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Anri Dinan, punim imenom Žan-Anri Dinan (8. maj 1828 - 30. oktobar, 1910), švajcarski humanista, osnivač Crvenog krsta (sada Crveni krst i Crveni polumesec), uz Frederika Pasija, prvi je dobitnik Nobelove nagrade za mir, 1901. Njegov rođendan, 8. maj, slavi se svake godine kao Svetski dan Crvenog krsta i Crvenog polumeseca. Taj dan ustanovljen je sa ciljem da se istakne značaj ovih organizacija i njihovih članova u spasavanju života i pružanju pomoći nezaštićenima širom sveta.

Henri Dunant, full name Jean-Henri Dunant (May 8, 1828 - October 30, 1910), Swiss humanitarian, founder of the Red Cross (now Red Cross and Red Crescent) was cowinner (with Frédéric Passy) of the first Nobel Peace Prize in 1901. The date of his birth, May 8, is celebrated every year as the World Red Cross and Red Crescent Day. This day is established to emphasize the role of the Red Cross and Red Crescent and their members in saving lives and aiding the defenseless communities around the world.

Drage koleginice i kolege,

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# Autologna transplantacija matičnih ćelija hematopoeze u lečenju multiplog mijeloma – iskustvo jednog centra

## Autologous stem cell transplantation in the treatment of multiple myeloma – single center expirience

**Slobodan Marjanović*, Dragana Stamatović*, Ljiljana Tukić*, Olivera Tarabar*, Marija Elez*, Lavinika Madjaru*, Bela Balint†, Željka Tatomirović‡, Nada Kuljić-Kapulica‖, Nebojša Andjelković§**

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**Apstrakt**

**Uvod/Cilj.** Autologna transplantacija matičnih ćelija hematopoeze (ASCT) uz primenu visokih doza melfalana značajno poboljšava lečenje bolesnika sa multiplim mijelomom (MM) u odnosu na standardnu hemioterapiju. Cilj ovog rada bio je prikazivanje rezultata lečenja bolesnika sa MM u Klinici za hematologiju Vojnomedicinska akademija u Beogradu primenom ASCT, uz kondicioni režim sa melfalanom ili kombinacijom busulfana, ciklofosamida i melfalana. **Metode.** Analizom je bilo obuhvaćeno 47 bolesnika sa MM, lečenih u periodu od 1998. do 2008. Jednostruka ASCT rađena je posle 3–6 ciklusa hemioterapije po protokolu vinkristin, adriamicin, deksametazon (VAD) kod 32 (68%), a dvostruka kod šest (19%) bolesnika. Kod šest bolesnika (13%) rađena je sekundarna ASCT u vreme progresije bolesti posle prve ASCT. Protokoli mobilizacije matičnih ćelija hematopoeze bili su: granulocitni faktor stimulacije kolonija (G-CSF) i ciklofosfamid (17% bolesnika), odnosno G-CSF i ciklofosfamid + etopozid (83% bolesnika). Svi bolesnici primali su G-CSF od petog dana posle ACST, a terapija održavanja kod bolesnika sa kompletnom i parcijalnom remisijom (CR + PR) posle transplantacije bila je interferon alfa (30% bolesnika), talidomid (28% bolesnika) i druge vrste terapija (26% bolesnika). **Rezultati.** Medijana vremena do rekonstrukcije autologne hematopoeze bila je 12 dana. Preživljavanje bolesnika u periodu praćenja od 50 meseci bilo je 64%. Ukupan stepen odgovora na terapiju (ORR) postignut je kod 38 (80%) bolesnika i bio je bolji u grupi bolesnika lečenih u ranoj fazi MM. U toku 25 meseci posle transplantacije, bez progresije bolesti bilo je 25 (53%) bolesnika. Kriterijume za CR + vrlo dobru parcijalnu remisiju (VGPR) imalo je 20 bolesnika, što je za pet više nego broj bolesnika sa CR + VGPR pre ASCT. Umrlo je 14 (30%) bolesnika, a srednje vreme do smrtnog ishoda bilo je 17 meseci. **Zaključak.** ASCT, primenjena u ranoj fazi MM, posle indukcione terapije po protokolu VAD, predstavlja značajan napredak u lečenju ovog oboljenja. Pri tome, postizanje remisije (CR + VGPR) pre i posle transplantacije predstavlja važan prediktivni faktor za ukupno preživljavanje ili produženje perioda do recidiva, progresije, odustajanja od terapije ili smrti.

**Ključne reči:**
**multipli mijelom; lečenje kombinovanjem antineoplastika, protokoli; transplantacija, autologna; ćelije, matične; preživljavanje, analiza.**

**Abstract**

**Background/Aim.** In comparison to standard therapy autologous stem cell transplant (ASCT) with high doses melphalane has improved treatment of multiple myeloma (MM) patients. The aim of this study was to evaluate the results of treatment of MM patients in our center with ASCT conditioning with melphalane or combining busulphane, cyclophosphamide and melphalane. **Methods.** We performed 62 ASCT procedures in 47 patients from 1998 till 2008. Single ASCT were performed in 32 patients (68%), after 3-6 cycles of vincristine, adriamycin, dexamethasone (VAD) protocol and double in 9 patients (19%). Secondary ASCT was performed in 6 (13%) patients during progression of the disease after single ASCT. Mobilization of stem cells (SC) was either with a combination of etoposide and cyclophosphamide with granulocyte colony-stimulating factor (G-CSF) in 39 (83%) patients or cyclophosphamide plus G-CSF in 8 (17%) patients. All the patients received G-CSF five days after the ASCT and maintenance therapy afterwards in the patients with a complete remission (CR) or a partial remission (PR) was interferon alpha in 14 (30%) patients, thalidomide in 13 (28%) and others in 12

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(26%) patients. **Results.** Median engraftment was on 12th day. In a 50-month follow-up period 64% patients were alive. The overall response rate (ORR), wich was reached in 38 (80%) patients, was better in the group of patients treated in the early phase of MM. Totally 25 (53%) patients were without progression in a 25-month follow-up period. Twenty patients met criteria for CR + VGPR (very good partial remission), that was 5 patients more than in the period before ASCT. Fourteen (30%) patients died and median time till death was 17 months. **Conclusion**. The ASCT perfomed in early phase of MM after VAD induction had a significant influence on the treatment of MM patients. Reaching CR + VGPR before and after the ASCT is predictive factor for overall survival (OS) or prolongation of period till recidive appears, progression, therapy withdrowal or death.

**Key words:**
**multiple myeloma; antineoplastic combined chemotherapy protocols; transplantation, autologous; stem cells; survival analysis.**

## Uvod

Multipli mijelom (MM) drugi je najčešći hematološki malignitet koji predstavlja neizlečivu bolest, sa medijanom preživljavanja kod nelečenih bolesnika u stadijumu III manjom od jedne godine [1]. Alkilišući lekovi i kortikosteroidi uvedeni u terapiju ranih šezdesetih godina omogućili su stepen odgovora (RR) oko 50%, sa medijanom preživljavanja do 30 meseci. U poslednjih 30 godina primena različitih hemioterapijskih protokola nije dovela do poboljšanja ukupnog preživljavanja (OS).

Od ranih osamdesetih godina McElwain i Powles [2] pokazali su da se primenom visokodozne hemioterapije (HDCT) može postići poboljšanje ukupnog preživljavanja. Autologna transplantacija matičnih ćelija hematopoeze (ASCT) sa visokim dozama melfalana značajno je poboljšala RR, EFS (period do recidiva, progresije, odustajanje od terapije ili smrti) i OS u odnosu na standardnu terapiju. Zbog toga se ASCT u poslednjih 20 godina, kod bolesnika mlađih od 65 godina, smatra standardnim lečenjem u Evropi i Americi, bez obzira na fazu bolesti [3].

Dvostruka ASCT u odnosu na jednostruku pokazala je u nekim studijama prednost, kada se analizira EFS i OS. Sekundarna ASCT koristi se u relapsu ili refrakternoj bolesti nakon prve ASCT, čime se produžava trajanje odgovora za dve do tri godine i medijana preživljavanja do 6,4 godine. Dosadašnji konvencionalni indukcioni režimi, kao protokol VAD (vinkristin, adriamicin, deksametazon), daju mali stepen kompletnih remisija (CR), < 10% [4, 5].

Poslednjih godina istaknut je značaj postizanja CR ili vrlo dobre parcijalne remisije (VGPR), kao važnih faktora za dugotrajnije preživljavanje, odnosno bolji ishod nakon prve ASCT. U tom cilju u indukciono lečenje uključuju se novi lekovi ili njihove kombinacije (talidomid, bortezomib, lenalidomid) čime se posttransplantaciono poboljšava medijana preživljavanja i smanjuje potreba za drugom ASCT [6–9]. Primena visokih doza melfalana (200 mg/m$^2$) smatra se optimalnim kondicionim režimom [10].

Internacionalni sistem stepenovanja (ISS), koji se dobija kombinovanjem značaja vrednosti serumskih albumina i serumskog beta-2-mikroglobulina [11], najvažniji je klasifikacioni sistem za predhodno nelečene bolesnike sa MM.

U ovom radu data je analiza rezultata Klinike za hematologiju Vojnomedicinske akademije (VMA) u Beogradu u lečenju bolesnika sa MM. Bolesnici su lečeni visokodoznom hemioterapijom praćenom jednostrukom, dvostrukom ili sekundarnom ASCT. Takođe, istaknut je značaj primene terapije održavanja posle ASCT radi produženja trajanja postignute remisije.

## Metode

Od decembra 1998. do oktobra 2008. u Klinici za hematologiju VMA urađene su 62 procedure ASCT kod 47 novodijagnostikovanih bolesnika sa MM kao konsolidaciona terapija posle prve ili druge linije hemioterapije. Isključeni su bolesnici sa aktivnom infekcijom, značajnim komorbiditetima kao što su srčana slabost (EF < 50%), insuficijencija jetre, respiratorna i bubrežna insuficijencija koje nisu bile povezane sa osnovnim oboljenjem, kao i bolesnici stariji od 65 godina. U ispitivanoj grupi bolesnika nisu rađene citogenetske analize.

Od 47 bolesnika bilo je 28 muškog (60%) i 19 ženskog (40%) pola, sa starosnom medijanom od 52 godine (opseg 39–64 godine). Treći klinički stadijum bolesti imala su 32 bolesnika (68%), a sa ISS skorom 3 bilo je 11 bolesnika (23%). Srednja vrednost vremena od dijagnoze do ASCT bila je 13,9 meseci (opseg 3–90 meseci).

Jednostruka ASCT urađena je kod 32 (68%), dvostruka kod devet (19%) i sekundarna (u vreme progresije bolesti nakon prve ASCT) kod šest (13%) bolesnika. U vreme transplantacije CR + VGPR imalo je 15 (32%) bolesnika, parcijalnu remisiju (PR) 19 (40%), < PR 8 (17%), a progresiju bolesti (PD) imalo je pet (11%) bolesnika.

Posle 3–6 ciklusa VAD hemioterapije ASCT primenjena je kao deo primarne strategije lečenja kod 28 bolesnika tokom poslednje četiri godine, dok je kod 19 bolesnika transplantacija učinjena od 10 do 90 meseci nakon dijagnoze.

Osim primene G-CSF-a, protokol mobilizacije matičnih ćelija hematopoeze (MĆH) uključivao je: ciklofosfamid + etoposid kod 39 (83%) bolesnika, a kod osam (17%) bolesnika mobilizacija MĆH učinjena je samo ciklofosfamidom ili faktorom stimulacije kolonija posle inicijalne terapije. Najčešće je bila dovoljna jedna terapijska primena afereznog produkta velikog volumena.

Kao visokodozna hemioterapija (HDCT) korišćene su visoke doze melfalana (kondicioni režim) kod 33 (70%) bolesnika, a protokol sa busulfanom, ciklofosfamidom i melfalanom (BU/Cy2 + M) kod 14 (30%) bolesnika. Medijana broja autotransplantovanih mononuklearnih ćelija (MNĆ) bila je $8,6 \times 10^8$/kg TT (opseg 3,8–16,2). Svi bolesnici primali su G-CSF posle ASCT od petog dana posle transplantacije.

Odgovor na terapiju procenjivan je tri meseca posle ASCT prema kriterijumima Evropskog udruženja za transplantaciju kostne srži (EBMT) [12] (tabela 1), a trajanje odgovora definisano je intervalom vremena između potvrđenog odgovora i relapsa bolesti.

Medijana vremena do rekonstitucije autologne hematopoeze (broj neutrofila preko 500/mm$^3$ i trombocita preko 20 000/mm$^3$) bila je 12 dana (opseg 8–36), vreme do rekonstitucije leukocita iznosilo je 8–20 dana, a trombocita 9–36 dana. Kod dva bolesnika nije došlo do rekonstitucije hematopoeze zbog prethodno primenjenih više hemioterapijskih ciklusa.

