Torsion in the knee joint resulting from sudden change of direction is considered to be the cause of ACL tearing [17]. Within the frame of our study, the injury mechanisms include change of direction, landing and collision, and by type (for the purpose of easier comparison) non-contact (change of direction, landing) and contact (collision). In our clinical material, 80% of patients suffered non-contact and 20% contact injuries.

The same or similar results were found in two other studies, one including 120 patients [18], and in the other non-contact injuries accounted for 78% and contact injuries for 22% [13]. In a study conducted by Krosshaug et al., 72% of injuries were non-contact injuries and similar results were obtained by Hurd et al. In their study, non-contact injuries were sustained in 71.3% of cases, and contact in 26.4% [10, 19]. In a study by Salem et al., 518 injuries were sustained through non-contact and 169 through contact injury mechanisms [20]. This is in agreement with the results of our study. Of the injuries sustained through non-contact mechanisms, the most common were during a sudden change of direction (47%) and landing (30.5%), while other non-contact mechanisms accounted only for 2.1% of cases. Đuričin also reported the change of direction as the most frequent mechanism of injury in 43.3%, while the results obtained by Ristić et al. showed that the greatest number of injuries occurred during landing [13, 18]. This may be caused by presenting more handball (22%) and volleyball players (7%) compared to our sample (10%:3.7%) since volleyball and handball have a high frequency of injury during landing after a jump.

The kind of sport was proven to have a statistically significant impact on ACL injuries. Change of direction is the most frequent injury mechanism in skiers (65%), hokey players (55%) and football players (51%), landing in volleyball players (72%), handball players (43%) and basketball players (38%), and collision in rugby players (46%). Professional athletes more frequently sustained injuries during collision.

In a study performed by Ristić et al., non-contact mechanisms were the leading cause of injury in volleyball, basketball and handball players, gymnasts and skiers, while contact mechanisms were more prevalent in football players and martial artists [13]. As far as non-contact injuries are concerned our results match, but in our sample rugby players had the highest incidence of contact injuries followed by football players (25%). This is in accordance with the study of Montgomery et al., describing injury mechanisms in professional rugby players, who found that contact injuries accounted for 57% of cases and non-contact for 43%. Rugby is a contact sport, which explains higher incidence of these injuries compared to basketball or football [21].

Devetag et al. reported that the greatest number of injuries in female volleyball players were sustained through non-contact mechanisms, and that the leading injury mechanism was landing, which is a part of blocking and smashing in volleyball [22]. Landing was also the most frequent mechanism of injury in basketball players reported by Krosshaug et al., and two most frequent situations in volleyball during which ACL injuries occur are the cut shot maneuver and landing on one foot after a stroke [19]. The difference in rates of non-contact and contact injuries comes from the fairly limited number of patients playing contact sports in our sample.

Increased popularity of sports and elevated risk of knee injuries, particularly in women, has lead to a remarkable increase in ACL injuries in sports [11]. This is further corroborated by the fact that, in Novi Sad, ACL reconstructions accounted for 19% of surgeries in 2005 And for 29% in 2008. Due to the prevalence of men in sports activities, ACL injuries are more frequent in men, but female athletes are between two to ten times more likely to sustain ACL injury, depending on the sport [16, 23]. In their study, Arendt and Dick found that the rate of ACL injury in football is 2.4 times higher in women, and 4.1 times higher in basketball [24]. The causes of ACL epidemic in women are due to anatomical differences between the sexes, such as the size of the Q angle, higher valgus of the knee, narrow intercondylar notch of the femur, wider pelvis, the influence of estrogen on ligaments during the menstrual cycle, ligament laxity and different timings between contractions of the quadriceps and hamstring muscles [16]. Out of 1,471 patients in our sample, 81% (1.192) were male, and 19% (279) female. Our study showed that sex has a significant impact on the injury mechanism. The percentage of injuries sustained during a change of direction (50.7%) and landing (34.8%) is higher in women, while collision injuries are more common in men (22.6%). In our study, the percentage of non-contact injuries is significantly higher in women, while contact injuries are more frequent in men.

In order to compare our results with literature data, we calculated that the total percentage of non-contact injuries in women in our sample was 85.5%, and 75.7% in men. Kobayashi et al. reported similar results, showing that the percentage of non-contact injuries in women was 70%, which is significantly higher than the percentage of non-contact injuries in men (52%) [6]. Mountcastle et al. found that the percentage of non-contact injuries in men is 67.2% and in women 89.4% [25]. In a study by Takahashi et al., 279 women and 261 men sustained non-contact ACL injuries, while 239 men and 221 women sustained contact injuries; this matches our findings that women more frequently suffer injuries through non-contact and men through contact mechanisms [26]. Since the percentage of women who suffered a contact injury in our sample is small (11.5%), this indicates their lower participation in contact sports.

In 90% of cases, ACL injuries occur between the second and the fourth decade of life, and the younger demographic is at the highest risk of sustaining this injury [13]. The average age of patients in our study was 25.33 ± 7.79 years, ranging from 13 to 57 years. Most patients were 21 years old or less (39.2%), and

67% of them were less than 27 years old, which supports the findings that the younger population which is actively training is at highest risk [26]. Our results confirm the results of Renstrom et al., that the incidence of ACL injury is still high, especially among young athletes between the age of 14 and 19 years [27]. Devetag et al. divided the participants into five age groups, and the most injuries were sustained between the age of 21 and 25 (44%) [22]. In a study by Majewski et al., 43.1% of participants were between the age of 20 and 29 years, 20.9% were between 30 and 39, and 16.9% were between the age of 10 and 19 years [28]. In their study, Walden et al. found that at the time of injury the average age of women (20.6 ± 2.2) was lower than the average age of men (25.2 ± 4.5), and similar results were obtained by Roos et al. who found that the injured women were also younger than men and were at a higher risk of sustaining an injury before the age of 20 [29, 30]. The reason for high percentage of participants older than 27 (33%) in our study is due to the sample itself, since there were 62% recreational and non-athletes, while the remaining 38% were professional athletes. In our study, age did not show a significant impact on the mechanism of injury, but the level of sports activity was proven to be statistically significant. The most frequent case of injury in non-athletes was landing (42%), recreational participants most frequently sustained injuries during change of direction (51%), while the professionals most frequently sustained injuries during collision (22%).

Anthropometric parameters, such as body height, body weight and BMI are considered to be potential risk factors for sustaining non-contact ACL injuries [28, 29, 31]. Elevated BMI can result in higher intensity of forces transferred onto the ligamentous and muscular structures of the knee. A high BMI also implies greater expansion in the knee joint during landing, which increases the risk of ACL tearing [31]. Our results showed that the vast majority of patients (59.9%) had normal BMI, followed by overweight patients (32.9%), while there were only 0.7% of malnourished patients. The average BMI in our pool of participants was 24.68 ± 3.75 kg/m². Faude et al. reported an average BMI of 21.5 kg/m² in injured participants and players who were injured through non-contact mechanisms had significantly higher body weight [32]. Al-Jassir et al. compared contact and non-contact ACL injuries in participants with BMI > 30, who were considered overweight, and participants with BMI < 30. Their results showed that the percentage of both contact and non-contact injuries in overweight patients was 27%, and in patients with normal weight it was 73%; thus, the BMI has no impact on the mechanism of injury [33]. In our study, the BMI showed no statistically significant effect on injury mechanisms either.

In our sample, 47% of patients sustained a left knee and 53% a right knee injury. The impact of the side of the body on injury mechanisms was shown to be statistically significant. Left knee injuries happened most frequently through non-contact and right knee injuries through contact mechanisms. Walden et al. believe that the ACL injury affects both knees to the same degree, as was shown in our results, and that injury of the dominant leg is less frequent [29]. In a study by Devetag et al., 64.7% of participants sustained a left knee and 35.3% a right knee injury. In their opinion, the side of the injury represents useful information for professional trainers, who can use it as basis for improving the skill and strength of their players [22].