**Tabela 1**

**Procena odgovora na terapiju kod bolesnika sa multiplim mijelomom**

| Kriterijumi | Klinička remisija (SWOG) | Kompletna remisija (EBMT) | Parcijalna remisija (EBMT) | Minimalni odgovor (EBMT) |
|---|---|---|---|---|
| Redukcija proteina u serumu (s) | > 75% | 100% | > 50% | > 25% |
| Redukcija proteina u urinu (u) | > 90% | 100% | > 90% | > 50% |
| Imunofiksacija (s/u) | – | nagativna | – | – |
| Kostna srž | – | < 5% plazma ćelija | > 50% smanjenja plazma ćelija | > 25% smanjenja plazma ćelija |
| Bolest kostiju | | Stabilna | | |
| Kalcijum | | Normalan nivo | | |

**SWOG – Jugozapadna onkološka grupa; EBMT – Evropsko udruženje za transplantaciju kostne srži**

Terapija održavanja posle ASCT kod bolesnika sa CR + PR bila je: interferon alfa kod 14 (30%) bolesnika, talidomid kod 13 (28%) i druge terapije kod 12 (26%) bolesnika. Kod osam (18%) bolesnika sa CR iza ASCT nije primenjivana terapija održavanja.

## Rezultati

Karakteristike bolesnika sa MM, tipovi transplantacije MĆH i status bolesnika pre i posle ASCT date su u tabelama 2 i 3.

U periodu praćenja od 50 meseci preživelo je 30 (68%) bolesnika, od toga 20 bolesnika imalo je jednostruku, šest dvostruku i četiri sekundarnu transplantaciju. Umrlo je 14 (32%) bolesnika. Posle jednostruke ASCT umrlo je 12 bolesnika, a posle dvostruke i sekundarne transplantacije umro je po jedan bolesnik zbog progresije bolesti.

Od ukupnog broja bolesnika koji su umrli, 12 bolesnika pre transplantacije primilo je više hemioterapijskih ciklusa, dok su dva bolesnika bila rezistentna na primenjenu terapiju.

**Tabela 2**

**Karakteristike bolesnika sa multiplim mijelomom i ASCT**

| Karakteristika bolesnika | Vrednosti |
|---|---|
| Pol [n (%)] | |
| ukupno | 47 (100) |
| muški | 28 (60) |
| ženski | 19 (40) |
| Godište - medijana (opseg) | 52 (39–64) |
| Klinički stadijum bolesti [n (%)] | |
| I | 1 (2) |
| II | 14 (30) |
| III | 32 (68) |
| Vreme od dijagnoze do ASCT, [$\bar{x}$ (opseg)], meseci | 13,9 (3–90) |
| Tip transplantacije [n (%)] | |
| jednostruka | 32 (68) |
| dvostruka | 6 (13) |
| sekundarna | 9 (19) |

**ASCT – autologna transplantacija matičnih ćelija hematopeze**

**Tabela 3**

**Status bolesnika sa multiplim mijelomom pre i posle ASCT**

| Odgovor na terapiju | pre ASCT | | posle ASCT | |
|---|---|---|---|---|
| | n | % | n | % |
| CR +VGPR | 15 | 32 | 20 | 42 |
| PR | 19 | 40 | 18 | 38 |
| > PR | 8 | 17 | 6 | 12 |
| PD | 5 | 11 | 3 | 6 |

**ASCT – autologna transplantacija matičnih ćelija hematopoeze;**
**CR – kompletna remisija; VGPR – vrlo dobra parcijalna remisija;**
**PR – parcijalna remisija; PD – progresija bolesti**

Srednje vreme do smrtnog ishoda bilo je 17 meseci (opseg 1–50), i to sa ISS 1 umrla su dva bolesnika, sa ISS 2 devet, a sa ISS 3 tri bolesnika (za tri bolesnika ne postoje adekvatni podaci o praćenju posle ASCT, jer se gube iz evidencije praćenja u periodu od 6 do 17 meseci).

Stepen odgovora posle transplantacije analiziran je kod svih bolesnika: kriterijume za CR + VGPR imalo je 20 (42%) bolesnika, za PR 18 (38%), za manje od PR šest (12%) bolesnika, a za PD tri (6%) bolesnika. Ovi rezultati pokazuju da se nakon ASCT broj bolesnika sa CR + VGPR povećao za pet bolesnika. Od njih, jedan bolesnik je imao kriterijume PR pre ASCT, dva su imala kriterijume manje od PR, a dva kriterijume PD (tabela 3).

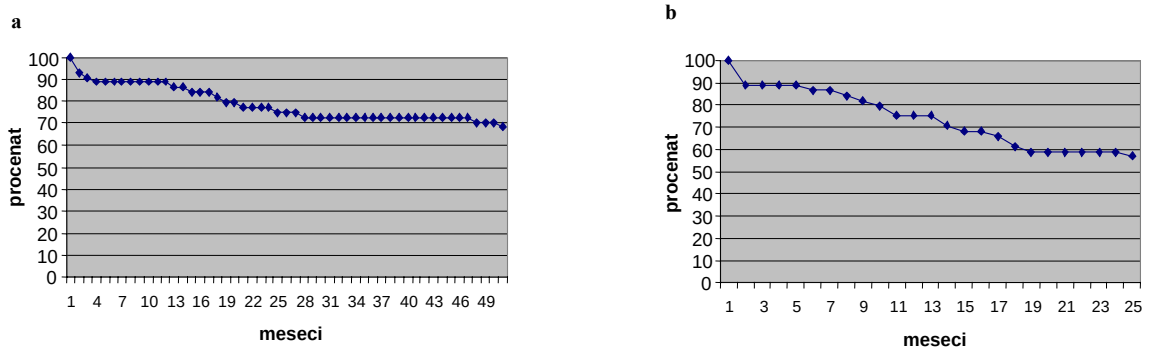
Ukupan stepen odgovora na terapiju (ORR) postignut je kod 38 (80%) bolesnika. Srednje vreme do progresije bolesti kod 19 (40%) bolesnika, koji su progredirali posle ASCT, bilo je 9,28 meseci (opseg 1–24), od kojih je, od transplantacije do progresije bolesti, remisija (CR + VGPR) postignuta kod dva bolesnika, PR kod devet, manje od PR kod pet, a PD kod tri bolesnika. Od bolesnika koji su bili u progresiji, kod šest je urađena sekundarna ASCT.

Najčešći uzrok morbiditeta bile su febrilna neutropenija, gastrointestinalna toksičnost i mukozitis.

U periodu praćenja od 50 meseci, 30 (64%) bolesnika bilo je živo (slika 1a).

U periodu od 25 meseci praćenja posle transplantacije, bez progresije bolesti bilo je 25 (53%) bolesnika (slika 1b).

U poslednjih 25 godina, upoređujući ASCT sa konvencionalnom hemioterapijom, meta analize na velikom broju bolesnika pokazale su jasnu prednost ASCT za EFS, ali ne




**Sl. 1 – Preživljavanje bolesnika (a) i vreme do progresije bolesti (b) kod bolesnika sa multiplim mijelomom**

## Diskusija

Cilj ovog rada bio je da se retrospektivnom analizom prikažu rezultati lečenja bolesnika sa MM u Klinici za hematologiju VMA primenom ASCT. Zbog heterogenosti bolesnika uključenih u program transplantacije, različitih protokola mobilizacije matičnih ćelija, kondicionog režima, broja ASCT i lečenja u posletransplantacionom periodu bilo je teško formirati adekvatne grupe na osnovu čega bi se vršile analize korišćenjem naučnog metoda. Zbog toga, bila nam je namera da se istaknu koristi ove terapije, naglase problemi izbora bolesnika za program transplantacije, ali i nove mogućnosti lečenja hemioterapijom u kombinaciji sa ASCT.

Iako je poslednjih godina postignut napredak u poboljšanju standardnih kondicionih protokola visokodozne hemioterapije, nijedan od njih nije pokazao značajno poboljšanje ukupnog preživljavanja [10, 13], te melfalan (200 mg/m$^2$) sa primenom autolognih perifernih matičnih ćelija hematopoeze i dalje ostaje zlatni standard HDCT.

U našoj grupi, kod 20 (42%) bolesnika postignuta je remisija (CR + VGPR), prema EBMT kriterijumu, tri meseca posle ASCT u odnosu na 15 bolesnika posle indukcione terapije. Postizanje remisije u našem ispitivanju, bez obzira na broj bolesnika, predstavlja snažan prediktivni faktor za produžen EFS i OS, što je i primarni cilj indukcione i visokodozne hemioterapije, i takođe je u saglasnosti sa većinom objavljenih studija.

Prva randomizirana studija o ulozi ASCT nasuprot konvencionalnoj hemioterapiji kod nelečenih bolesnika sa praćenjem od sedam godina (IFM-90) pokazala je da se procenat kompletnih remisija sa ASCT povećava u odnosu na procenat remisija postignutih konvencionalnom hemioterapijom na 20–40%, a stepen odgovora na 75–90%, što koreliše sa dužim EFS i OS [14, 15]. I u ostalim randomiziranim studijama duže trajanje EFS bilo je u korelaciji je sa produženim OS, kao i uloga ASCT u cilju povećanja procenta remisija. Bolesnici kod kojih se posle ASCT postigne CR iz PR imaju medijanu preživljavanja od 8,3 godine, a oni koji ostanu u PR imaju medijanu preživljavanja od samo pet godina [16–18].

U poslednjih 25 godina, upoređujući ASCT sa konvencionalnom hemioterapijom, meta analize na velikom broju bolesnika pokazale su jasnu prednost ASCT za EFS, ali ne značajno i za OS. U velikoj studiji koju su sproveli Child i sar. [17] medijana OS bila je značajno produžena za skoro godinu dana u grupi bolesnika sa ASCT, posebno onih sa medijanom starosti od 51 godine, nasuprot onima koji su primali konvencionalnu hemioterapiju. Za bolesnike starije od 65 godina u studiji koju su sproveli Facona i sar. [18] pokazano je da je melfalan, prednizon, talidomid (MPT) protokol bio bolji u pogledu OS nego ASCT. Samo dve skorašnje studije nisu pokazale prednost u preživljavanju bolesnika mlađih od 70 godina, iako je dokazana jasna korist za EFS. Moguće objašnjenje u studiji PETHEMA [19] je da se ASCT koristi kao terapija spašavanja (*salvage*) kod bolesnika bez odgovora na terapiju i kod onih sa ranim relapsom posle konvencionalne hemioterapije. U drugu *US Intergroup* studiju [20] bio je uključen veliki broj starijih bolesnika, kao i podgrupa bolesnika

gde ASCT nije bila primenjena u prvoj liniji lečenja, zbog uključivanja novih lekova u inicijalnu terapiju.

Koncept dvostruke ASCT uveden je kasnih osamdesetih godina sa ciljem daljeg povećanja stepena CR, a dobijeni rezultati pokazali su poboljšanje RR i povećanje medijane EFS i moguće OS u odnosu na jednostruku ASCT, dok se rezultati nemačke i francuske studijske grupe tek očekuju. Zaključak većine studija je da se kod bolesnika kod kojih se nakon jednostruke ASCT postignu kriterijumi za CR ili VGPR postiže isti OS, sa ili bez dvostruke ASCT [21–24]. Zbog toga je zaključeno da je dvostruka ASCT indikovana u podgrupi bolesnika, kod kojih se nakon jednostruke ASCT ne postignu kriterijumi za VGPR, sa napomenom da se ovom transplantacijom ne postiže dobar ishod kod bolesnika sa lošim prognostičkim faktorima. Sekundarna transplantacija u relapsu sve češće se primenjuje, jer su studije pokazale da je kod tih bolesnika produženo trajanje odgovora za više od 2 do 3 godine u odnosu na one kod kojih ona nije urađena posle relapsa nastalog posle prve transplantacije [4, 9, 16, 21, 25].

Poznato je da i kada se primenjenom terapijom kod bolesnika sa MM postigne remisija, može doći do pojave relapsa, pa se u cilju održavanja postignute remisije primenjuje više različith protokola terapije održavanja. Pošto u ispitivanjima uloge interferona alfa i prednizolona nije dokazana njihova jasna prednost u OS, primena talidomida u terapiji održavanja pokazala je prednost za duži EFS u nekim studijama [20, 22, 24]. U našoj studiji medijana preživljavanja nije dostignuta. Razlozi mogu biti ograničeno vreme praćenja i mali broj bolesnika.

Primena novih lekova u inicijalnoj terapiji (bortezomib, talidomid, lenalidomid) pokazala je impresivne rezultate u pogledu stepena inicijalne CR, kao i poboljšanja stepena CR nakon ASCT, dok se njihova uloga i prednost u OS u odnosu na dosadašnju inicijalnu standardnu terapiju, kao i uloga ASCT u prvoj liniji lečenja, tek proverava kroz randomizovane studije. Noviji rezultati dobijeni posle analiza dugotrajne primene ovih lekova (npr. Len-Dex posle četiri ciklusa inicijalne terapije daje trogodišnje OS kod 79% bolesnika) potvrdili su nedoumicu da li visokodoznu hemioterapiju praćenu ASCT primeniti u prvoj liniji ili nakon relapsa, što je i dalje otvoreno pitanje. Do tada transplantacija matičnih ćelija hematopoeze ostaje terapija prve linije [23, 25], zbog niskog stepena mortaliteta (1–2%), koristi u stepenu odgovora, posebno u EFS koji se kreće između 25 i 42 meseca, što predstavlja produženje od 9 do 12 meseci u poređenju sa standardnom hemioterapijom.

## Zaključak

Naši rezultati pokazuju da je ASCT korisna i pouzdana metoda lečenja MM kod bolesnika mlađih od 65 godina, posebno ako se transplantacija MĆH sprovodi u ranoj fazi lečenja nakon indukcione terapije po protokolu VAD. Primena talidomida kao terapije održavanja, utiče na bolji EFS. Naši rezultati, takođe, pokazuju da je prikupljanje autolognih MĆH za dvostruku transplantaciju potrebno učiniti tokom prvih meseci indukcione terapije.