Out of 559 professional athletes, 17% sustained injury during training and 47% during a game or a competition. Similar results were obtained by Kobayashi et al., who found that the percentage of injuries sustained during a competition was 49.2%, and the percentage sustained during training was 34.8% [6]. Myklebust et al. reported that 75% of all injuries happened during a game and 25% during training [34]. Although athletes spend far more time training than in a game or a competition, where they practice new techniques and formations and are therefore subjected to elevated risk of injury, the stress an athlete experiences during a game, both physical and mental, results in greater risk of injury than during training [6]. When it comes to the time when the injury was sustained, athletes most often sustained injuries halfway through (45.3%) and at the start of a game (35.6%), while more than half of those injured during training sustained their injury halfway through the activity (55.7%). In their study, Ristić et al. reached the opposite conclusion, claiming that injuries sustained at competitions most frequently happen towards the end due to landing or sudden change of direction with no contact with other participants, on a dry surface, in insufficiently prepared athletes [35]. Apart from the stages of training, games or competitions, we also examined the stage of the season when the ACL injury occurred. In athletes injured during training, the injury was most frequently sustained during the preparation phase (38.3%), with the instance of injuries decreasing as the season continued. Injuries sustained during a game happened throughout the season, with fewest occurring during preparations (17.4%), and most of them at the start of a season (29.9%). Studying the injury mechanisms in football players, Agel et al. found a significantly higher frequency of contact injury during games (61%) compared to contact injuries sustained during training (26%), while the percentage of non-contact injuries sustained during training (47%) greatly exceeded the percentage of non-contact injuries sustained during games (19.9%) [36]. In our case, the stage of games showed no effects on injury mechanisms, but the stage of training sessions was proven to be statistically significant. Non-contact injuries were sustained during the warm-up, beginning and end of training, while collision injuries happened most frequently halfway through the activity. This may be the case because halfway through a training session athletes often split into teams for technical and tactical preparations, which can result in duels or collisions and therefore ACL injuries.

The ACL injuries most often occurred on the following surfaces: grass – 39% of cases, parquet 28%, concrete 12%, and training mats and taraflex in 4% of cases. In our sample, grass was proven to be the most dangerous surface for contact injuries (28%), while injuries due to landing mostly happened on parquet and

concrete (41%). Our results showed that the surface has a significant impact on injury mechanisms, and that contact injuries happened most often on grass and training mats, while non-contact injuries were predominant on other surfaces. Alentorn-Geli et al. confirmed that the properties of the surface, regardless of whether they are subjected to weather conditions or not, affect the rates of ACL injuries [11]. In a study conducted by Hagel et al., rates of injury of the lower extremities on synthetic grass were higher than those on natural grass in both dry and wet conditions [37]. Footwear traction is higher on hard and dry surfaces, or dense grass coverage. Games played on hard surfaces, where footwear traction is high, are probably more dynamic, which can increase the risk of injury [38]. High level of friction between floors and footwear is identified as the main risk factor for non-contact ACL injuries [23]. Myklebust et al. reported that activities where there was a high level of friction between the footwear and the floor caused 55% of ACL injuries [34]. Higher frequency of contact injuries on grass and training mats is the result of contact sports played on such surfaces. Taraflex, parquet and concrete lead to increased friction coefficient when the foot is firmly planted, which makes it easier for non-contact ACL injury to occur.

To reach a complete insight, it is necessary to perform an analysis of combined injuries, and compare their incidence in contact and non-contact mechanisms of ACL injuries. Different sports vary in popularity in different countries, which makes international comparison of study results difficult. There is also the difference in frequency between contact and non-contact injuries due to the limited number of patients who play contact sports in our sample. The results collected and processed in our sample are geographically and ethnically representative; it would therefore be interesting to compare them to data gathered from different ethnic groups. Further work should be done to investigate how much neuromuscular training improves active stabilization of ACL and reduces the incidence of injury. Investigation into risk factors leading to ACL injury and their identification through screening could provide the foundation for an effective strategy for reducing the incidence of ACL injury.

Conclusion

Most of the study participants (80%) sustained injury through non-contact mechanisms, and the most frequent non-contact mechanism is change of direction (47%). Change of direction is the most frequent mechanism of injury in both men and women, while collision injuries are more frequent in men (22.6%). Age and body mass index did not show statistically significant impact on injury mechanisms. The percentage of left knee injuries is higher in non-contact, and right knee injuries are more frequent in contact injuries. Non-athletes most frequently sustained injury during landing (42%), and recreational (51%) and professional athletes (43%) during change of direction. Contact injuries were most frequent in professional athletes (22%). The highest frequency of injury due to change of direction was found in skiers, hokey players, football players, martial artists, basketball and handball players. Landing was the most common cause of injury in volleyball and handball players, and collision in rugby players. During training, injuries were most frequently caused by change of direction, while collision injuries most often happened halfway through the training session (29%). Injuries sustained during warm-ups and at the beginning of the game were most often caused by landing (58%), and during the rest of the game the most frequent injury mechanism was change of direction. In regard to surface, most injuries were caused by change of direction on grass, parquet, taraflex and training mats, while landing injuries happened most frequently on concrete (41%). The percentage of contact injuries was highest on grass (28%) and training mats (21%).

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CASE REPORTS
PRIKAZI SLUČAJEVA

General Hospital Novi Pazar, Novi Pazar

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GIANT BREAST HAMARTOMA IN A MIDDLE-AGED WOMAN - A CASE REPORT

DŽINOVSKI HAMARTOM DOJKE KOD ŽENE SREDNJIH GODINA - PRIKAZ SLUČAJA

Enes ZOGIĆ and Džemail S. DETANAC

Summary
Introduction. Breast hamartomas are benign breast lesions with extremely rare, but not unseen, malignant transformation. They most often occur in middle-aged women and are usually up to 5 cm in diameter. Hamartomas of about 10 cm and larger are designated as giant and they are extremely rare. **Case Report.** We present a 47-year-old female patient with a giant hamartoma of the right breast. After radiological diagnosis and core biopsy, the patient underwent surgery. Histopathological findings confirmed the diagnosis of hamartoma, without signs of malignant transformation. The postoperative course was without complications. **Conclusion**. Regardless of the fact that breast hamartoma is a benign lesion with a low potential for malignant transformation, we believe that surgical excision of these tumors is justified along with histopathological tissue processing. Recurrence is rare and the prognosis is good.
Key words: Giant breast hamartoma, surgery, diagnostic imaging, breast

Sažetak
Uvod. Hamartomi dojke su benigne lezije dojke sa izuzetno retkom, ali ne i nemogućom malignom transformacijom. Hamartomi dojke najčešće se javljaju kod žena srednjih godina i obično su do 5 cm u prečniku. Hamartomi od oko 10 cm i veći označeni su kao džinovski i javljaju se izuzetno retko. **Prikaz slučaja.** Predstavljamo 47-godišnju pacijentkinju sa džinovskim hamartomom desne dojke. Nakon radiološke dijagnostike i *core* biopsije, pacijentkinja je operisana. Histopatološkim nalazima potvrđena je dijagnoza hamartoma, bez znakova maligne transformacije. Postoperativni tok protekao je bez komplikacija. **Zaključak.** Bez obzira na to što se radi o benignoj leziji sa malim potencijalom maligne transformacije, smatramo da je opravdana hirurška ekscizija ovih tumora uz histopatološki proces obrade tkiva. Recidiv je nizak, a prognoza je dobra.
Ključne reči: džinovski hamartom dojke, hirurgija, dijagnostika, dojka

Introduction

The pathogenesis of hamartomas is still unclear. They are usually benign tumors resulting from overgrowth of normal tissue caused by a developmental error in different anatomical locations. Although most of these tumors are benign, malignant transformation may occur. Hamartomas can be found anywhere in the body, but they are most often found in the lungs, breasts, and colon [1, 2].

Breast hamartomas are rare, poorly defined benign breast neoplasms, mostly asymptomatic, but may also present as painless lesions with an incidence of less than 4.8% of all benign breast diseases. The average size is up to 5 cm, and they are most often found in women in the 4th and 5th decades. Giant hamartomas are rare and are mostly presented in the literature as case reports [1–4]. We present a rare case of a giant breast hamartoma in a middle-aged woman.

Case Report

A 47-year-old healthy female patient was referred by a gynecologist for a surgical examination of a palpable tumor mass in the right breast. The patient noticed the mass a year before, but she did not see a doctor. There was no reported history of malignant diseases in the family. She had a menarche at 12 years of age; she had 3 natural births, breastfed her children for 12 months each, and denied use of hormonal therapy. The examination revealed a slightly larger right breast, with a palpable soft and mobile mass in the upper quadrants of the breast (about 13 x 13 cm), without palpable axillary lymph nodes and no signs of nipple secretion. The Breast Imaging Reporting and Database System (BI RADS 3) and mammography (BIRADS IVa) were performed and revealed a lesion in the right breast. A core biopsy was performed and the histopathological finding was a benign change (dysplasia fibrosa cystica mammae with a focus of mod-

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Abbreviations
BI-RADS – Breast Imaging Reporting and Database System
MRI – magnetic resonance imaging

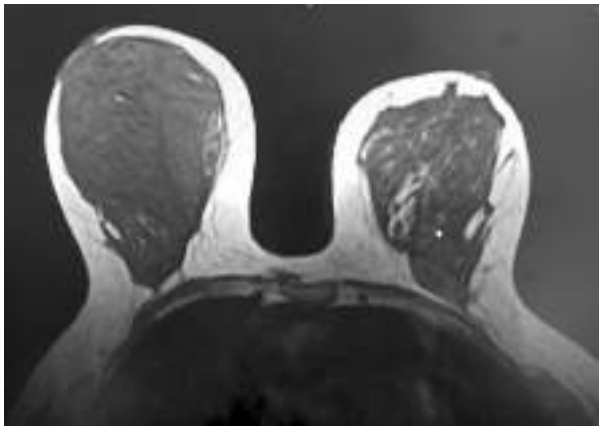

Figure 1. Breast magnetic resonance image
Slika 1. *Snimak magnetne rezonancije dojke*

erate hyperplasia of the ductal epithelium). Due to a mammography finding suspicious for malignancy, a magnetic resonance imaging (MRI) of the breast was performed **(Figure 1)**. The surgery was performed in accordance with the decision of the multidisciplinary team. The surgery was without complications and the mass was excised completely. The tumorous mass removed from the right breast was about 125 x 120 x 50 mm in size **(Figure 2)**, solid consistency, encapsulated, whitish in cross-section, with rare cystic formations several mm in diameter.