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ORIGINAL ARTICLE

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# Frequency and characteristics of myocardial ischemia recorded during stress echocardiography in patients with high coronary risk

## Učestalost i karakteristike miokardne ishemije tokom ehokardiografskog stres testa kod asimptomatskih osoba sa visokim koronarnim rizikom

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**Abstract**

**Background/Aim.** Ischemic heart disease is the major cause of morbidity and mortality in the world as well as in our country. Ischemic heart disease has the multifactorial origin and the presence of several risk factors increases the risk of myocardial ischemia. The aim of the study was to evaluate the frequency and characteristics of myocardial ischemia in asymptomatic subjects with two or more risk factors for coronary artery disease during stress echocardiography. **Methods.** In 240 high risk asymptomatic subjects (an absolute risk of fatal cardiovascular disease of more than 5%, according to the Systemic Coronary Risk Evaluation Chart), the exercise stress echocardiography test was performed. The criterion for myocardial ischemia was the appearance of transient segmental wall motion abnormality (WMA). The wall motion score index was calculated before and after the exercise stress echocardiography. **Results.** During exercise stress echocardiography, in 36 (15%) subjects WMA occurred. Out of 36 subjects with myocardial ischemia, in 10 (27.8%) subjects WMA and ST segment depression were accompanied with the first occurrence of chest pain (the subgroup with symptomatic myocardial ischemia), in 20 (55.6%) subjects WMA and ST segment depression were detected and in 6 (16.6%) subjects only WMA occurred (the subgroup with silent myocardial ischemia). There were no significant differences between the subgroups with symptomatic and silent myocardial ischemia with regard to exercise tolerance, heart rate at the onset of WMA, and time to the onset of WMA, but the wall motion score index was significantly higher in the subjects with symptomatic myocardial ischemia ($p < 0.01$). In all the individuals with symptomatic myocardial ischemia, significant stenosis of the coronary arteries was found by coronary angiography. Out of 26 subjects with asymptomatic myocardial ischemia, coronary angiography was performed in 18 and significant stenosis of the coronary arteries was diagnosed in all of them. The number and grade of coronary stenosis in subjects with symptomatic and silent myocardial ischemia were similar. **Conclusion.** The obtained results presented the incidence of myocardial ischemia in 15% of asymptomatic subjects with high coronary risk during stress echocardiography. Silent myocardial ischemia was markedly more frequent than symptomatic one, but in the subjects with symptomatic ischemia, the wall motion score index was significantly higher.

**Key words:**
**myocardial ischemia; echocardiography, stress; risk factors.**

**Apstrakt**

**Uvod/Cilj.** Ishemijska bolest srca uzrokovana koronarnom aterosklerozom vodeći je uzrok smrti u svetu i kod nas. Mnogobrojne epidemiološke studije potvrdile su da je koronarna ateroskleroza multifaktorijalnog nastanka. Udruženost faktora rizika povećava verovatnoću pojave ishemijske bolesti srca. Otkrivanje miokardne ishemije pre njene kliničke manifestacije od velikog je značaja za prevenciju kardiovaskularnih događaja. Cilj rada bio je određivanje učestalosti i procena karakteristika miokardne ishemije kod asimptomatskih osoba sa dva ili više faktora rizika od ishemijske bolesti srca tokom ehokardiografskog stres testa. **Metode.** Kod 240 asimptomatskih osoba sa visokim rizikom (veći od 5% apsolutnog rizika od fatalnog kardiovaskularnog oboljenja, prema kriterijumima za određivanje ukupnog koronarnog rizika), urađen je ehokardiografski stres test. Kriterijum za miokardnu ishemiju bila je pojava poremećaja segmentne pokretljivosti (*wall motion abnormality* – WMA) zida leve komore. Indeks WMA izračunat je pre i posle ehokardiografskog stres testa. **Rezultati.** U stres ehokardiografskom testu kod 36 (15%) osoba registrovani su WMA zida leve komore. Iz grupe od 36 ispitanika sa miokardnom ishemijom, kod 10 (27,8%) osoba WMA bili su praćeni anginoznim bolom (koji se u testu po prvi put javio) i depresijom ST segmenta na elektrokardiogramu ishemijskog tipa (podgrupa sa simptomatskom miokardnom ishemijom), kod 20 (55,6%) osoba registrovani su WMA i depresija ST segementa, ali bez pojave anginoznog bola, a kod šest (16,6%) osoba registrovani su samo WMA (podgrupa sa asimptomatskom miokardnom ishemijom). Tolerancija fizič-

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kog napora, vreme do pojave WMA i vrednost srčane frekvencije pri pojavi WMA nisu se značajno razlikovali između osoba sa simptomatskom i osoba sa asimptomatskom miokardnom ishemijom, dok je indeks segmentne pokretljivosti zida leve komore bio značajno veći kod bolesnika sa simptomatskom miokardnom ishemijom ($p < 0,01$). Kod svih osoba sa simptomatskom miokardnom ishemijom, koronarnom angiografijom nađene su ozbiljne stenoze koronarnih arterija. Od 26 osoba sa asimptomatskom miokardnom ishemijom, koronarna angiografija urađena je kod 18 osoba i kod svih je dijagnostikovana značajna stenoze koronarnih arterija. Broj zahvaćenih arterija i stepen stenoza koronarnih arterija nije se značajno razlikovao između osoba sa simptomatskom i asimptomatskom miokardnom ishemijom. **Zaključak.** Dobijeni rezultati pokazali su učestalost miokardne ishemije 15% kod asimptomatskih osoba sa visokim rizikom od koronarne ateroskleroze tokom ehokardiografskog stres testa. Asimptomatski tip je značajno češći od simptomatskog tipa miokardne ishemije, ali kod osoba sa simptomatskom miokardnom ishemijom indeks segmentne pokretljivosti zida leve komore značajno je veći.

**Ključne reči:**
**koronarna bolest; ehokardiografija, stres; faktori rizika.**

## Introduction

Ischemic heart disease caused by coronary atherosclerosis is the leading cause of death throughout the world and in our country [1–3]. Numerous epidemiologic studies have confirmed that coronary atherosclerosis is a multifactorial disease in origin, and identification of all factors associated with increased risk for the coronary artery disease is of utmost importance [4–6]. A large number of risk factors has been described, some of which are related to lifestyles, others to biochemical or physiologic characteristics (modified risk factors), and some of them are personal characteristics of individuals (non-modified risk factors).

In the assessment of the impact of risk factors on occurrence of ischemic heart disease, multiple risk factors phenomenon play the important role. The risk of ischemic heart disease is increased in the presence of multiple risk factors. Moreover, also important are the intensity of risk factors (blood pressure value, glycemia level, number of cigarettes smoked) and duration of exposure to risk factors. The principal aim of both the doctors and their patients is to prevent atherosclerosis or to delay the disease until later in life by modification of variable risk factors [7, 8].

Myocardial infarction and sudden cardiac death are commonly the first clinical manifestations of ischemic heart disease, and in order to reduce mortality, it should be detected and treated early in its course. Exercise electrocardiography is considered to be the first method in detecting myocardial ischemia in individuals with a suspected ischemic heart disease. However, electrocardiography during exercise stress testing has relatively low sensitivity and specificity [9], so that nowadays radionuclide or echocardiography methods have been increasingly used in detecting myocardial ischemia [10–12].

The aim of the paper was to establish the frequency and assess the characteristics of myocardial ischemia in asymptomatic subjects with two or more risk factors for ischemic heart disease during stress echocardiography test (SET).

## Methods

The study enrolled 240 subjects (160 men and 80 women, mean age $53.5 \pm 6.8$ years). The inclusion criteria were as follows: age from 40 to 65 years, absence of anginal pain or its equivalent, absence of contraindications for exercise test, without diagnosis of ischemic heart disease, presence of two or more risk factors for coronary atherosclerosis lasting at least five years (arterial hypertension: blood pressure $\geq 140/90$ mmHg, active smoking, type 2 diabetes mellitus, and hypercholesterolemia: total cholesterol $\geq 5$ mmol/L). All of the examined subjects had high values of risk (more than 5% of absolute risk for a fatal cardiovascular event in a period of ten years, according to the Systemic Coronary Risk Evaluation Criteria – SCORE) [13]. The study did not enroll the patients with symptomatic or asymptomatic left ventricular dysfunction, complex and frequent ventricular arrhythmias, atrial fibrillation, conduction abnormalities, ST segment changes, T wave changes suspect of myocardial ischemia, and subjects with technically poor two-dimensional echocardiographic image.

In all the examinees SET was performed on bicycle ergometer in a sitting position, with the initial workload of 25 W and progressive increases of 25 W every four minutes. Maximal exercise test was performed, and test was stopped earlier in cases of ischemic chest pain of increasing intensity, left ventricular wall motion abnormality (WMA), complex ventricular arrhythmias, high blood pressure values ($\geq 220/120$ mmHg). Before and during the exercise and in the period of rest, 12-lead electrocardiography and 2D echocardiography (Acuson – Sequoia C256, Mountain View, CA USA, Harmonic mode) were continually recorded. Heart rate and blood pressure values were measured before SET, at the end of each workload level, and in the period of rest. For the purpose of echocardiographic analysis of segmental motion, the left ventricle was divided into 11 segments, according to the model by Edwards et al. [14], modified so that apex represented one segment. Segmental wall motion was analyzed and numerically scored as follows: 1 = normo/hyperkinesia; 2 = hypokinesia; 3 = akinesia; 4 = dyskinesia. Segmental wall motion score index (WMSI) was obtained by dividing the sum of scores with the number of segments of the left ventricle. WMSI was calculated before and at the end of SET. The criterion for myocardial ischemia was the onset of left ventricle segmental WMA.

The results were presented as means with standard deviations. The student's *t*-test with a statistically significant cutoff of $p < 0.05$ was used to assess the statistical significance of parameters observed.

**Results**

Most common risk factors for coronary disease were smoking and arterial hypertension (Table 1).

**Table 1**

**Frequency of risk factors in the examined subjects**

| Risk factors | Patients | |
|---|---|---|
| | n | % |
| Male | 160 | 67 |
| Smoking | 186 | 78 |
| Arterial hypertension | 172 | 72 |
| Hypercholesterolemia | 98 | 41 |
| Diabetes mellitus type 2 | 74 | 31 |
| Two risk factors | 43 | 18 |
| Three risk factors | 145 | 60 |
| Four risk factors | 52 | 22 |

Left ventricular wall motion analysis before SET demonstrated normal segmental motion in all our subjects. During the test, WMA were detected in 36 (15%) examinees, while in 204 subjects there were no new WMA during SET. In the group without WMA, there was no anginal pain or its equivalent, but in 15 (6%) subjects ST segment depression was recorded on electrocardiogram during exercise.

In the group of 36 patients with myocardial ischemia on SET, WMA were associated with anginal pain (occurring for the first time during the exercise stress test) and ischemic type of ST segment depression on ECG in 10 (27.8%) patients (the subgroup of those with symptomatic myocardial ischemia). WMA and ST segment depression, without anginal pain, were detected in 20 (55.6%), and only WMA was detected in 6 (16.6%) patients (these 26 individuals comprised the group with asymptomatic myocardial ischemia), (Table 2).

Asymptomatic myocardial ischemia was significantly more frequent in the diabetic patients (Figure 1).

The level of physical workload and SET duration, time to WMA, and value of heart rate at the onset of WMA were not significantly different between those with symptomatic and those with asymptomatic myocardial ischemia (Table 3). The value of ST segment depression in our stress test (mean value of ST segment depression in all ECG leads) did not differ significantly between the patients with symptomatic and those with asymptomatic myocardial ischemia (Table 3).

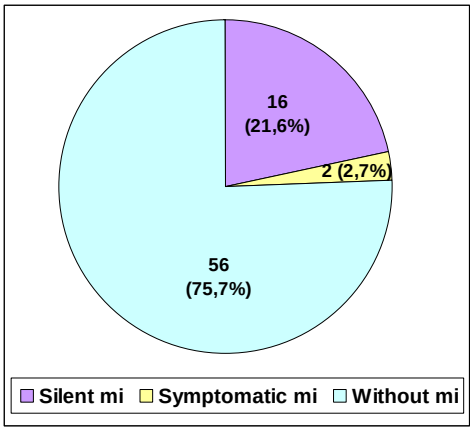


**Fig. 1 – Frequency of symptomatic and asymptomatic myocardial ischemia (MI) in the patients with diabetes mellitus type 2**

The wall motion score index was significantly higher in the patients with symptomatic than in those with asymptomatic myocardial ischemia in SET (Figure 2).