Figure 2. Excised breast tumor
Slika 2. *Uklonjeni tumor dojke*

The patient was discharged on the next day. The histopathological findings indicated a tumor consisting of a duct, a lobule, and a fibrous stroma. Pseudoangiomatous hyperplasia was observed within the connective tissue and microcalcifications within the lobules. Sclerosing adenosis and cysts were lined by apocrine epithelium. The described changes corresponded to breast hamartoma. There was no evidence of in situ or invasive malignancy.

The postoperative follow up was uneventful, with no complications. A control breast ultrasound 3 months later showed a smaller tumorous mass of about 1 x 1 cm in size, with radiologically benign characteristics, corresponding to a fibroadenoma. The patient refused further surgical treatment.

Discussion

According to literature data, the term "breast hamartoma" was first introduced in the early 70s of the last century [1]. These tumors are slow-growing benign breast tumors composed of mesenchymal glandular, fatty and connective tissues, often asymptomatic and detected incidentally on screening mammography. They can occur at any age, often in women after the age of 35, but are most commonly seen in perimenopausal women [4]. To our knowledge, there are only a few published cases of male breast hamartoma [5]. The incidence of breast hamartoma is up to 5%, but with the introduction of mandatory breast screening programs, that percentage will increase [6].

Considering the structure of these lesions, which usually present as breast lumps with a lack of clear microscopic presentation consisting of varying amounts of epithelial elements in a fibro-fatty stroma, and the fact that they are mostly asymptomatic, histological diagnosis of the sample can often show "normal breast tissue", which can lead to repeated core biopsies. Hamartoma contains a high percentage of fatty tissue and may contain pseudo-angiomatous stromal and epithelial changes including hyperplasia, cystic changes, and metaplasia. That is why core biopsy is not reliable, because it often shows a normal tissue [7].

During physical examinations, these lesions can easily be mistaken for other benign tumors, because they are usually soft, mobile and compressible. They can be completely or partially encapsulated and are usually 2 - 5 cm in size. Giant hamartomas are extremely rare, and those over 10 cm in diameter are usually described in the literature as individual case reports [5–8]. Due to their size, giant hamartomas can represent a psychological problem for patients, depriving them of the comfort of life with the appearance of pain due to pressure on the surrounding structures.

When they are typical, ultrasound and mammography examination are sufficient for the radiological diagnosis of hamartomas. Ultrasound images of hamartomas differ due to the different content of fatty and fibrous tissue. Diagnosis may be difficult if the

tumor is small in size with low fat content and an incomplete pseudocapsule. Hamartomas with a high percentage of fatty tissue may resemble lipomas [9]. Typical mammographic appearance of hamartoma is often described as a "slice of salami". On mammography, hamartomas with a large amount of fibrous tissue can hardly be distinguished from fibroadenomas, and those with a large percentage of fatty tissue can mimic lipomas [9]. Usually, these two diagnostic procedures are sufficient for establishing the diagnosis, but if there are doubts, especially with mammography findings, breast MRI is indicated in establishing the diagnosis.

Considering that our patient's mammography findings were marked as changes with the probability of malignancy, MRI was performed.

Breast hamartomas are not premalignant conditions and they rarely lead to malignant transformation, which is why the final histopathological diagnosis is very important. The incidence of malignancy in breast hamartoma is about 0.1% [10–13].

Therapy of giant breast hamartomas involves surgical excision and histopathological examination to verify the absence of malignant transformation, which was also done in our case.

Conclusion

Breast hamartomas are uncommon slowly growing breast lesions and giant hamartomas are extremely rare. If imaging methods, such as ultrasonography or mammography, are unclear or suspicious for malignancy, core biopsy and magnetic resonance imaging are required. These tumors may be difficult to diagnose with imaging and core biopsy and a definitive diagnosis can be made only after surgical excision. Although hamartomas are benign lesions, considering the described cases of malignant alterations in focus hamartoma, this fact should always be considered when making the decision on therapy and follow-up of such patients.

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DISSEMINATED INTRAVASCULAR COAGULATION IN A PREGNANT WOMAN WITH CORONAVIRUS DISEASE 2019 INFECTION – A CASE REPORT

DISEMINOVANA INTRAVASKULARNA KOAGULACIJA KOD TRUDNICE OBOLELE OD KOVID 19 INFEKCIJE – PRIKAZ SLUČAJA

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Summary

Introduction. Coronavirus infection may cause numerous complications in pregnant women, as well as an increased risk for the fetus. Disseminated intravascular coagulation and other coagulopathies can be caused by coronavirus disease 2019 infection. **Case Report.** A 22-year-old primigravida presented with a nine-day history of dry cough, myalgia, nausea and fever. A nasopharyngeal swab for severe acute respiratory syndrome coronavirus 2 infection was positive. The patient's condition rapidly deteriorated, resulting in severe liver damage and disseminated intravascular coagulation. Fetal cardiotocography showed a silent curve with late decelerations, while the umbilical artery Doppler showed end-diastolic block, indicating a fetal distress. Emergency cesarean section was performed at 28+5 weeks of gestation. After the cesarean section, the patient was treated with blood derivatives, thromboprophylaxis and supportive therapy and recovered quickly. Unfortunately, the premature infant died three hours after birth. **Conclusion.** It is very important to simultaneously monitor the parameters of the mother's coagulation system, as well as the condition of the fetus, because there is a possibility of developing coagulopathies, including disseminated intravascular coagulation.

Key words: Disseminated Intravascular Coagulation; COVID-19; Pregnant Women; Pregnancy; Treatment Outcome; Pregnancy Outcome; Blood Coagulation Factors; Fetus

Sažetak

Uvod. Infekcija virusom korone može dovesti do opasnih komplikacija kod trudnica, kao i povećanog rizika za fetus. Diseminovana intravaskularna koagulacija, kao i druge koagulopatije, mogu biti uzrokovane *COVID-19* infekcijom. **Prikaz slučaja**. Dvadesetdvogodišnja trudnica (prvorotka) javlja se devet dana nakon početka simptoma u vidu kašlja, bolova u mišićima, mučnine i povišene telesne temperature. Nazofaringealni bris na teški akutni respiratorni sindrom korona virusa 2 bio je pozitivan. Stanje pacijentkinje se promptno pogoršalo u pravcu razvoja lezije jetre i diseminovane intravaskularne koagulacije. Kardiotokografski zapis pokazao je silentnu krivu sa kasnim deceleracijama, dok je dopler umbilikalne arterije pokazao enddijastolni blok, što je ukazivalo na fetalni distres. Trudnoća je završena hitnim carskim rezom u 28+5 gestacijskoj nedelji. Postoperativno pacijentkinja je lečena krvnim derivatima, tromboprofilaksom i suportivnom terapijom što je dovelo do brzog oporavka pacijentkinje, dok je kod nedonoščeta zabeležen smrtni ishod. **Zaključak.** Veoma je važno istovremeno pratiti parametre koagulacionog sistema majke, kao i stanje fetusa jer postoji mogućnost razvoja koagulopatija, uključujući diseminovanu intravaskularnu koagulaciju.

Ključne reči: diseminovana intravaskularna koagulacija; COVID-19; trudnica; trudnoća; ishod lečenja; ishod trudnoće; faktori koagulacije krvi; fetus

Introduction

Caused by a novel type of virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), coronavirus disease 2019 (COVID-19) has exposed vulnerable populations and healthcare systems to a global public health crisis. Pregnant women are at a higher risk of morbidity and even mortality due to the susceptibility to pathogens and particularly immunologic status [1]. Pregnant women with COVID 19 infection are at an increased risk of adverse maternal and neonatal outcomes. Premature rupture of membranes, preterm labor, fetal growth restriction, intrauterine fetal demise and neonatal death are more frequently observed in pregnant patients with SARS-CoV-2 infection [2]. Although most pregnant women infected with COVID-19 have good outcomes, a recent systematic analysis showed that up to 3% of pregnancies were associated with severe maternal morbidity [3]. High mortality and its relationship with thromboembolic diseases in COVID-19 have attracted increased attention [4, 5]. The COVID-19 appears to cause a hypercoagulable state through unique mechanisms linking thrombosis and inflammation [6]. Disseminated intravascular coagulation (DIC) syndrome has the highest morbidity and mortality rate of all the complex obstetric coagulopathies [7, 8].

We present a rare case of DIC induced by COVID-19 infection. It is unusual that the patient developed a potentially fatal complication in the third trimester

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Abbreviations

COVID-19	– coronavirus disease 2019
SARS-CoV-2	– severe acute respiratory syndrome coronavirus 2
DIC	– disseminated intravascular coagulation
APTT	– activated partial thromboplastin time
CPR	– cardiopulmonary resuscitation
ISTH	– International Society on Thrombosis and Haemostasis
HELLP	– hemolysis elevated liver enzymes, and low platelet
TXA	– tranexamic acid

of pregnancy, although she had mild clinical symptoms of COVID-19, absence of inflammatory signs on chest X-ray, and absence of the signs of hemorrhagic syndrome. The purpose of the study was to present our first experience with such a rare pathology and to point to the challenges in diagnosing and treating pregnant women with COVID-19 infection.

Case Report

A 22-year-old primigravida, in the 28th week of gestation, was admitted to the Department of Obstetrics and Perinatology of the Clinical Center of Vojvodina in Novi Sad. She presented with a nine-day history of runny nose, anosmia, dry cough, myalgia, and fever. The nasopharyngeal swab for SARS-CoV-2 infection was positive nine days before admission. Other than that, the course of the pregnancy was uneventful. On admission, physical, ultrasound, laboratory and microbiological examinations were performed. The patient did not receive any dose of the COVID-19 vaccine. On admission, the patient showed cardiovascular and respiratory stability: blood pressure 90/60 mmHg, heart rate 92 bpm, respiratory rate 17 breaths/minute, body temperature 36.5 °C, oxygen saturation of 99% on ambient air. The initial vaginal examination showed that the vaginal part of the cervix was slightly shortened, directed posteriorly and closed (Bishop Score of 1). The uterine muscle tension was normal, without contractions, and there was no active vaginal bleeding or leakage of amniotic fluid during the examination. The ultrasound examination revealed a vital pregnancy with the fetus in the cephalic presentation. The placenta with calcifications was located on the anterior wall of the uterine cavity without signs of ablation or retroplacental hematoma. The fetal Doppler flow was normal on admission: umbilical artery pulsation index was 1.02, and amniotic fluid index was 12.8 cm. The cardiotocography was normal, revealing normal cardiac activity and reactive variability. A chest X-ray was performed and it was normal, without signs of inflammation and pathological changes in the lung parenchyma. The initial laboratory tests showed a high D-dimer, a decreased platelet level, prolonged activated partial thromboplastin time (aPTT), elevated liver enzymes, and normal fibrinogen levels **(Table 1)**. The patient was prescribed a prophylactic dose of low-molecular-weight heparin and a prophylactic antibiotic therapy with third-generation cephalosporin, because of symptoms of the upper respiratory tract infection and elevated values of inflammatory parameters. As there was a risk of preterm labor, the patient received corticosteroid therapy (dexamethasone) to aid the fetal lung maturity. However, the control laboratory test showed a disturbingly high concentration of D-dimer, a decreased platelet level, and low fibrinogen levels **(Table 1)**. A multidisciplinary team with a hemostaseology specialist believed that differential diagnosis

Table 1. Laboratory test results
Tabela 1*. Laboratorijski rezultati*

	On admission/*Na prijemu*	6h from admission/*6č nakon prijema*	12h from admission/*12č nakon prijema*
WBC	3.72 x 10^6/l	3.65 x 10^6/l	3.16 x 10^6/l
RBC	4.18 x 10^{12}/l	3.95 x 10^{12}/l	3.78 x 10^{12}/l
HGB	127 g/l	123 g/l	114 g/l
HCT	0.36	0.35	0.31
PLT	98 x 10^9/l	80 x 10^9/l	68 x 10^9/l
PT	0.99	1.09	1.88
APTT	1.30	1.49	1.55
Fibrinogen	3.0 g/l	2.1 g/l	1.0 g/l
D-dimer	46.24 mg/l FEU	67.68 mg/l FEU	102.40 mg/l FEU
AST	95 u/l	/	125 u/l
ALT	37 u/l	/	56.5 u/l
LDH	472 u/l	/	645 u/l
CRP	71.12 mg/l	60.9 mg/l	53.94 mg/l
PCT	0.26 ng/ml	0.33 ng/ml	0.28 ng/ml

Legend: WBC - white blood cells; RBC- red blood cells; HGB - hemoglobin; HCT - hematocrit; PLT - platelet count; PT - prothrombin time; APTT - activated partial thromboplastin time; AST - aspartate aminotransferaze; ALT - alanine aminotransferaze; LDH - lactate dehydrogenase; CRP - C-reactive protein; PCT - procalcitonin
Legenda: WBC – leukociti; RBC– eritrociti; HGB – hemoglobin; HCT – hematokrit; PLT – trombociti; PT – protrombinsko vreme; APTT – aktivirano parcijalno tromboplastinsko vreme; AST – aspartat aminotransferaza; ALT – alanin aminotransferaza; LDH – laktat dehidrogenaza; CRP –C-reaktivni protein; PCT – prokalcitonin

Figure 1. Umbilical artery Doppler (end-diastolic block)
Slika 1. *Dopler umbilikalne arterije (end-dijastolni blok)*

Figure 2. Postoperative ultrasound image of minimal free intraperitoneal fluid collection
Slika 2. *Ultrazvučni prikaz kolekcije minimalne slobodne intraperitonealne tečnosti postoperativno*

should include the onset of DIC. In the meantime, the fetal cardiotocography showed a silent curve with late decelerations, and the umbilical artery Doppler ultrasound showed an end-diastolic block **(Figure 1)**, suggesting impending fetal distress.

Given the deterioration of the mother's laboratory findings, the development of DIC, and fetal hypoxia, an emergency cesarean section was performed at 28+5 weeks of gestation. The anesthesiologist used general anesthesia because of the coagulation disturbances and emergency of the procedure. During the operation, the patient received 2 units of fresh-frozen plasma. Uncomplicated operation was completed within 40 minutes, and the total blood loss was 300 ml. Pelvic drainage was performed to control possible bleeding into the abdominal cavity in the early postoperative period. The patient received broad-spectrum antibiotic therapy (ceftriaxone, metronidazole). The local hospital guidelines were followed to prevent the spread of COVID-19 [9]. The Apgar score of the newborn at 1 and 5 minutes was 0, and 1 at 10 minutes. Immediately after birth, the baby (960 g/39 cm) was in an extremely poor condition, without heart activity, hypotonic, unresponsive and cyanotic. Following European Resuscitation Council guidelines, cardiopulmonary resuscitation (CPR) was started. After 10 min of CPR, the first fetal heartbeats were obtained. The premature baby was intubated and on mechanical ventilation with all the support measures, but unfortunately with lethal outcome 3 hours after birth.

During the following days of hospitalization, the mother's general condition was stable. She was treated with blood derivatives, thromboprophylaxis, antibiotics, uterotonics, and supportive therapy. Postoperatively, the patient received a total of 3 units of resuspended red cells and 1 unit of fresh frozen plasma. The ultrasound showed a collection of minimal free intraperitoneal fluid **(Figure 2)**. Pelvic drainage comprised 10 - 100 mL of serous blood daily and was removed on the fifth postoperative day. The microbiological smear of the uterine cavity taken during cesarean section, and hemoculture and urine culture came back negative. The histopathology examination of the placenta showed small foci of inflammatory infiltrates composed of neutrophils in the villi of the placenta. Since the patient was recovering rapidly, she was discharged in good general condition on the 10th day of hospitalization.

A written consent to publish this case report was obtained from the patient. The review was approved by the Clinical Center of Vojvodina Ethics Committee.