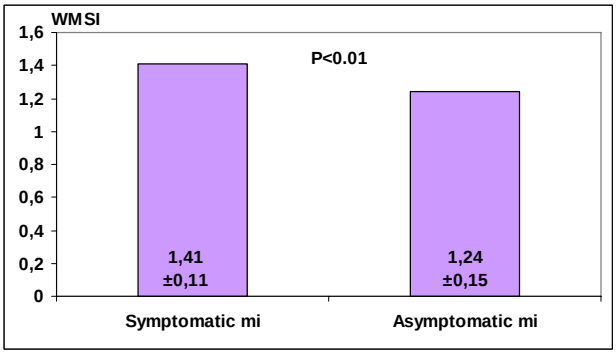


**Fig. 2 – Wall motion score index (WMSI) in the patients with symptomatic and asymptomatic myocardial ischemia (MI)**

**Table 2**

**Markers of myocardial ischemia during stress echocardiography test**

| Markers of myocardial ischemia | Patients | |
|---|---|---|
| | n | % |
| WMA+ ST↓ + chest pain | 10 | 27.8 |
| WMA+ ST↓ | 20 | 55.6 |
| WMA | 6 | 16.6 |

**WMA – wall motion abnormality; ST↓ – ST segment depression**

**Table 3**

**Parameters of stress echocardiography in the patients with symptomatic and asymptomatic myocardial ischemia (MI)**

| Parameters | Symptomatic MI $\bar{x} \pm SD$ | Asymptomatic MI $\bar{x} \pm SD$ |
|---|---|---|
| Level of physical workload (W) | 82 ± 12.6 | 78 ± 10.8 |
| Duration of stress (min) | 13.9 ± 2.9 | 12.7 ± 2.7 |
| HR at onset WMA (beats/min) | 124.3 ± 12.8 | 121.2 ± 13.7 |
| Time to onset WMA (min) | 11.0 ± 3.5 | 10.4 ± 3.8 |
| ST segment depression (min) | 2.4 ± 0.3 | 2.5 ± 0.4 |

**HR – heart rate; WMA – wall motion abnormality**

In all patients with symptomatic myocardial ischemia, significant coronary artery stenoses were found by coronary angiography. Out of 26 patients with asymptomatic myocardial ischemia, coronary angiography was done in 18 (8 patients did not accept the suggested diagnostic procedure) and in all of them significant stenosis of the coronary arteries was diagnosed. Angiographic finding of stenosis of the coronary arteries matched the registered WMA in SET. The number of involved arteries and degree of coronary artery stenosis was not significantly different between the patients with symptomatic and those with asymptomatic myocardial ischemia.

**Discussion**

Anginal pain is the most important symptom in the clinical presentation of ischemic heart disease, but it is commonly absent, and its first clinical manifestation can be acute myocardial infarction or a sudden cardiac death. Numerous studies performed in recent decades have shown that asymptomatic myocardial ischemia is very common in coronary patients, with prognostic significance similar to symptomatic ischemia [15–17]. Early detection of myocardial ischemia is of utmost importance for prevention of adverse cardiac events in patients with ischemic heart disease [18].

In individuals with high risk of coronary atherosclerosis and without symptoms and/or signs of ischemic heart disease, the procedures should be undertaken to detect coronary disease before it becomes clinically evident. Exercise test is the first method to detect ischemic heart disease in asymptomatic individuals [11]. If the symptoms of coronary disease do not occur during the test and ischemic changes cannot be identified in ECG, the existence of coronary disease can be excluded with a high degree of probability. In such individuals periodic retesting is required, together with modification of risk factors. However, ECG changes identical to those in myocardial ischemia can be sometimes observed in persons without the disease (false positive ECG finding in exercise test). In order to overcome the limitations of ECG in exercise test, and in view of the well-known sequence of events in an ischemic cascade [19], echocardiographic observation of the left ventricular wall motion has been increasingly used in recent years to detect myocardial ischemia. At the Institute for Treatment and Rehabilitation in Niška Banja stress echocardiographiy has been done since 1990 in order to detect myocardial ischemia, to monitor the course of ischemic heart disease, or to observe the effects of medicament and/or surgical treatment [20, 21].

In this study, by assessment of segmental wall motion of the left ventricle in completely asymptomatic subjects during SET, WMA was detected in 36 (15%) patients. Coronary angiography, done in 28 out of 36 patients with WMA during SET, revealed significant stenoses of coronary arteries. In 15 (6%) individuals ST segment depression was detected in the absence of left ventricular WMA (false positive ECG finding), and in six persons there were abnormalities of segmental motion in the absence of ECG signs of ischemia (false negative ECG finding). This finding clearly confirmed the advantage of SET over electrocardiography during exercise testing to detect myocardial ischemia.

Symptomatic myocardial ischemia, detected for the first time in the subgroup of our patients with myocardial ischemia is significantly rarer compared to asymptomatic disease, which can be explained by the selection of tested subjects. The absence of coronary disease symptoms during everyday activities in these persons can be explained by a lower level of workload than in exercise tests.

Asymptomatic myocardial ischemia is a common type of ischemia in coronary patients. It can be observed in completely asymptomatic individuals (type I), those with survived myocardial infarction (type II), and patients with episodes of symptomatic or asymptomatic myocardial ischemia (type III) [22]. Asymptomatic myocardial ischemia has a prognostic significance in coronary patients similar to symptomatic ischemia [23, 24]. The frequency of asymptomatic myocardial ischemia in asymptomatic population is not known, but its detection is of an utmost importance regarding the prevention of cardiovascular events. Stress echocardiography has been proven to be more sensitive, more specific, and diagnostically more accurate compared to exercise testing detecting myocardial ischemia [25]. However, stress echocardiography screening of the general population is expensive, so that stress echocardiography should be reserved for individuals with higher probability of coronary disease – these are asymptomatic individuals with a high coronary risk [11]. On that account, in order to establish the frequency of myocardial ischemia, we selected the individuals with an absolute risk of over 5% for fatal cardiovascular disease.

The reason why myocardial ischemia is not accompanied by pain in some patients is the question that still awaits a full explanation. Some studies have shown that the episodes of asymptomatic myocardial ischemia are of lower intensity and never reach the "anginal threshold" [26, 27]. There is some evidence of no difference between symptomatic and asymptomatic episodes of myocardial ischemia in the parameters of severity of the disease, including the number of involved coronary arteries and the degree of stenosis of coronary arteries, the magnitude of ST depression in exercise tests, or the degree of reversible thallium defects during exercise [10].

In our study, the parameters obtained during SET (level and duration of stress, time to WMA, and heart rate at the onset of WMA) did not differ significantly between the persons with symptomatic and those with asymptomatic myocardial ischemia. However, the index of WMA is significantly higher in patients with symptomatic myocardial ischemia, indicating a higher degree of myocardial ischemia.

The diseases accompanied by autonomous neuropathy, such as diabetes, are traditionally regarded as responsible for the manifestation of asymptomatic myocardial ischemia. There are contradictory data on asymptomatic ischemia in diabetic patients. Some studies have confirmed a higher prevalence of asymptomatic ischemia in stress tests or during Holter monitoring in diabetics [28, 29]. Study of Caracciolo et al. [30] has shown similar frequencies of symptomatic and

asymptomatic myocardial ischemia in diabetics. In our patients, asymptomatic myocardial ischemia was significantly more common in the individuals with diabetes.

Our study demonstrated that asymptomatic myocardial ischemia is common in subjects with a high coronary risk. Although the etiopathogenesis of asymptomatic ischemia has not been fully elucidated, it can be said with certainty that it is not a benign ischemia and that it has prognostic effects similar to symptomatic ischemia. It is therefore necessary to look for myocardial ischemia in any individual with a higher number of risk factors for coronary disease.

**Conclusion**

The results obtained in this study demonstrated a frequency of myocardial ischemia of 15% in asymptomatic subjects with two or more risk factors for coronary atherosclerosis during stress echocardiography. Asymptomatic myocardial ischemia is more frequent than symptomatic one. Asymptomatic myocardial ischemia is more common in patients with type 2 diabetes.

Exercise tolerance, time to the onset of WMA, and magnitude of ST segment depression in stress echocardiography did not differ significantly between the patients with symptomatic and asymptomatic myocardial ischemia, while the wall motion score index of the left ventricle was significantly higher in patients with symptomatic myocardial ischemia. The number of involved arteries and degree of stenosis of coronary arteries were similar in patients with symptomatic and asymptomatic myocardial ischemia.

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# Unstable intertrochanteric fractures: How to prevent uncontrolled impaction and shortening of the femur

## Nestabilni intertrohanterni prelomi: kako sprečiti nekontrolisanu impakciju i skraćenje femura

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**Abstract**

**Background/Aim.** Unstable intertrochanteric (IT) fractures, especially fractures with a reverse or transverse fracture line, have tendencies to make significant impaction on shortening of the femoral neck and lower extremity. The biomechanical complexity of the fracture, the type and the position of the implant are known to influence postoperative outcome. The aim of this study was to compare characteristics of two versions of dynamic hip implants in controlling the dynamization of unstable IT fractures of the femur. **Methods.** In the prospective study that included 1,115 patients with fractures of the proximal femur, 61 patients had IT fractures with a reverse or transverse fracture line. All the patients were treated surgically with the same implant in two versions: Dynamic Hip Screw – DHS-MB-S implant with a rigid part of standard length (40 mm) and DHS-MB-I implant, with a rigid part of the implant individualized for each patient depending on the transverse diameter of the proximal femur. The patients were under gradual radiographic and clinical control. Six months postoperatively we measured the length of the extremity and the degree of the medialization of the distal part of the femur. **Results.** All the fractures healed six months after the operation. Medialization and shortening of the extremity were significantly less in the group with fractures fixed by the DHS-MB-I implant, in which length of the rigid part of the implant was preoperatively measured individually for each patient. **Conclusion.** In order to achieve a desired functional result, the control of dynamisation in unstable IT fractures is significant in the fixation of these fractures of the femur. We presented possible methods to realize it by the contact of the rigid part of our implant with medial cortex of the proximal fragment of the femur.

**Key words:**
**hip fractures; orthopedics; prostheses and implants; contracture; movement; prognosis.**

**Apstrakt**

**Uvod/Cilj.** Nestabilni intertrohanterni (IT) prelomi, naročito frakture sa reverznom ili poprečnom frakturnom linijom, imaju tendenciju ka značajnoj impakciji i skraćenju femoralnog vrata i donjeg ekstremiteta. Kompleksnost preloma, tip i položaj implantata mogu značajno da utiču na postoperativni ishod lečenja. Cilj ove studije bio je da se uporede karakteristike dve verzije dinamičkog implantata kuka u kontroli dinamizacije nestabilnih IT preloma femura. **Metode.** U prospektivnoj studiji koja je uključila 1 115 bolesnika sa prelomom proksimalnog dela butne kosti, 61 bolesnik imao je IT prelom sa reverznom ili transverznom frakturnom linijom. Svi bolesnici lečeni su hirurški istim tipom implantata u dve verzije: *Dinamic Hip Screw* – DHS-MB-S implantat sa standardnom dužinom krutog dela (40 mm) i DHS-MB-I implantat, čiji je kruti deo prilagođen svakom bolesniku zavisno od transverzalnog prečnika proksimalnog femura. Bolesnici su kontrolisani u pravilnim vremenskim razmacima, klinički i radiografski. Šest meseci postoperativno merili smo dužinu ekstremiteta i stepen medijalizacije distalnog dela femura. **Rezultati.** Sve frakture zarasle su tokom šest meseci od operacije. Medijalizacija i skraćenje femura bili su značajno manje izraženi u grupi u kojoj su frakture fiksirane DHS-MB-I implantatom, u kojoj je dužina krutog dela implantata preoperativno merena individualno, za svakog bolesnika ponaosob. **Zaključak.** U cilju postizanja željenih funkcionalnih rezultata, kontrola dinamizacije kod nestabilnih IT preloma je značajna za fiksaciju ovih fraktura. Pokazali smo da je kontaktom krutog dela implantata sa medijalnim korteksom proksimalnog fragmenta moguće uspešno kontrolisati dinamizaciju i tako sprečiti nepoželjnu medijalizaciju i skraćenje donjeg ekstremiteta.

**Ključne reči:**
**kuk, prelomi; ortopedija; proteze i implantati; kontraktura; pokretljivost; prognoza.**

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**Introduction**

Fixation of unstable intertrochanteric (IT) fractures still does not completely solve the problem. Operative procedures for the reduction and fixation of IT fractures are technically challenging. Reoperation rates of 4% to 12% have been reported following the standard technique of fixation with a sliding compression hip screw [1–5].

Using fixation with dynamic characteristics leads to a significant interfragmentary transfer of the load and the decrease of postoperative complications. The deficiency of this fixation method is seen in uncontrolled impaction of main fragments and shortening of the femur neck in unstable fractures (AO/OTA 31-A3) [6] with a significant comminution of the posteromedial cortex [2, 4].

In unstable IT fractures with a reverse fracture line there is no bone barrier, which leads to uncontrolled medialisation of the distal fragment. Attempts to solve this problem with rigid implants have added lateral barriers on the implant itself, implants with biaxial dynamisation and intramedullary implants have not given a definite solution and have been followed by complications [3, 4, 7–9].

The way we deal with this problem introduces a new concept of controlled impaction and dynamisation. The concept has been realized by introducing an implant which can control the process of impaction and medialisation of the distal fragment. This process is made by the contact of the rigid part of the implant and the medial cortex of the proximal fragment.

We have not so far found in literature any other attempt to use the cortical structure of the medial cortical complex of the proximal fragment in fixation of IT fractures.

We designed a new dynamic hip implant that rigidly controls rotation of the proximal fragment of the fractured femur with two parallel head neck screws [10]. Besides that, the implant can control the level of impaction and medialisation of the distal fragment which is achieved by the contact of the rigid part of the implant and the medial cortex of the neck. Choosing different lengths of the rigid part of the implant allows individualization of the contact of the femur and the implant [11].

**Methods**

From 1995 to 2001 a total of 1,115 patients with a hip fracture were treated in the Orthopaedic-Trauma Ward of the General Hospital in Požarevac. There were 705 extracapsular fractures in 682 patients. In the study group, 61 fractures were classified as one out of three types of AO/OTA 31-A3. From the whole number of proximal femur fractures (1,115), 5% belonged to this type, in comparison to all IT fractures (682) which was 9%. All IT fractures were fixed by the below described implant (DHS-MB) [10].