Discussion

The course of SARS-CoV-2 infection in most pregnant women is usually mildly symptomatic. However, it has been proven that both COVID-19 and pregnancy increase the prothrombotic potential [10]. Even in healthy women, pregnancy triggers many changes in the hemostatic system. The COVID-19 infection appears to cause a hypercoagulable state through unique mechanisms linking thrombosis and inflammation [11]. An inflammatory process of the endothelium damages its cells and disrupts the anticoagulation process. This results with a high level of von Willebrand factor [12]. The interaction between activated response mechanisms, neutrophils, monocytes, cytokines that they release, the coagulation system, and the complement system, triggers a process similar to immune thrombosis resulting in the formation of blood clots in large and small vessels [13]. Several studies describe pregnant patients affected by COVID-19-induced coagulopathies, and very few resulted in adverse outcomes for both the mother and the baby [14–16]. In 2021, Servante et al. presented a literature review on thromboembolic complications in pregnant patients with SARS-CoV-2 infection, which included 1,063 patients. Maternal mortality due to coagulopathies was 0.01%, with two deaths caused by the development of DIC. The condition of 132 (0.12%) patients was serious and required admission to the Intensive Care Unit [17]. In our case, monitoring the laboratory findings over time helped to establish an early diagnosis. Such an approach allows for detecting abnormalities in the

Table 2. Disseminated intravascular coagulation score using the International Society on Thrombosis and Hemostasis
Tabela 2. *Skor diseminovane intravaskularne koagulacije (DIK) Međunarodnog društva za trombozu i hemostazu*

Platelet count (x10⁹/l) *Broj trombocita*	185 = 0 point 100 - 185 = 1 point 50 - 100 = 2 points < 50 = 1 point
Prothrombin time *Protrombinsko vreme*	< 0.5 = 0 point 0.5 - 1.0 = 5 points 1.0 - 1.5 = 12 points > 1.5 = 25 points
Fibrinogen (g/l) *Fibrinogen*	< 3.0 = 25 points 3.0 - 4.0 = 6 points 4.0 - 4.5 = 1 point > 4.5 = 0 point
Total points/*Ukupno*	≥ 26 points = high probability of DIC/*Velika verovatnoća za DIK*

coagulation system and planning treatment in advance. A modified DIC risk assessment scale for pregnant women was developed - the International Society on Thrombosis and Haemostasis (ISTH) DIC score **(Table 2)** [18]. A score of > 26 suggests a high probability of DIC. The scale is characterized by a high percentage of sensitivity (81%) and specificity (96%) for the diagnosis of intravascular coagulation during pregnancy [19]. Our patient scored 52, but the scale was used retrospectively. In our opinion, adaptation and use of the scale in daily clinical practice would be helpful. According to the ISTH guidelines, besides routine laboratory analysis, D-dimer levels, platelet count, and prothrombin time should be measured in all individuals having symptoms of COVID-19 [20].

Endothelial damage results in thrombotic microangiopathy, which accompanies other severe pregnancy complications such as hemolysis, elevated liver enzymes and low platelet (HELLP) syndrome, thrombotic thrombocytopenic purpura, pregnancy-related hemolytic-uremic syndrome and systemic lupus erythematosus. Furthermore, abnormalities in laboratory test results in these syndromes make it difficult to make a diagnosis, which is not always possible due to the overlap of symptoms [19]. For example, the atypical presentation of HELLP cannot be ruled out. Therefore, a multidisciplinary team is critical in treating and managing severe COVID-19 during pregnancy. The use of tranexamic acid (TXA), an antifibrinolytic agent, during a pregnancy complicated by intravascular coagulation, is still controversial. It acts by stabilizing clot formation, which is often reduced by systemic fibrinolysis. The WOMAN trial shows that TXA significantly reduces the risk of postpartum bleeding and maternal mortality. However, it must be used with extreme caution. The use of TXA may be indicated in DIC with enhanced fibrinolysis and severe hemorrhage [21]. As there were no signs of a hemorrhagic syndrome, and in consultation with the hemostaseology specialist, a decision was made not to apply TXA. Our patient was also at high risk because of the gestational age. Studies have shown that SARS-CoV-2 infection in the 2nd or 3rd trimester of pregnancy may increase the risk of death due to cardiopulmonary complications [22, 23]. In this case, after giving birth, there was a quick, complete recovery and withdrawal of symptoms. Unfortunately, the neonatal outcome was unfavorable, which can be attributed to extreme prematurity. At this time, there is a lack of evidence on the adverse effects of maternal SARS-CoV-2 infection on the fetus [24], to be limited and associated with some adverse consequences such as stillbirth and miscarriage [25]. It is important that fetuses have poor toleration for acidosis and hypoxemia due to COVID-19 infection, which leads to complications such as preterm labor [26].

Despite all the efforts, data on pregnancy outcomes in women with COVID-19 are limited. It is currently known that pregnant women are a vulnerable population at risk of severe infections. The infected pregnant women need intensive care unit admission five times and mechanical ventilation four times more than non-pregnant women with a similar death rate [27]. The results of a multi-central adjudicated case series performed in Iran demonstrated that out of 9 pregnant women with severe infection, 1 recovered after a long hospitalization, 1 remained ventilator-dependent with severe illness, and 7 died [28]. Several authors researched the effects of the virus on the placenta. The pathohistological findings of the placenta in our case correlate with those in the literature. The placenta's pathological landmarks in most viral infections are lymphoplasmacytic villitis with the corresponding thickening of villi and intervillous hemosiderin deposition [29]. Only two case reports established pathological placental findings during the second-trimester miscarriages in women suffering from COVID-19 infection [30]. A case-report study from China reported placental findings in three patients suffering from COVID-19 [31]. The perivillous fibrin diffusion, presence of thrombi in the fetal vessels and induced vascular malperfusion, maternal vascular malperfusion, decidual arterio-

pathy choriohemangioma, and multi-focal infarctions were described for placenta from mother with SARS-CoV-2 infection [29, 32, 33].

The COVID-19 infection during pregnancy raises major concerns as its numerous aspects are still to be discovered. Firstly, we still do not know all the possible complications and adverse pregnancy outcomes. Secondly, the vertical transmission of the virus from the mother to the child needs further investigation. Thirdly, the treatment of pregnant women infected with the virus is still a matter of debate among experts. They believe that clinical recommendations for treating COVID-19 in pregnancy should be based on findings of the current epidemic, while case reports of rare complications of COVID-19 infection in pregnant women are particularly important [22].

There are some limitations of our report. We did not evaluate the presence of SARS-CoV-2 in amniotic fluid, cord blood, or placental tissue, which could further clarify the possibility of vertical transmission. On the other hand, the complete diagnostic protocol for the mother, including antinuclear, anticardiolipin and anti-beta-2-glycoprotein antibody tests, which came back negative, can be considered an advantage of our study.

Conclusion

In summary, we described a case of maternal coronavirus disease 2019 infection during the third trimester of pregnancy, which led to liver and coagulation impairment and preterm delivery. We believe that these findings have significant public implications because of the severity of the disease progression, which endangers not one but two patients, and that is why we presented the diagnostic and treatment protocol for such a rare pathology. As there is a possibility of developing a disseminated intravascular complication, a dangerous condition that negatively affects both the maternal and neonatal outcomes, the recommendation is to pay attention to coagulation status in the treatment of pregnant women suffering from coronavirus disease 2019.

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Case report
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FREE-FLOATING RIGHT HEART THROMBUS WITH PULMONARY EMBOLISM – A CASE REPORT

SLOBODNO FLOTIRAJUĆI TROMB U DESNOM SRCU SA PLUĆNOM EMBOLIJOM – PRIKAZ SLUČAJA

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Summary

Introduction. Right heart thrombus is uncommon and it is usually detected by echocardiography in patients with venous thromboembolism. Thrombi attached to the atrial or ventricular wall have a good prognosis; however, free-floating "snake-like" thrombi are usually associated with massive, unstable pulmonary embolism and high mortality. **Case Report.** A 43-year-old male patient visited a cardiologist complaining about rapid fatigue and shortness of breath with minimal effort in the last week. An echocardiographic examination confirmed a right heart thrombus and a pulmonary embolism. After the examination, the case was presented to the Heart Team, which made a decision to perform a surgery. After the usual preoperative preparation for emergency surgery, the patient underwent surgery under general endotracheal anesthesia via median sternotomy. **Conclusion.** The right heart thrombus is associated with risks of possible embolization to the pulmonary circulation and potential circulatory collapse. There was a considerable discrepancy between the apparently mild clinical presentation and the alarming echocardiographic finding of a huge free-floating thrombus. Despite the lack of standardized and precise recommendations for the optimal therapeutic strategy, surgical approach seems to be the best option in emergency cases with large free-floating thrombi.

Key words. Pulmonary Embolism; Thrombosis; Heart; Echocardiography; Cardiac Surgical Procedures; Diagnosis

Sažetak

Uvod. Tromb u desnom srcu je redak i obično se otkriva ehokardiografijom kod pacijenata sa venskom tromboembolijom. Trombi pričvršćeni za zid pretkomore ili komore imaju dobru prognozu, međutim, slobodno-flotirajući „zmijoliki" tromb je obično udružen sa masivnom, nestabilnom plućnom embolijom i sa visokim mortalitetom. **Prikaz slučaja.** Četrdesettrogodišnji pacijent se javio kardiologu zbog tegoba u vidu brzog zamaranja i kratkog daha pri minimalnom naporu, koji se javljaju u poslednjih nedelju dana. Ehokardiografskim pregledom potvrđeno je prisustvo trombne mase u desnom srcu i plućne embolije. Nakon pregleda slučaj ovog pacijenta je prezentovan timu za srce, koji je doneo odluku da se pacijent operiše. Nakon uobičajene preoperativne pripreme za hitne operacije, pacijent je operisan u opštoj endotrahealnoj anesteziji, pristupom kroz medijalnu sternotomiju. **Zaključak.** Značaj tromba u desnom srcu leži u mogućoj embolizaciji plućne cirkulacije i potencijalnom cirkulatornom kolapsu. Postojala je znatna nesrazmera između naizgled blage kliničke slike i alarmantnog ehokardiografskog nalaza ogromnog slobodno-flotirajućeg tromba kod našeg pacijenta. Uprkos nedostatku standardizovanih i preciznih preporuka za optimalnu terapijsku strategiju, čini se da je hirurški pristup poželjan za hitne slučajeve sa velikim slobodno-flotirajućim trombom.

Ključne reči. plućna embolija; tromboza; srce; ehokardiografija; kardiohirurške procedure; dijagnoza

Introduction

Right heart thrombus (RHT) is uncommon and it is usually detected by echocardiography in patients with venous thromboembolism [1]. In contrast to the tumor, a thrombus is irregularly shaped and most commonly has no pedicle [2]. Most of the thrombi are found in the right atrium (RA) [3]. Thrombi that are attached to the atrial or ventricular wall have a good prognosis; however, free-floating "snake-like" thrombi are usually associated with massive, unstable pulmonary embolism (PE) and high mortality [3]. There are no evidence-based guidelines for the treatment of free-floating thrombi in the right heart, so the choice is based mainly on case reports or small case series [3, 4]. Treatment options include anticoagulation therapy, thrombolytic therapy (systemic or local), and surgical embolectomy [5].

Here, we present a patient with a free-floating "snake-like" RHT associated with PE, who was successfully treated by surgery.

Case Report

A 43-year-old male patient visited a cardiologist in a private practice complaining about rapid fatigue and shortness of breath with minimal exertion in the last week. After an echocardiographic examination,

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Abbreviations

RHT – right heart thrombus
RA – right atrium
PE – pulmonary embolism
RV – right ventricle
CPB – cardiopulmonary bypass

which revealed a RA thrombus, he was immediately referred to the Institute of Pulmonary Diseases, Department of Pulmonary Thromboembolism. The echocardiography was repeated revealing a left ventricle with regular endocavitary dimensions, regular systolic function (ejection fraction 65%), and concentric thickening of the left ventricular walls. Direct and indirect signs of PE were observed. The right ventricle (RV) was enlarged. In the RA, with a transition to the RV, a floating hyperechoic mass with heterogeneous echo density, 27 x 35 mm in diameter was observed, prolapsing into the RV in diastole. A moderate degree of tricuspid regurgitation was registered, with a RV systolic pressure of 60 - 65 mmHg. A right leg venous ulcer was a risk factor for embolism, so he spent 10 days in bed without immobilization. Four years ago, he underwent vein surgery on the right leg. Since then, the leg was occasionally swelling and lesions appeared on the skin. His brother had a pulmonary thromboembolism. Among the comorbidities, he reported chronic obstructive pulmonary disease (used no de-obstructive therapy) and smoking.

After the examination, the patient was presented to the Heart Team, which made a decision to perform a surgery. Upon admission to the Clinic of Cardiac Surgery, the patient was hemodynamically and rhythmically stable with cardiac compensation. Transesophageal echocardiography confirmed a free-floating "snake-like" thrombus in the right heart **(Figure 1)**. After the usual preoperative preparation for emergency surgery, the patient underwent surgery under general endotracheal anesthesia via median sternotomy. After total heparinization, arterial cannulation of the ascending aorta, cannulation of the right heart (bicaval dual lumen cannulation), cardiopulmonary bypass (CPB) was started. The thrombus mass was removed from the RA **(Figures 2 and 3**) through the RA. No thrombus mass was registered in the RV cavity. Total aortic cross-clamp time was 13 minutes, with a total CPB time of 28 minutes. The postoperative course was uneventful. The control echocardiography showed a normal finding, without thrombotic masses.

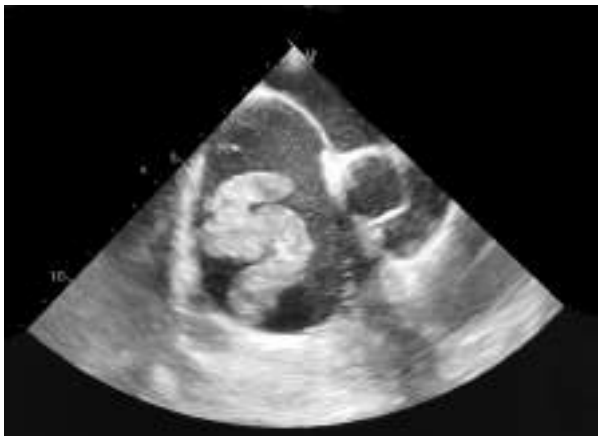

Figure 1. Transesophageal echocardiography showing a free-floating "snake-like" thrombus in the right heart
Slika 1. *Transezofagealna ehokardiografija – slobodno flotirajući "zmijoliki" tromb u desnom srcu*

Figure 2. The surgical view of the thrombus after opening the right atrium
Slika 2. *Hirurški prikaz tromba posle otvaranja desne pretkomore*

Figure 3. Thrombus after extraction from the right heart
Slika 3. *Tromb nakon ekstrakcije iz desnog srca*

Discussion

While thrombus formation inside the left heart chambers has been fairly well explored and is relatively more common, right heart thrombus is often under-diagnosed and can be much more challenging for management. Although thrombi from the left

heart can frequently lead to dramatic and lethal consequences [6–9], the right heart thrombi are mainly associated with possible embolization to the pulmonary circulation and potential circulatory collapse.

According to the European Working Group on Echocardiography [10], three distinct patterns of thrombi can be located inside the right heart. Type A thrombi are referred to as thrombi-in-transit; they occur in the setting of venous thromboembolism and are usually only temporarily located inside the right heart chambers, in transit from systemic veins to pulmonary circulation, thus ending up forming PE. They are highly mobile and free-floating with typical snake-like shape, which is the shape of the peripheral vein at their origin. Type B thrombi are developed in situ inside right heart chambers; they are not mobile and are usually associated with underlying structural abnormalities of the heart. Type C thrombi are the least frequent; they are also mobile and resemble cardiac myxomas.

Free-floating right heart thrombus is an extreme medical emergency, with mortality close to 100% in untreated patients and about 27% in treated patients [11]. Considering the clinical presentation and echocardiographic features in our patient, the thrombus could most likely be classified as type A, i.e. thrombus in the setting of acute PE. Across the literature, the prevalence of right heart thrombi ranges from 4 - 18% in patients with acute PE [12–14]. Predisposing factors for their confinement inside the right heart chambers include prominent Eustachian valves, tricuspid regurgitation, reduced cardiac output and pulmonary hypertension [15].

The main complaint in our patient was shortness of breath, which is reported as the most common symptom of free right heart thrombus [4, 16]. Dyspnea develops in this setting most probably due to embolization of small thrombotic particles disintegrating from the main thrombus and passing into the peripheral branches of pulmonary arteries. Other less common symptoms include chest pain, syncope and palpitations [4], which were not present in our patient. In fact, in our patient there was a considerable disproportion between the seemingly mild clinical presentation and alarming echocardiographic finding of a huge free-floating thrombus. Such inconsistency has already been reported [17], although a more dramatic clinical presentation is more frequently observed in similar cases [1, 18, 19].

Treatment options for right heart thrombus include anticoagulation therapy, thrombolytic therapy (systemic or local), and surgical embolectomy [5]. Due to the lack of prospective randomized clinical trials, the clear consensus on the optimal management approach remains missing. Echocardiography is considered as sufficient and reliable for diagnosis, so immediate treatment can be started without further delay for additional investigations (i.e. computerized tomography, lung scintigraphy, pulmonary angiography) [5, 16]. In the presented case, after a short initial anticoagulation therapy with unfractionated heparin infusion, surgical embolectomy was selected as the preferred management option.