The operation was performed on a patient in the supine position. We approached the lateral aspect of the proximal femur by a lateral incision which begins about 6 to 8 cm distally to the greater trochanter along the shaft of the femur. The incision is as long as the part of the implant that lies on the femoral shaft. Reduction of fracture and radiographic control preceded fixation.

First, we introduced a guide wire under the angle of 135º. The optimal position of the wire is in the lower third of the femoral neck and head in the antero-posterior (AP) projection and centrally in the lateral projection (Figure 1a).

The rest of the procedure was done by a pattern and was very easily carried out. Next, we did perforation of holes on the lateral cortex and application of the self-cutting canullated nail (6 mm in diameter) (Figure 1b).

On the self-cutting nail we slided a specially designed drill guide that made it possible to perforate a hole 11 mm in diameter (Figure 1c, middle). Processing the two holes resulted in a definitive oval-shaped perforation on the lateral cortex with the guide nail in the distal third (Figure 1c, right). Then, we did application of the implant. Its fixation to the femur shaft with cortical screws, application of the proximal head-neck screw and replacing of the guide nail with the distal head-neck screw we showed at Figure 1d.

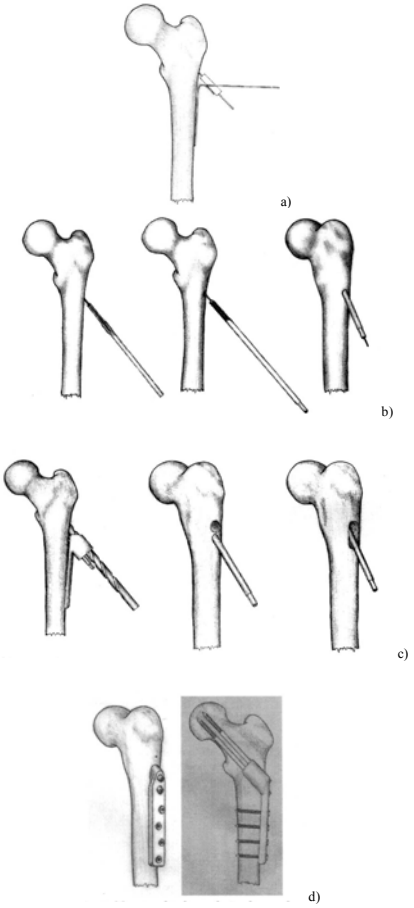



**Fig. 1 – a) Introducing a guide wire; b) introducing a self cutting canullated nail; c) making a proximal perforation; d) final implant application**

The rigid part of the implant was shaped like a wedge-plate of 135º angle. The proximal wedge was like a console that has two parallel self-cutting screws of 6 mm diameter at the distance of 4 mm. The lateral side of the plate had 2–12 perforations for cortical screws. Femoral head-neck screws

were placed subchondrally. They had to control varus, anteversion, retroversion and rotation of the proximal fragment. Femoral head-neck screws have an unrestrained possibility of telescoping.

The two different versions of the implant were used: implant with a standard length of the rigid part (DHS-YU-S) of 40 mm (Figure 2a), and implant with individualised length of the rigid part (DHS-YU-I) (Figure 2b). The lenght of the implant was determined as follows. It is known that the form

We assessed the patients' mental condition [12, 13], physical status [14, 15], social status [16], and the ability to walk before surgery [17].

All the fractures were reduced by closed reduction, by traction and external or internal rotation.

We defined position of the implants in two plains by operative radiography (in the anterior – posterior view: in the upper third, centrally and in the lower third of the proximal fragment; in the lateral view: in front, centrally and back).

**a)**

**b)**

**Fig. 2 – Implant with standard length rigid part (DHS-YU-S) of 40 mm (a) and Implant with individualized length rigid part of the implant (DHS-YU- I) (b)**

and length of the proximal wedge make contact between the rigid part of the implant and the medial cortex of the proximal fragment possible, so the implant can control medialisation of the distal fragment and impaction of major fractural fragments.

On the preoperative AP radiography of the healthy femur, we measured the diameter of the proximal femur (a) (Figure 3).

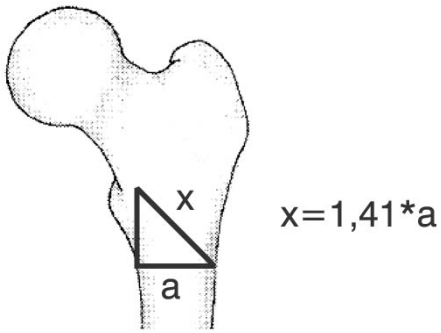



**Fig. 3 – The distance (x) is calculated by using the formula**
**$x^2 = 2 * a^2 \rightarrow$ $x = \sqrt{2} * \sqrt{a^2} \rightarrow$ *$x = 1{,}41 * a$***

On the basis of the formula:

$$x^2 = 2 * a^2 \rightarrow x = \sqrt{2} * \sqrt{a^2} \rightarrow x = 1{,}41 * a$$

the distance (x) was calculated which, in fact, represents the optimal length of the rigid part of the implant that achieves contact with the medial cortex of the proximal femur and disallows unwanted impaction and dynamisation [11].

On the second postoperative day, the patients were allowed full-weight bearing (without restriction) on the operated leg.

Patients were under gradual radiographic and clinical control at the three points in time: at six weeks and then at three and six months.

Six months after the surgery, postoperative radiographs were used to measure the diameter of the proximal femur in AP projection. Its length was shown in mm. The percentage of medialisation of the distal fragment was assessed in relation to the diameter of the proximal femur [18–20]. Also, six months after the surgery, destabilization of fracture was notified and the length of the extremity was clinically measured.

The data were analyzed by the $\chi^2$ test with the Yates correction and Student's *t*-test for small independent samples. The *p* values < 0.05 were considered to be significant.

## Results

There was no statistically significant difference between the two studied groups regarding age, gender, value of the mini mental test and prefracture mobility test (Table 1).

There were no statistically significant differences in the anterior – posterior orientation of the implant between the studied groups. In the lateral view, in the patients with fractures fixed by the DHS-MB-S implant, there was a statistically significantly larger number of cases with the implant

**Table 1**

**The data on the patients**

| Patients caracteristics | DHS-MB-S (n = 28) | DHS-MB-I (n = 24) | *p* |
|---|---|---|---|
| Age (years), $\bar{x} \pm SD$ | 71 ± 3.9 | 73 ± 4.8 | |
| Sex (n) | | | |
| female | 16 | 12 | |
| male | 12 | 12 | |
| ASA [14] (n) | | | |
| I | 9/28 | 3/24 | |
| II | 13/28 | 17/24 | |
| III | 4/28 | 4/24 | |
| Mini mental test score [12, 13], $\bar{x} \pm SD$ | 11 ± 1.5 | 12 ± 1.3 | |
| Type of fracture (n) | | | |
| A3.1 | 6/28 | 3/24 | |
| A3.2 | 12/28 | 10/24 | |
| A3.3 | 10/28 | 11/24 | |
| Placement of the implant (n) | | | |
| AP | | | |
| up | 1/28 | 2/24 | |
| central | 6/28 | 5/24 | |
| down | 21/28 | 17/24 | 0.041† |
| LL | | | |
| forward | 0/28 | 0/24 | |
| central | 18/28 | 22/24 | |
| back | 10/28 | 2/24 | |
| Mobility score [17], $\bar{x} \pm SD$ (before fracture) | | 8.6 ± 2.1 | 8.6 ± 1.9 |
| Jensen index [16] (n) | | | |
| I | 21/28 | 18/24 | |
| II | 6/28 | 6/24 | |
| III | 1/28 | 0/24 | |

****t*-test; †$\chi^2$ test; ASA – American Society of Anesthesiology; AP – anterior-posterior projection; LL – lateral projection**

**Table 2**

**Parameters after surgery using two modifications of implants**

| Parameters | DHS-YU-S (n = 28) | DHS-YU-I (n = 28) | *p* |
|---|---|---|---|
| Medialization (%) | 32.29 | 5.18 | 0.127* |
| Length of the extremity (n) | | | |
| shortening | 20/28 | 2/24 | 0.023† |
| without changes | 8/28 | 19/24 | |
| lengthening | 0/28 | 3/24 | |
| Mobility score [17], $\bar{x} \pm SD$ (six months after surgery) | 7.0 ± 2.3 | 7.6 ± 1.8 | |

****t*-test; †$\chi^2$ test**

oriented to the posterior, in comparison to the patients with fractures fixed by the DHS-MB-I implant.

From 1995 to 1998, fractures were stabilized with implant of standard rigid part length of 40 mm (DHS-YU-S) (Figure 3a).

In this group of the patients, 34 fractures were classified as one of three types of AO/OTA 31-A3. Six patients died within six months, the remaining 28 patients were studied.

From 1999 to 2001, we determined the length of the proximal part of the plate (console) in relation to the diameter of the proximal femur (DHS-MB-I) (Figure 3b). We classified 27 fractures as AO/OTA 31-A3 in this group. Three patients died within six months. We had the final results in 24 patients.

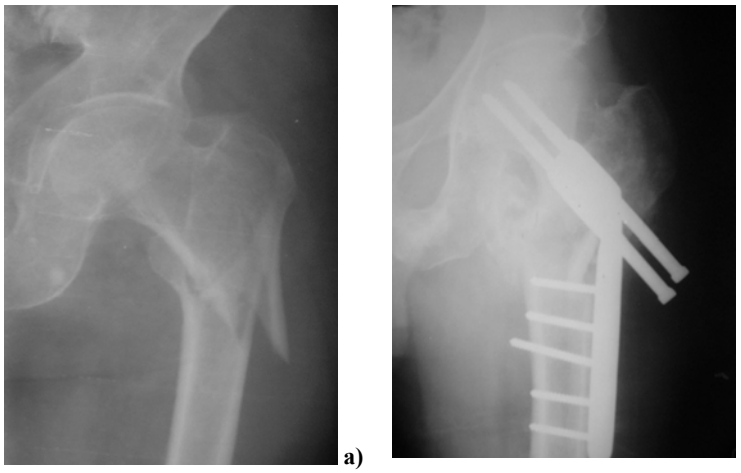
There was no statistically significant difference between the two studied groups in relation to the type of fracture.

There was deep infection in one patient from the DHS-YU-I implant group. The fracture was consolidated and the infection was surgically treated after removal of the implant. In one patient from the DHS-YU-I implant group, diaphyseal destabilization occurred, but without repercussion to the healing of the fracture or the function of the lower extremity within six months.

A significant average of medialization occurred in the group of fractures stabilized with the DHS-YU-S implant (32% of the proximal femur diameter), did not cause destabilization and lack of the healing process of the fracture, but this medialization caused a significant average shortening of the extremity. Also, different application in the implant in lateral view did not have an influence in the sense of destabilization and the healing process.

In the group of fractures stabilized with the DHS-YU-I implant, individualization of length of the rigid part of the implant caused a significant reduction of the average medialisation (5% diameter of the proximal femur) which produced lower levels of extremity shortening (Figures 5 a–d).

The average values of the mobility score after the surgery show that there were no statistically significant differences between the studied groups of patients.



a) b)

**Fig. 4 – Radiography of IT fracture with reverse line: a) preoperative radiography of IT fracture with a reverse line; b) six months after the surgery (consolidation with significant medialisation)**

a) b) c) d)

**Fig. 5 – Radiography of intratrochonteric fracture with a reverse line: a) preoperative finding; b) intraoperative finding; c) finding six month after the surgery; d) finding after the removal of the implant (consolidation without significant medialisation)**

**Discussion**

In previously published studies, the incidence of the fracture type AO/OTA 31-A3 is comparable with our findings: Brammar et al. [18] reported 3% of the sum-total of hip fractures and 7% of the sum-total of extracapsular fractures and Haidukewych et al. [19] 5% of extracapsular fractures.

Early destabilization and pseudoarthrosis are known complications in treatment of unstable IT fractures [18–21].

Complications as destabilization and the lack of healing process of fractures did not occur in our study.

Medialization of the distal fragment was statistically significantly higher in the group of patients with the DHS-YU-S implant. In the group of patients with the DHS-YU-S implant, the percentage of patients in whom the shortening of the lower extremity occurred was statistically significantly higher than in those with the DHS-YU-I implant, too. The number of patients in the DHS-YU-I group in whom neither the shortening nor the lengthening of the lower extremity occurred six months after the operation was statistically significantly higher in comparison to the DHS-YU-S group of patients.

Rotation control of the proximal fragment is crucial in the fixation of unstable intertrochanteric fractures (AO/OTA 31-A). This control can be implemented by applying two or more parallel screws that make close contact with the femoral head. Also, it is important to control medialisation gained by the contact of the rigid part of the implant with the internal side of the medial cortex (medial, anteromedial or posteromedial). The medial cortex of the proximal femur is a very compact structure whose significance has been neglected up to now. By achieving the intimate contact of the medial cortex and the rigid part of the implant by the most favourable way under the angle of 135º, we transfer the load to the lateral cortex. The implant dynamic part allows close and continuous contact of the medial cortex and the rigid part of the implant without any danger of breaching (selfcutting) the femoral head.

In this way, all advantages of dynamization are used and the unwanted effect of medialisation of the distal fragment is prevented. According to the suggested solution, dynamization can be planned before surgery by choosing an adequate length of the rigid part of the implant and the extremity shortening can be prevented.