Conclusion

The right heart thrombus is associated with risks of possible embolization to the pulmonary circulation and potential circulatory collapse. There was a considerable disproportion between the seemingly mild clinical presentation and alarming echocardiographic finding of a huge free-floating thrombus in our patient. Despite the lack of standardized and precise recommendations for the optimal therapeutic strategy, surgical approach seems to be the preferred choice for emergency cases with large free-floating thrombi.

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U poglavlju Uvod potrebno je jasno definisati predmet istraživanja (prirodu i značaj istraživanja), navesti značajne navode literature i jasno definisati ciljeve istraživanja i hipoteze.

Materijal i metode

Materijal i metode rada treba da sadrže podatke o vrsti studije (prospektivna/retrospektivna, uslove za uključivanje i ograničenja studije, trajanje istraživanja, demografske podatke, period praćenja). Detaljno treba opisati statističke metode da bi čitaoci rada mogli da provere iznesene rezultate.

Rezultati

Rezultati predstavljaju detaljan prikaz podataka koji su dobijeni istraživanjem. Sve tabele, grafikoni, sheme i slike moraju biti citirani u tekstu rada i označeni brojevima po redosledu njihovog navođenja.

Diskusija

Diskusija treba da bude koncizna, jasna i da predstavlja tumačenje i poređenje rezultata studije sa relevantnim studijama koje su objavljene u domaćoj i međunarodnoj literaturi. U poglavlju Diskusija potrebno je naglasiti da li su postavljene hipoteze potvrđene ili nisu, kao i istaknuti značaj i nedostatke istraživanja.

Zaključak

Zaključci moraju proisteći isključivo iz rezultata istraživanja rada; treba izbegavati uopštene i nepotrebne zaključke. Zaključci koji su navedeni u tekstu rada moraju biti u saglasnosti sa zaključcima iz Sažetka.

4. Literatura

Potrebno je da se literatura numeriše arapskim brojevima redosledom kojim je u tekstu navedena u parentezama; izbegavati nepotrebno velik broj navoda literature. Časopise bi trebalo navoditi u skraćenom obliku koji se koristi u *Index Medicus* (*http://www.nlm.nih.gov/tsd/serials/lji.html*). Pri citiranju literature koristiti Vankuverski sistem. Potrebno je da se navedu svi autori rada, osim ukoliko je broj autora veći od šest. U tom slučaju napisati imena prvih šest autora praćeno sa *et al*.

Primeri pravilnog navođenja literature nalaze se u nastavku.

Radovi u časopisima

∗ Standardni rad

Ginsberg JS, Bates SM. Management of venous thromboembolism during pregnancy. J Thromb Haemost 2003;1:1435-42.

∗ Organizacija kao autor

Diabetes Prevention Program Research Group. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. Hypertension 2002;40(5):679-86.

∗ Bez autora

21st century heart solution may have a sting in the tail. BMJ. 2002;325(7357):184.

∗ Volumen sa suplementom

Magni F, Rossoni G, Berti F. BN-52021 protects guinea pig from heart anaphylaxix. Pharmacol Res Commun 1988;20 Suppl 5:75-8.

∗ Sveska sa suplementom

Gardos G, Cole JO, Haskell D, Marby D, Pame SS, Moore P. The natural history of tardive dyskinesia. J Clin Psychopharmacol 1988;8(4 Suppl):31S-37S.

∗ Sažetak u časopisu

Fuhrman SA, Joiner KA. Binding of the third component of complement C3 by Toxoplasma gondi [abstract]. Clin Res 1987;35:475A.

Knjige i druge monografije

∗ Jedan ili više autora

Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. Medical microbiology. 4th ed. St. Louis: Mosby; 2002.

∗ Urednik (urednici) kao autor (autori)

Danset J, Colombani J, eds. Histocompatibility testing 1972. Copenhagen: Munksgaard, 1973:12-8.

∗ Poglavlje u knjizi

Weinstein L, Shwartz MN. Pathologic properties of invading microorganisms. In: Soderman WA Jr, Soderman WA, eds. Pathologic physiology: mechanisms of disease. Philadelphia: Saunders; 1974. p. 457-72.

∗ Zbornik radova sa kongresa

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.

∗ Disertacija

Borkowski MM. Infant sleep and feeding: a telephone survey of Hispanic Americans [dissertation]. Mount Pleasant (MI): Central Michigan University; 2002.

Elektronski materijal

∗ Članak iz časopisa u elektronskom formatu

Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [Internet]. 2002 Jun [cited 2002 Aug 12];102(6):[about 1 p.]. Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htmArticle

∗ Monografija u elektronskom formatu

CDI, clinical dermatology illustrated [monograph on CD-ROM]. Reevs JRT, Maibach H. CMEA Multimedia Group, producers. 2nd ed. Version 2.0. San Diego:CMEA;1995.

∗ Kompjuterska datoteka

Hemodynamics III: the ups and downs of hemodynamics [computer program]. Version 2.2. Orlando (FL): Computerized Educational Systems; 1993.

5. Prilozi (tabele, grafikoni, sheme i slike)

BROJ PRILOGA NE SME BITI VEĆI OD ŠEST!

Tabele, grafikoni, sheme i slike se postavljaju kao posebni dokumenti.

– Tabele i grafikone bi trebalo pripremiti u formatu koji je kompatibilan programu u kojem je napisan tekst rada. Slike bi trebalo poslati u jednom od sledećih oblika: *JPG, GIF, TIFF, EPS*.

– Svaki prilog mora biti obeležen arapskim brojem prema redosledu po kojem se navodi u tekstu rada.

– Naslovi, tekst u tabelama, grafikonima, shemama i legende slika bi trebalo da budu napisani na srpskom i engleskom jeziku.

– Nestandardne priloge označiti u fusnoti uz korišćenje sledećih simbola: *, †, ‡, §, | |, ¶, **, † †, ‡ ‡ .

– U legendi slika trebalo bi napisati korišćeno uveličanje okulara i objektiva mikroskopa. Svaka fotografija treba da ima vidljivu skalu.

– Ako su tabele, grafikoni, sheme ili slike već objavljene, navesti originalni izvor i priložiti pisano odobrenje autora za njihovo korišćenje.

– Svi prilozi će biti štampani kao crno-bele slike. Ukoliko autori žele da se prilozi štampaju u boji, obavezno treba da plate dodatne troškove.

6. Dodatne obaveze

AUTORI I SVI KOAUTORI RADA OBAVEZNO TREBA DA PLATE GODIŠNJU PRETPLATU ZA ČASOPIS *MEDICINSKI PREGLED*. U PROTIVNOM, RAD NEĆE BITI ŠTAMPAN U ČASOPISU.

INFORMATION FOR AUTHORS

Medical Review publishes papers (previously neither published in nor submitted to any other journals) from various fields of biomedicine intended for broad circles of doctors.

Since January 1th, 2013 the Medical Review has been using the service e-Ur: Electronic Journal Editing. All users of the Registration system, i.e. authors, reviewers, and editors have to be registered users with only one e-mail address. Registration should be made on the web address:

http://aseestant.ceon.rs/index.php/medpreg/user/register.

Manuscript submission should be made on the web address:

http://aseestant.ceon.rs/index.php/medpreg/

A SUPPLEMENTARY FILE, WITH THE STATEMENT THAT THE PAPER HAS NOT BEEN SUBMITTED OR ACCEPTED FOR PUBLICATION ELSEWHERE AND A CONSENT SIGNED BY ALL AUTHORS, HAVE TO BE ENCLOSED WITH THE MANUSCRIPT.

Authors may not send the same manuscript to more than one journal concurrently. If this occurs, the Editor may return the paper without reviewing it, reject the paper, contact the Editor of the other journal(s) in question and/or contact the author's employers.

Papers should be written in English language, with an abstract and title page in English, as well as in Serbian language.

All papers submitted to ***Medical Review*** are seen by one or more members of the Editorial Board. Suitable articles are sent to at least two experts to be reviewed, thier reports are returned to the assigned member of the Editorial Board and the Editor. Revision of an article gives no guarantee of acceptance and in some cases revised articles are rejected if the improvements are not sufficient or new issues have arisen. Material submitted to *the Journal* remains confidential while being reviewed and peer-reviewers' identities are protected unless they elect to lose anonymity.

Medical Review publishes the following types of articles: editorials, original studies, preliminary reports, review articles, professional articles, case reports, articles from history of medicine and other types of publications.

1. Editorials – up to 5 pages – convey opinions or discussions on a subject relevant for the Journal. Editorials are commonly written by one author by invitation.

2. Original studies – up to 12 pages – present the authors' own investigations and their interpretations. They should contain data which could be the basis to check the obtained results and reproduce the investigative procedure.

3. Review articles – up to 10 pages – provide a condensed, comprehensive and critical review of a problem on the basis of the published material being analyzed and discussed, reflecting the current situation in one area of research. Papers of this type will be accepted for publication provided that the authors confirm their expertise in the relevant area by citing at least 5 self-citations.

4. Preliminary reports – up to 4 pages – contain scientific results of significant importance requiring urgent publishing; however, it need not provide detailed description for repeating the obtained results. It presents new scientific data without a detailed explanation of methods and results. It contains all parts of an original study in an abridged form.

5. Professional articles – up to 10 pages – examine or reproduce previous investigation and represent a valuable source of knowledge and adaption of original investigations for the needs of current science and practice.

6. Case reports – up to 6 pages – deal with rare casuistry from practice important for doctors in direct charge of patients and are similar to professional articles. They emphasize unusual characteristics and course of a disease, unexpected reactions to a therapy, application of new diagnostic procedures and describe a rare or new disease.

7. History of medicine – up to 10 pages – deals with history with the aim of providing continuity of medical and health care culture. They have the character of professional articles.

8. Other types of publications – The journal also publishes feuilletons, book reviews, extracts from foreign literature, reports from congresses and professional meetings, communications on activities of certain medical institutions, branches and sections, announcements of the Editorial Board, letters to the Editorial Board, novelties in medicine, questions and answers, professional and vocational news and In memoriam.

Preparation of the manuscript

The complete manuscript, including the text, all supplementary material and covering letter, is to be sent to the web address above.

The covering letter:

– It must contain the proof given by the author that the paper represents an original work that it has neither been previously published in other journals nor is under consideration to be published in other journals.

– It must confirm that all the authors meet criteria set for the authorship of the paper, that they agree completely with the text and that there is no conflict of interest.

– It must state the type of the paper submitted (an original study, a review article, a preliminary report, a professional article, a case report, history of medicine).

The manuscript:

General instructions.

Use Microsoft Word for Windows to type the text. The text must be typed in font *Times New Roman*, page format A4, space 1.5 (for tables as well), margins set to 2.5 cm and font size 12pt. All measurements should be reported in the metric system of the International System of Units – SI. Temperature should be expressed in Celsius degrees (°C) and pressure in mmHg.

The manuscript should contain the following elements:

1. The title page.

The title page should contain a concise and clear title of the paper, without abbreviations, then a short title (up to 40 characters), full names and surnames of the authors (not more than 6) indexed by numbers corresponding to those given in the heading along with the full name and place of the institutions they work for. Contact information including the academic degree(s), full address, e-mail and number of phone or fax of the corresponding author (the author responsible for correspondence) are to be given at the bottom of this page.

2. Summary.

The summary should contain up to 250 words, without abbreviations, with the precise review of problems, objectives, methods, important results and conclusions. It should be structured into the paragraphs as follows:

– Original and professional papers should have the introduction (with the objective of the paper), materials and methods, results and conclusion

– Case reports should have the introduction, case report and conclusion

– Review papers should have the introduction, subtitles corresponding to those in the paper and conclusion.

The authors should provide up to 10 keywords below the summary. These keywords will assist indexers in cross-indexing the article and will be published with the summary, but the authors' keywords could be changed in accordance with the list of Medical Subject Headings, MeSH of the American National Medical Library.

The summary should be written in both languages, English as well as Serbian. The summary in Serbian language should be the translation of the summary in English; therefore, it has to contain the same paragraphs.

3. The text of the paper.

The text of original studies must contain the following: introduction (with the clearly defined objective of the study), materials and methods, results, discussion, conclusion, list of abbreviations (if used in the text) and not necessarily, the acknowledgment mentioning those who have helped in the investigation and preparation of the paper.

The text of a case report should contain the following: introduction (with clearly defined objective of the study), case report, discussion and conclusion.

Introduction contains clearly defined problem dealt with in the study (its nature and importance), with the relevant references and clearly defined objective of the investigation and hypothesis.

Materials and methods should contain data on design of the study (prospective/retrospective, eligibility and exclusion criteria, duration, demographic data, follow-up period). Statistical methods applied should be clear and described in details.

Results give a detailed review of data obtained during the study. All tables, graphs, schemes and figures must be cited in the text and numbered consecutively in the order of their first citation in the text.

Discussion should be concise and clear, interpreting the basic findings of the study in comparison with the results of relevant studies published in international and national literature. It should be stated whether the hypothesis has been confirmed or denied. Merits and demerits of the study should be mentioned.

Conclusion must deny or confirm the attitude towards the 0based solely on the author's own results, corroborating them. Avoid generalized and unnecessary conclusions. Conclusions in the text must be in accordance with those given in the summary.

4. References are to be given in the text under Arabic numerals in parentheses consecutively in the order of their first citation. Avoid a large number of citations in the text. The title of journals should be abbreviated according to the style used in Index Medicus (http://www.nlm.nih.gov/tsd/serials/lji.html). Apply Vancouver Group's Criteria, which define the order of data and punctuation marks separating them. Examples of correct forms of references are given below. List all authors, but if the number exceeds six, give the names of six authors followed by 'et al'.

Articles in journals

∗ *A standard article*

Ginsberg JS, Bates SM. Management of venous thromboembolism during pregnancy. J Thromb Haemost 2003;1:1435-42.

∗ *An organization as the author*

Diabetes Prevention Program Research Group. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. Hypertension 2002;40(5):679-86.

∗ *No author given*

21st century heart solution may have a sting in the tail. BMJ. 2002;325(7357):184.

∗ *A volume with supplement*

Magni F, Rossoni G, Berti F. BN-52021 protects guinea pig from heart anaphylaxix. Pharmacol Res Commun 1988;20 Suppl 5:75-8.

∗ *An issue with supplement*

Gardos G, Cole JO, Haskell D, Marby D, Pame SS, Moore P. The natural history of tardive dyskinesia. J Clin Psychopharmacol 1988;8(4 Suppl):31S-37S.

∗ *A summary in a journal*

Fuhrman SA, Joiner KA. Binding of the third component of complement C3 by Toxoplasma gondi [abstract]. Clin Res 1987;35:475A.

Books and other monographs

∗ *One or more authors*

Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. Medical microbiology. 4th ed. St. Louis: Mosby; 2002.

∗ *Editor(s) as author(s)*

Danset J, Colombani J, eds. Histocompatibility testing 1972. Copenhagen: Munksgaard, 1973:12-8.

∗ *A chapter in a book*

Weinstein L, Shwartz MN. Pathologic properties of invading microorganisms. In: Soderman WA Jr, Soderman WA, eds. Pathologic physiology: mechanisms of disease. Philadelphia: Saunders; 1974. p. 457-72.

∗ *A conference paper*

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.

∗ *A dissertation and theses*

Borkowski MM. Infant sleep and feeding: a telephone survey of Hispanic Americans [dissertation]. Mount Pleasant (MI): Central Michigan University; 2002.

Electronic material

∗ *A journal article in electronic format*

Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [Internet]. 2002 Jun [cited 2002 Aug 12];102(6):[about 1 p.]. Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htmArticle

∗ *Monographs in electronic format*

CDI, clinical dermatology illustrated [monograph on CD-ROM]. Reevs JRT, Maibach H. CMEA Multimedia Group, producers. 2nd ed. Version 2.0. San Diego:CMEA;1995.

∗ *A computer file*

Hemodynamics III: the ups and downs of hemodynamics [computer program]. Version 2.2. Orlando (FL): Computerized Educational Systems; 1993.

5. Attachments (tables, graphs, schemes and photographs).

THE MAXIMUM NUMBER OF ATTACHMENTS ALLOWED IS SIX!

– Tables, graphs, schemes and photographs are to be submitted as separate documents, on separate pages.

– Tables and graphs are to be prepared in the format compatible with Microsoft Word for Windows programme. Photographs are to be prepared in JPG, GIF, TIFF, EPS or similar format.

– Each attachment must be numbered by Arabic numerals consecutively in the order of their appearance in the text

– The title, text in tables, graphs, schemes and legends must be given in both Serbian and English languages.

– Explain all non-standard abbreviations in footnotes using the following symbols *, †, ‡, §, | |, ¶, **, † †, ‡ ‡ .

– State the type of color used and microscope magnification in the legends of photomicrographs. Photomicrographs should have internal scale markers.

– If a table, graph, scheme or figure has been previously published, acknowledge the original source and submit written permission from the copyright holder to reproduce it.

– All attachments will be printed in black and white. If the authors wish to have the attachments in color, they will have to pay additional cost.

6. Additional requirements

SHOULD THE AUTHOR AND ALL CO-AUTHORS FAIL TO PAY THE SUBSCRIPTION FOR MEDICAL REVIEW, THEIR PAPER WILL NOT BE PUBLISHED.