A parallel study that suggests fixation of IT fractures with other methods of fixation, above all with intramedullary implants, waits to be reported.

## Conclusion

In order to achieve a desired functional result, the control of dynamization in unstable IT fractures is significant in the fixation of IT fractures of the femur. We presented possible methods to realize it by the contact of the rigid part of our implant with medial cortex of the proximal fragment of the femur.

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# Mini-sternotomija: preliminarno iskustvo u valvularnoj hirurgiji srca

## Ministernotomy: A preliminary experience in heart valve surgery

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**Apstrakt**

**Uvod/Cilj.** Poslednja decenija 20. veka donela je značajan napredak u razvoju mini invazivnih pristupa u hirurgiji srčanih valvula. Potencijalne prednosti ovih pristupa uključuju dobar estetski aspekt, smanjenu bolnost, redukciju krvarenja i mogućnosti infekcije, kraći boravak u jedinici intenzivne nege i kraću hospitalizaciju. Parcijalna gornja sternotomija je trenutno metoda izbora za minimalno invazivnu hirurgiju srčanih valvula. Cilj rada bio je prikaz preliminarnih rezultata pristupa kroz gornju parcijalnu mini-sternotomiju u hirurgiji mitralnih i aortnih valvula. **Metode.** Ova prospektivna studija obuhvatila je sve bolesnike operisane pristupom kroz parcijalnu gornju sternotomiju u periodu novembar 2008 – avgust 2009. Analizirani su podaci o prosečnoj starosti bolesnika, prosečnom vremenu do ekstubiranja, prosečnom gubitku krvi na dren, prosečnoj dužini hospitalizacije i učestalosti postoperativnih komplikacija (krvarenje, infekcija operativnog mesta, cerebrovaskularni inzult). **Rezultati.** U posmatranom periodu u Klinici za kardiovaskularnu hirurgiju Instituta za kardiovaskularne bolesti Vojvodine u Sremskoj Kamenici izvedeno je 17 mini-sternotomija, pri čemu je izvršena zamena aortne valvule kod 14 bolesnika (82,35%), a mitralne valvule kod 3 bolesnika (17,65%). Prosečna starost bolesnika iznosila je 60,78 ± 12,99 godina (bilo je 64,71% muškaraca i 35,29% žena). Prosečno vreme do ekstubacije iznosilo je 12,53 ± 8,87 časova sa 23,5% bolesnika ekstubiranih za manje od 8 časova. Prosečna dužina hospitalizacije iznosila je 12,35 ± 10,17 dana (kod 29,4% bolesnika manje od 8 dana). Prosečan gubitak krvi na dren iznosio je 547,06 ± 335,2 mL. Postoperativne komplikacije bile su krvarenje (5,88%) i cerebrovaskularni inzult (5,88%). Konverzija u punu sternotomiju učinjena je kod jednog bolesnika (5,88%). **Zaključak.** Parcijalna gornja središnja sternotomija omogućuje optimalan hirurški pristup za intervencije na čitavoj ascendentnoj aorti (uključujući aortni zalistak) i mitralnom zalisku kroz krov leve pretkomore i ima nekoliko značajnih prednosti u odnosu na klasičan pristup totalnom sternotomijom.

**Ključne reči:**
**zalisci srca, bolesti; zalistak, aortni; zalistak, mitralni; lečenje; hirurgija, minimalno invazivne procedure; lečenje, ishod.**

**Abstract**

**Background/Aim.** The last decade of the 20th century brought up a significant development in the field of minimally invasive approaches to the valvular heart surgery. Potential benefits of this method are: good esthetic appearance, reduced pain, reduction of postoperative hemorrhage and incidence of surgical site infection, shorter postoperative intensive care units (ICU) period and overall in-hospital period. Partial upper median sternotomy currently presents as a state-of-the art method for minimally invasive surgery of cardiac valves. The aim of this study was to report on initial experience in application of this surgical method in the surgery of mitral and aortic valves. **Methods.** The study was designed and conducted in a prospective manner and included all the patients who underwent minimally invasive cardiac valve surgery through the partial upper median sternotomy during the period November 2008 – August 2009. We analyzed the data on mean age of patients, mean extubation time, mean postoperative drainage, mean duration of hospital stay, as well as on occurance of postoperative complications (postoperative bleeding, surgical site infection and cerebrovascular insult). **Results.** During the observed period, in the Institute for Cardiovascular Diseases of Vojvodina, Clinic for Cardiovascular Surgery, 17 ministernotomies were performed, with 14 aortic valve replacements (82.35%) and 3 mitral valve replacements (17.65%). Mean age of the patients was 60.78 ± 12.99 years (64.71% males, 35.29% females). Mean extubation time was 12.53 ± 8.87 hours with 23.5% of the patients extubated in less than 8 hours. Mean duration of hospital stay was 12.35 ± 10.17 days (in 29.4% of the patients less than 8 days). Mean postoperative drainage was 547.06 ± 335.2 mL. Postoperative complications included: bleeding (5.88%) and cerebrovascular insult (5.88%). One patient (5.88%) required conversion to full sternotomy. **Conclusion.** Partial upper median sternotomy represents the optimal surgical method for the interventions on the whole ascendant aorta (including aortic valve) and mitral valve through the roof of the left atrium, with a few significant advantages compared to the full sternotomy surgical approach.

**Key words:**
**valvular heart diseases; aortic valve; mitral valve; therapeutics; surgical procedures, minimally invasive; treatment outcome.**

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**Uvod**

Konvencionalna valvularna hirurgija srca podrazumeva klasičan pristup kroz punu sternotomiju, upotrebu kardiopulmonalnog *bypass*-a (CPB) i zamenu ili reparaciju obolele valvule. Medijalna sternotomija predstavlja standardni metod pristupa srcu i velikim krvnim sudovima tokom poslednjih 50 godina. Takav pristup omogućava izuzetno dobru eksponiranost svih srčanih struktura uz lak pristup ascendentnoj aorti i aortoj valvuli [1].

Jasan uspeh laparoskopije u abdominalnoj hirugiji tokom poslednje decenije 20. veka podstakao je interes, kako kardiohirurga, tako i bolesnika za minimalno invazivnu hirurgiju srca. Cosgrove i sar. [2] bili su prvi koji su izvestili o minimalno invazivnom pristupu prilikom zamene aortnog zaliska uz desnu parasternalnu inciziju. Drugi minimalno invazivni pristupi koji su usledili razvijani su sa tendencijom daljeg smanjivanja dužine reza. Taj period doneo je značajan napredak u razvoju manje invazivnih pristupa u hirurgiji srčanih valvula [1, 3]. Potencijalne prednosti ovih pristupa uključuju dobar estetski aspekt, smanjenu bolnost, redukciju krvarenja i mogućnosti infekcije, kraći boravak u jedinici intenzivne nege i trajanje hospitalizacije, kao i sniženje troškova lečenja [4–8]. Međutim, smanjenje veličine operativnog polja može povećati tehničku zahtevnost hirurške procedure. Da bi operativna tehnika bila uspešna, neophodne su adekvatna preglednost i dostupnost, a mini invazivni pristup srcu ne sme kompromitovati kvalitet operacije.

Inicijalni pokušaji mini invazivnih hirurških tehnika pristupa srčanim valvulama bili su vezani za desnu parasternalnu inciziju. U većini slučajeva, ta incizija omogućavala je dobar pristup aortnoj valvuli. Nedostaci tog pristupa uključivali su žrtvovanje desne *arteriae thoracicae internae*, čestu potrebu za femoralnom kanulacijom, kasnije otežanu konverziju u totalnu sternotomiju i povremenu postoperativnu nestabilnost zida grudnog koša [9–11]. Kasnije se pokazalo da transverzalna transsekciona sternotomija u nivou drugog interkostalnog prostora omogućava bolju ekspoziciju aortnog korena [12]. Takva incizija zahtevala je žrtvovanje obe unutrašnje grudne arterije i bilo je teško konvertovati je u punu sternotomiju, uz relativno čest razvoj kasne nestabilnosti zida grudnog koša.

Iako su dve prethodno spomenute tehnike bile uspešne, imale su i značajne nedostatke. Dalja iskustva pokazala su da je parcijalna gornja sternotomija metoda izbora [1, 12]. Parcijalna gornja sternotomija do nivoa četvrtog međurebarnog prostora omogućava pristup poznatom operativnom polju i laku centralnu kanulaciju. Ukoliko je neophodna, konverzija u punu sternotomiju je laka. Središnja struktura, aortna valvula, nalazi se u centru operativnog polja. Kardijalna reparacija (aneurizma leve komore, trauma srca, pojedini oblici ventrikularnog septum defekta i sl) i potreba za koronarnim *bypass* graftingom predstavljaju dve jedine kontraindikacije za ovaj pristup. Kod svih ostalih bolesnika, parcijalna gornja sternotomija trenutno je metoda izbora za minimalno invazivnu hirurgiju aortne valvule [1].

Cilj ove studije bio je da prikaže inicijalne rezultate dobijene primenom ove tehnike u hirurgiji srčanih valvula u Klinici za kardiovaskularnu hirurgiju Instituta za kardiovaskularne bolesti Vojvodine.

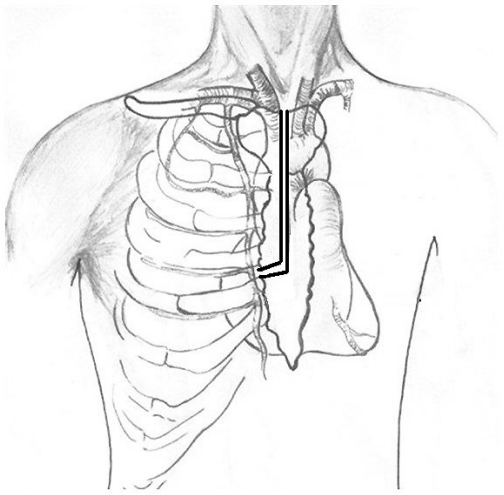
**Metode**

Ova prospektivna studija obuhvatila je sve bolesnike koji su operisani pristupom kroz parcijalnu gornju sternotomiju u periodu novembar 2008 – avgust 2009. godine. Indikacije za hirurški zahvat bile su aortna stenoza, aortna insuficijencija, mitralna stenoza i mitralna insuficijencija. Kontraindikacije za mini invazivni operativni zahvat bile su istovremena potreba za hirurškom revaskularizacijom miokarda i valvularnom hirurgijom. Zamena zalistaka vršena je implantacijom bioloških valvula (St. Jude Medical, Medtronic) ili implantacijom mehaničkih proteza (St. Jude Medical, Medtronic). Svi bolesnici potpisali su pristanak posle informisanja o izvođenju operativnog zahvata. Sve kliničke, proceduralne i operativne informacije, neophodne za izvođenje studije prikupljene su iz zajedničkog informacionog sistema i arhive Instituta za kardiovaskularne bolesti Vojvodine.

Za analizu grupe bolesnika kod kojih je primenjen minimalno invazivni pristup u hirurgiji kardijalnih valvula korišćene su deskriptivne statističke metode. Dobijeni podaci predstavljeni su u vidu aritmetičke sredine, kao i standardne devijacije (SD). Za statističku obradu podataka korišćen je softverski paket SPSS 16.0.

*Operativna tehnika*

Bolesnik je postavljen u položaj supinacije na operacionom stolu sa obe ruke pripojene uz telo i intubiran jednolumenskim endotrahealnim tubusom. Stanje bolesnika kontinuirano je praćeno standardnim monitoringom, uključujući Swan-Ganz-ov kateter, a bila je stavljena i transezofagealna ehografska (TEE) sonda. Incizija dužine 8 cm vršena je od sternalnog ugla do visine IV interkostalnog prostora (slika 1 i 2). Meka tkiva disecirana su termokauterom, a kožni režanj izdignut je da bi se omogućio pristup sternalnom rezu. Sternum je otvaran od jugularne incizure do nivoa IV interkos-



**Sl. 1 – Šematski prikaz mini-sternotmije za pristup aortnoj valvuli**

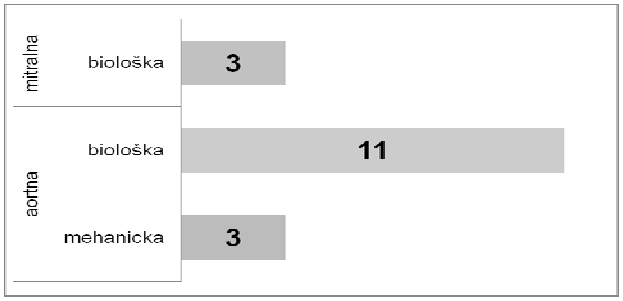
**Sl. 2 – Veličina reza nakon gornje parcijalne mini-sternotmije**

talnog prostora. Sternotomija je rađena uz mere predostrožnosti da se ne bi oštetila *arteria thoracica interna*. U slučaju planiranja hirurgije aortnog zaliska, vršena je sternotomija u desnu stranu, a u slučaju mitralne valvule u levu stranu. Mali dvodelni retraktor je plasiran u rez i otvaran. Timično tkivo je presečeno po sredini i ligirano. Prednja strana perikarda otvarana je malo udesno i fiksirana za zid grudnog koša podržnim šavovima. To je omogućilo podizanje srca napred i dalo dobru eksponiranost aorte i desne pretkomore. U cilju prevencije vazdušne embolizacije, operativno polje je natapano ugljen dioksidom ($CO_2$) (6 L/min) koji istiskuje vazduh iz srčanih struktura (rastvorljivost $CO_2$ u krvi je oko 25 puta veća u odnosu na vazduh, tako da se mehurići $CO_2$ koji ostanu zarobljeni unutar srčanih strukutra u potpunosti apsorbuju smanjujući verovatnoću pojave neuroloških komplikacija). Kanule za CPB stavljane su direktno u ascendentnu aortu i desnu pretkomoru, odnosno u obe šuplje vene. Dalji tok operacije bio je identičan onom kod pune sternotmije. Određena razlika postojala je u slučaju pristupa mitralnoj valvuli. Mitralnoj valvuli se pristupalo transseptalnom incizijom, koja se protezala do krova leve pretkomore. Desna pretkomorska incizija počinjala je u visini aurikule i protezala se kranijalno do krova leve pretkomore i kaudalno do donje šuplje vene. Septum se otvarao kroz fosu ovalis i incizija je učinjena gore do krova leve pretkomore. Pledžet šavovi su bili plasirani kroz gornji deo septuma i zategnuti levo.

## Rezultati

Od novembra 2008. do avgusta 2009. godine, urađena je mini-sternotomija kod 17 bolesnika. Primenom tog pristupa kod 14 (82,35%) bolesnika, izvršena je zamena aortne, a kod 3 (17,65%) bolesnika zamena mitralne valvule. Ni kod jednog bolesnika nije načinjena reparacija srčanog zaliska. Prosečno životno doba bolesnika iznosilo je 60,78 ± 12,99 godina (u rasponu od 31 do 78 godina). Ukupno 11 (64,71%) bolesnika bilo je muškog, a šest (35,29%) ženskog pola.

Izolovana aortna stenoza bila je pristuna kod 11 (78,57%) bolesnika iz grupe bolesnika kojima je zamenjen aortni zalistak. Kod dva (14,28%) bolesnika aortna stenoza bila je udružena sa značajnom aortnom regurgitacijom, dok je jedan (7,14%) bolesnik bio operisan zbog izolovane aortne regurgitacije. U slučaju mitralne valvule, dva (66,66%) bolesnika imala su značajnu mitralnu regurgitaciju, dok je jedan (33,33%) bolesnik imao mitralnu regurgitaciju udruženu sa značajnom stenozom mitralne valvule. Na slici 3, prikazan je tip valvula koji je korišćen za zamenu zalistaka.




**Sl. 3 – Tip i broj valvula koje su korišćene prilikom zamene obolelih valvula**

Svi bolesnici ostali su intubirani nakon zahvata i prebačeni su u jedinicu intenzivne nege. Prosečno vreme do ekstubacije iznosilo je 12,53 ± 8,87 časova sa 23,5% (4/17) bolesnika koji su ekstubirani za kraće od 8 h. Najduže vreme do ekstubacije iznosilo je 44 časa (jedan bolesnik, 5,88%), a najkraće 6 časova (dva bolesnika, 11,76%) Prosečna dužina hospitalizacije iznosila je 12,35 ± 10,17 dana (najduža hospitalizacija iznosila je 49 dana, a najkraća 7 dana). Pet (29,4%) bolesnika otpušteno je iz bolnice tokom prve postoperativne nedelje. Uobičajene postoperativne komplikacije bile su: krvarenje koje je zahtevalo reviziju hemostaze (kod jednog bolesnika, 5,88%) i cerebrovaskularni inzult (kod jednog bolesnika, 5,88%). Prosečan gubitak krvi na dren iznosio je 547,06 ± 335,2 mL. Konverzija u punu sternotomiju učinjena je kod jednog (5,88%) bolesnika, zbog razvoja hemodinamske nestabilnosti tokom operativnog zahvata. Produžena mehanička ventilacija, zbog respiratorne insuficijencije, bila je neophodna kod jednog (5,88%) bolesnika. Nije uočena infekcija hirurškog mesta, kao ni razvoj postoperativne nestabilnosti grudnog koša. Nije bilo postoperativnog mortaliteta (tokom narednih 30 dana).

## Diskusija

I hirurzi i bolesnici postali su svesni prednosti koje pruža minimalno invazivna valvularna hirurgija srca. Do 1995. godine, kardiohirurgija je daleko zaostajala za drugim specijalnostima u razvoju metoda minimalnog pristupa. Tada su Cohn i sar. [3] i Cosgrove i sar. [2], zajedno s još nekoliko evropskih kolega, prvi put izmenili tehniku vantelesnog krvotoka i smanjili veličinu reza sa ciljem sigurnog i efikasnog izvođenja minimalno invazivne valvularne hirurgije. Uprkos ranom entuzijazmu, većina hirurga bila je skeptična i kritički se ophodila prema kardiohirur-

giji rađenoj kroz male rezove, pre svega zbog mogućnosti nesigurnog toka same operacije i inferiornih rezultata. U kratkom vremenskom periodu postignut je značajan napredak koji je bio praćen pojavom obećavajućih kliničkih serija. Istovremen napredak u vantelesnoj perfuziji, intrakardijalnoj vizualizaciji, i instrumentalizaciji, kao i razvoj robotske telemanipulacije, omogućili su tehnološki pomak ka efikasnoj i sigurnoj minimalno invazivnoj hirurgiji srca. Zamena i reparacija srčanih zalistaka kroz male rezove postali su standardna praksa za mnoge hirurge, a bolesnici su sve svesniji prednosti ovih metoda.

I dalje postoji oprečno mišljenje o tome da li se ovim pristupom obezbeđuje dobra ekspozicija za hirurga, odnosno da li su rezultati, dovoljno dobri. U našoj ustanovi odlučili smo se za minimalno invazivni pristup kroz gornju parcijalnu sternotomiju. Gornja parcijalna sternotomija ima nekoliko prednosti nad desnom parasternalnom i transsekcionom sternotomijom. Mali rez čini otvaranje i zatvaranje grudne kosti lakšim i bržim. Unutrašnje grudne arterije ostaju sačuvane, a konverzija u punu sternotomiju lako se izvodi. Hirurški pristup aortnom korenu sličan je kao kod totalne sternotomije. Ovaj pristup ne zahteva disekciju čitavog prednjeg medijastinuma, tako da srce ostaje pozicionirano u prednjem aspektu, a dalje poboljšanje ekspozicije aortnog zaliska vrši se sa tri komisuralna šava koja izdižu valvulu. Postoji svega nekoliko kontraindikacija za ovaj pristup, a pojedini hirurzi su izvestili o uspešnoj reoperaciji aortne valvule tim pristupom [13, 14].

Cilj minimalno invazivne hirurgije srčanih zalistaka prvenstveno je obezbeđivanje koristi za bolesnike. Praktičnost mini invazivne hirurgije aortne valvule potvrdili su brojni operatori [1–3]. Skoriji podaci pokazuju da su novi pristupi hirurgiji srčanih zalistaka dali osetna poboljšanja. Nekoliko studija pokazalo je značajno sniženje gubitka krvi i potrebe za transfuzijom korišćenjem manje incizije [2, 14–18]. U studiji Cosgrove i sar. [19], 88% bolesnika nije primilo transfuziju krvnih produkata tokom postoperativnog perioda [19]. U našoj studiji, kod ukupno 5,88% bolesnika javilo se krvarenje kao postoperativna komplikacija, što je nešto slabiji rezultat od prikazanih u 11-godišnjoj studiji Tabat-a i sar. [1] na velikom uzorku, kada je postoperativno krvarenje zabeleženo kod svega 2,4% bolesnika, kao i od rezultata Liu i sar. [5], prema kojima je ova komplikacija zabeležena kod svega 0,3% operisanih bolesnika. Kim i sar. [20] su 2006. godine opisali krvarenje kao postoperativnu komplikaciju kod 2,7% bolesnika [20]. U studiji Olina i Peterffy-a [12] iz 1999, na malom broju bolesnika (18), prijavljen je nešto viši procenat ove postoperativne komplikacije (5,6%). Manja incizija i smanjena hirurška trauma omogućavaju raniju ekstubaciju, kraći boravak u jedinici intenzivne nege i kraću hospitalizaciju, što zajedno snižava hospitalne troškove za 10–20% [2, 15, 16]. U prethodno spomenutoj sudiji Gillinov-a i Cosgrove-a [19], prosečno vreme ekstubacije iznosilo je 11 časova (± 5), dok je u našoj studiji ono iznosilo 12,53 časova (± 8,87). Ipak, Liu i sar. [5] u svojoj studiji iz 1999. godine, navode prosečno vreme ekstubacije od 7,43 časova. U našoj studiji, pak, vreme hospitalizacije je nešto duže u odnosu na svetske rezultate (6,2 dana u studiji Liu-a i sar. [5], 6,9 dana u studiji Kim-a i sar. [20], 6 dana u studiji Tabat-a i sar. [1]) što se, pre svega, objašnjava potrebom za dužom opservacijom bolesnika nakon uvođenja nove tehnike. Iako većina ovih podataka dolazi iz retrospektivnih studija, Mächler i sar. [18] potvrdili su nekoliko ovih rezultata u velikoj prospektivnoj studiji sa bolesnicima podvrgnutim hirurgiji aortne valvule.

Potreba za konverzijom u punu sternotomiju relativno je retka pojava u savremenoj mini-invazivnoj hirurgiji srčanih zalistaka. U našoj studiji, prijavljen je jedan (5,88%) bolesnik sa konverzijom u punu sternotomiju zbog hemodinamske nestabilnosti, dok je u studiji Gillinov-a i Cosgrove-a [19] konverzija načinjena kod 2,19%, najčešće zbog krvarenja ili neadekvatnog pristupa. Kod naših bolesnika nije zabeležena infekcija hirurškog mesta kao postoperativna komplikacija što je, pre svega, posledica kraćeg reza, manje hirurške traume i doslednog pridržavanja pravila asepse. U studijama Gillinov-a i Casgrove-a [19] i Tabat-a i sar. [1], koje su obuhvatale veliki broj bolesnika, infekcija se, takođe, javljala kao veoma retka komplikacija (0,3% odnosno 0,5%), daleko ređa od krvarenja, moždanog udara i respiratorne insuficijencije. U našoj studiji nije zabeležen nijedan slučaj perioperativnog smrtnog ishoda, dok je u studijama Tabat-a i sar. [1] i Kim-a i sar. [20] stopa perioperativnog mortaliteta iznosila 1,9%.

Naša studija ograničena je, pre svega, malim brojem uključenih bolesnika, ali je, uprkos tome, ukazala na rezultate koji su u potpunosti uporedivi sa rezultatima koji se postižu klasičnom tehnikom.

## Zaključak

Parcijalna gornja središnja sternotomija pruža optimalan hirurški pristup za intervencije na čitavoj ascendentnoj aorti i mitralnom zalisku kroz krov leve pretkomore. U poređenju sa standardnom sternotomijom, ona ima nekoliko prednosti: manji bol, kraći rez na koži, kraći period postoperativne intubacije, manje postoperativno krvarenje, niži stepen infekcije hirurškog mesta i disrupcije grudne kosti i, konačno, kraće vreme hospitalizacije.

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# Nizak arterijski pritisak na prijemu kao prediktor smrtnog ishoda kod operisanih bolesnika sa disekcijom aorte tipa A

## Low arterial pressure on admission as a predictor of mortality in operated patients with type A aortic dissection

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**Apstrakt**

**Uvod/Cilj.** Arterijska hipertenzija je prediktor disekcije proksimalnog dela aorte, međutim, često nije prisutna u vreme kliničkog ispoljavanja ove bolesti. Povezanost prečnika ascendentne aorte sa faktorima rizika, hipertrofijom leve komore i koronarnom aterosklerozom, kao i ishod bolesti kod bolesnika sa akutnom disekcijom proksimalog dela aorte nisu u potpunosti poznati. **Metode.** Retrospektivna studija obuhvatila je 55 bolesnika sa akutnom disekcijom aorte tipa A, lečenih hirurški u našoj ustanovi u prethodne dve godine. Dijagnoza je postavljana tehnikama medicinskog slikanja. Prečnik ascendentne aorte meren je ehokardiografski. **Rezultati.** Prosečna starost bolesnika (72,7% muškaraca) bila je 55,4 ± 12,19 godina. Arterijsku hipertenziju u anamnezi imalo je 76,4% bolesnika. Maksimalni prečnik ascendentne aorte iznosio je 4,09 ± 0,59 cm, a aneurizma ascendentne aorte > 5,0 cm registrovana je kod 5,5% bolesnika. Sistolni krvni pritisak < 150 mmHg na prijemu imalo je 58,2% bolesnika, dijastolni < 90 mmHg 54,5% bolesnika, a srednji arterijski krvni pritisak bio je 104,9 ± 24,6 mmHg. Nije bilo povezanosti maksimalnog prečnika ascendentne aorte sa hipertrofijom leve komore, faktorima rizika, kao i koronarnom bolešću ($p > 0,05$). Nakon 6 meseci smrtni ishod registrovan je kod 11 (20%) bolesnika, od čega je intrahospitalnih bilo osam (72%). U logističku regresionu analizu bili su uključeni faktori rizika, ehokardiografski parametri, koronarna bolest i logistički euro skor; srednji arterijski krvni pritisak na prijemu bio je nezavisni prediktor 6-mesečnog mortaliteta [0,956; 95% IP (0,918–0,994); $p = 0,024$]. **Zaključak.** Akutna disekcija aorte tipa A retko se registrovala kod posmatranih bolesnika koji su imali aneurizmu ascendentne aorte prečnika > 5,0 cm. Najveći broj bolesnika imao je ranije arterijsku hipertenziju, što nije bilo u vezi sa prečnikom ascendentne aorte. Srednji arterijski pritisak bio je nezavisni prediktor 6-mesečnog mortaliteta ovih bolesnika.

**Ključne reči:**
**hipertenzija; aorta, aneurizma; aneurizma, disekantna; faktori rizika.**

**Abstract**

**Background/Aim.** Hypertension is a known predictor of proximal aortic dissection, but it is not commonly present in these patients on presentation. The associations between ascending aorta with left ventricular hypertrophy, cardiovascular risk factors and coronary atherosclerosis, and outcome of these patients are not fully elucidated. **Methods.** This retrospective study included 55 consecutive patients with acute type A aortic dissection treated surgically in our institution during the last 2 years. The diagnosis was based on imaging studies. Diameter of ascending aorta was measured with echocardiography. **Results.** The mean age of the patients was 55.4 ± 12.19 years, and 72.7% were men. A history of arterial hypertension was present in 76.4% of the patients. Maximal ascending aorta diameter was 4.09 ± 0.59 cm, while patients with frank aneurysm accounted for 5.5%. Systolic blood pressure on admission was < 150 mmHg in 58.2% of the patients. Diastolic blood pressure on admission was < 90 mmHg in 54.5% of the patients. Mean arterial pressure on admission was 104.9 ± 24.6 mmHg. No correlations were demonstrated between maximal ascending aorta diameter and diameter of the left ventricular wall, any obtained risk factor and with coronary artery atherosclerosis ($p > 0.05$). After six months 11 (20%) patients died, while intrahospital mortality was 72%. According to logistic regression analysis which included traditional risk factors, echo parameters, coronary artery disease and logistic euro scor, mean arterial blood pressure was the independent predictor of a six-month mortality [RR 0.956; CI (0.918–0.994 ); $p = 0.024$]. **Conclusion.** In our population the acute type A aortic dissection occurred rarely in the setting of frank ascending aortic aneurysms > 5.0 cm. The majority of patients had a history of arterial hypertension. A history of arterial hypertension was not associated with maximal ascending aorta diameter. Mean arterial blood pressure was the independent predictor of a six-months mortality.

**Key words:**
**hypertension; aortic aneurysm; aneurysm, dissecting; risk factors.**

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## Uvod

Arterijska hipertenzija je bolest sa najvećom prevalencijom, a oboleli od arterijske hipertenzije imaju dva puta veći mortalitet u odnosu na normotenzivne osobe [1, 2]. Ovo oboljenje predstavlja vodeći nezavisni faktor rizika od nastanka ateroskleroze, koja je u osnovi ishemijske bolesti srca i velikih krvnih sudova, cerebrovaskularne bolesti, bolesti perifernih arterija i hronične bubrežne insuficijencije [1, 2]. Kod većine bolesnika arterijska hipertenzija godinama protiče asimptomatski, a tek oštećenje „ciljnih organa", kao što je aneurizmatska dilatacija i disekcija aorte otkrivaju ovu često smrtonosnu bolest, zbog čega je neophodno njeno rano otkrivanje i lečenje. Incidencija bolesnika sa disekcijom aorte je u porastu [3]. Nove neinvazivne dijagnostičke tehnike, duži životni vek i duža izloženost povišenom krvnom pritisku doprinose sve većem broju bolesnika od akutnih i hroničnih aortnih sindroma.

Prema podacima najvećeg internacionalnog registra za akutne disekcije aorte (*International Registry of Acute Aortic Dissection* – IRAD) arterijska hipertenzija je najčešći faktor rizika od nastanka disekcije proksimalnog dela aorte [4]. Hronična izloženost zida aorte povećanim vrednostima krvnog pritiska dovodi do ubrzane razgradnje, apoptoze i elastolize ekstraćelijskog matriksa, što dovodi do slabljenja sloja medije aortnog zida, te većeg zidnog stresa, koji može dovesti do dilatacije aorte i stvaranja aneurizme, što na kraju dovodi do stvaranja pukotina u intimi, najčešće na ivicama aterosklerotskog plaka, krvarenja u zidu krvnog suda, disekcije ili rupture aorte [5–7]. Povezanost prečnika korena aorte i faktora rizika od kardiovaskularne bolesti nije konzistentna, dok prema rezultatima prospektivnih studija arterijska hipertenzija često nije prisutna u vreme kliničkog ispoljavanja ove bolesti, posebno kod bolesnika sa disekcijom proksimalnog dela aorte tipa A [4].

Savremena hronobiološka istraživanja pokazala su da postoje cirkadijalne, nedeljne i sezonske varijacije javljanja kardiovaskularnih oboljenja, infarkta miokarda, iznenadne srčane smrti, srčanog zastoja, ali i disekcije aorte [8–10]. S obzirom na to da određeni broj bolesnika sa akutnom disekcijom aorte nije dijagnostikovan, podaci u vezi sa temporalnim varijacijama ovog oboljenja nisu potpuni, a mogu biti od značaja za etiologiju same disekcije.

Akutna disekcija aorte je oboljenje sa veoma visokom stopom smrtnosti. Međutim, stope bolničke i dugoročne smrtnosti, kao i njihovi prediktori razlikuju se prema različitim studijama, u zavisnosti od broja ispitanika i vremena izvođenja studije, te nisu u potpunosti jasni.

Cilj našeg istraživanja bio je da se proceni značaj arterijske hipertenzije kod bolesnika sa disekcijom aorte tipa A, njihov intrahospitalni i 6-mesečni mortalitet i njihovi prediktori, kao i dnevna i sezonska hronobiologija ovog tipa disekcije aorte.

## Metode

Sprovedena je retrospektivna, delom prospektivna, studija u koju je bilo uključeno 55 bolesnika, koje je uputila služba Hitne medicinske pomoći u našu ustanovu u periodu od 2006. do 2008. godine, sa bolom u grudima, kod kojih se na osnovu karaktera bola, kliničkog nalaza i nalaza transtorakalne ehokardiografije posumnjalo na disekciju aorte. Nalaz disekcije aorte potvrđen je na osnovu tipičnog nalaza na transezofagelanoj ehokardiografiji, kompjuterizovanoj tomografiji ili magnetnoj rezonanci aorte. Analizirani podaci dobijeni su uvidom u istorije bolesti u okviru bolničko-epidemiološko-informacionog sistema Instituta za kardiovaskularne bolesti Vojvodine. Za svakog bolesnika analizirani su vreme prijema, faktori rizika od kardiovaskularne bolesti, fizikalni nalaz na prijemu, nalazi različitih tehnika medicinskog slikanja, kao i šestomesečni mortalitet. Svim bolesnicima pre kardiohirurške operacije učinjena je koronarografija i određen logistički EuroSCORE (*European System for Cardiac Operative Risk Evaluation*) [11]. Određeni su sledeći faktori rizika od kardiovaskularne bolesti: starost, pušački status, arterijska hipertenzija, dijabetes melitus i dislipidemija. Fizikalnim nalazom na prijemu kod svakog bolesnika registrovane su vrednosti sistolnog i dijastolnog krvnog pritiska na obe ruke, a u analizu su bili uključeni bolesnici kod kojih nije bilo značajne razlike u krvnim pritiscima. Na osnovu vrednosti krvnih pritisaka izračunat je srednji arterijski pritisak [(2 × dijastolni krvni pritisak)/3 + sistolni krvni pritisak/3] [12]. Arterijska hipertenzija definisana je kao vrednost sistolnog krvnog pritiska preko 120 mmHg i/ili dijastolnog krvnog pritiska preko 80 mmHg. Svi bolesnici lečeni su kardiohirurškom intervencijom i to kod 38 (70%) rađena je izolovana interpozicija tubus grafta, kod šest (11%) u kombinaciji sa zamenom aortnog zaliska ili resuspenzijom aortnih kuspisa, odnosno kod šest (11%) u kombinaciji sa revaskularizacijom miokarda, dok je kod pet (9%) bolesnika rađena operacija po Bentall-u.

Akutna disekcija ascendentne aorte definisana je kao svaka netraumatska disekcija zida aorte koja zahvata ascendentnu aortu tokom 14 dana od pojave kliničke simptomatologije. U studiju nisu bili uključeni bolesnici sa dokazanim Marfanovim sindromom, sekundarnom disekcijom aorte kao posledicom traume, pseudohipotenzijom kao posledicom značajne opstrukcije grana aortnog luka ili hemodinamski značajnim perikardnim izlivom, kao i bolesnici sa bubrežnom insuficijencijom. Klasifikacija disekcije aneurizme aorte vršena je prema klasifikaciji Stanford, a u studiju su bili uključeni bolesnici sa disekcijom aorte tip A, koji podrazumeva disekciju aorte koja zahvata ascendentnu aortu. Za analizu je korišten maksimalni prečnik ascendentne aorte određen transtorakalnom ehokardiografijom. U cilju određivanja varijacija nastanka disekcije aorte utvrđena je sezonska učestalost u četiri godišnja doba, kao i 24-časovna učestalost i to u tri perioda od 6 h do14 h, od 14 h do 22 h, kao i od 22 h do 6 h.

U statističkoj obradi podataka korišćeni su $\chi^2$ test i Mann-Withney *U*-test. Za procenu značajnosti povezanosti korišćene su korelaciona analiza (za parametarske i neparametraske podatke), kao i univarijantna i multivarijantna logistička regresiona analiza. Preživljavanje bolesnika analizirano je Kaplan-Meier-ovom krivom.

**Rezultati**

Ispitivanjem je obuhvaćeno 55 osoba oba pola (72,7% muškaraca), prosečne starosti 55,4 ± 12,19 godina. Arterijski krvni pritisak na prijemu i ehokardiografske karakteristike svih bolesnika ukupno, kao i prema ishodu, prikazane su u tabeli 1.

snika iznosio > 5,0 cm. Istisnu frakciju < 40% imala su četiri bolesnika, od kojih je umrlo dvoje.

Kod bolesnika koji su imali arterijsku hipertenziju u anamnezi nije bilo statistički značajne povezanosti između prečnika aorte i endokavitarnih prečnika i debljine zidova leve komore ($p > 0,05$).

**Tabela 1**

**Karakteristike bolesnika na prijemu, ukupno i prema 6-mesečnom ishodu**

| Varijabla | Ukupno (n = 55) | Preživeli (n = 44) | Umrli (n = 11) | *p* |
|---|---|---|---|---|
| Ehokardiografski parametri | | | | |
| prečnik ascendentne aorte (cm), x̄ ± SD | 4,09 ± 0,59 | 4,02 ± 0,62 | 4,34 ± 0,43 | 0,18 |
| ascendentn aorta >5 cm [n (%)] | 3 (8,3) | 3 (100) | 0 (0) | 0,334 |
| aortna insuficijencija III/IV stepena [n (%)] | 8 (18,6) | 7 (87,5) | 1 (12,5) | 0,600 |
| istisna frakcija [n (%)] | 46,44 ± 24,67 | 58,97 ± 8,19 | 53,88 ± 9,95 | 0,160 |
| IVSd (cm), x̄ ± SD | 1,38 ± 0,17 | 1,39 ± 0,18 | 1,37 ± 0,11 | 0,812 |
| PLWd (cm), x̄ ± SD | 1,70 ± 2,00 | 1,79 ± 2,24 | 1,36 ± 0,05 | 0,619 |
| LVESD (cm), x̄ ± SD | 3,31 ± 0,76 | 3,22 ± ,74 | 3,67 ± 0,76 | 0,169 |
| LVEDD (cm), x̄ ± SD | 5,25 ± 0,78 | 5,17 ± 0,81 | 5,60 ± 0,55 | 0,197 |
| Arterijski krvni pritisak na prijemu | | | | |
| arterijska hipertenzija na prijemu [n (%)] | 29 (52,7) | 26 (89,7) | 3 (10,3) | 0,059 |
| sistolni krvni pritisak (mmHg), x̄ ± SD | 144,00 ± 34,24 | 149,32 ± 33,09 | 122,73 ± 31,65 | 0,020 |
| dijastolni krvni pritisak (mmHg), x̄ ± SD | 85,36 ± 20,97 | 88,75 ± 20,60 | 71,82 ± 17,22 | 0,015 |
| srednji arterijski krvni pritisak (mmHg), x̄ ± SD | 104,91 ± 24,61 | 108,94 ± 24,00 | 88,79 ± 20,88 | 0,014 |

**IVS – prečnik interventrikularnog septuma leve komore; PLW – prečnik zadnjeg zida leve komore; LVESD – prečnik leve komore na kraju sistole; LVEDD – prečnik leve komore na kraju dijastole**

Od ukupnog broja, 42 (76,4%) bolesnika imalo je arterijsku hipertenziju u anamnezi ($p < 0,01$). Od bolesnika sa hipertenzijom u anamnezi 33 (78,6%) je preživelo ($p < 0,01$). Između grupa preživelih i umrlih bolesnika nije bilo statistički značajne razlike u pogledu faktora rizika, ehokardiografskih parametara, dok su preživeli bolesnici, u odnosu na umrle, na prijemu imali statistički značajno veće vrednosti sistolnog ($p = 0,020$), dijastolnog ($p = 0,015$) i srednjeg krvnog pritika ($p = 0,014$). Logistički *euroscore* iznosio je od 0,00 do 29,38. Logistički *euroscore* preko 12 imalo je 15 (27,3%) bolesnika. Nije bilo statistički značajne razlike u mortalitetu bolesnika sa logističkim euroskorom 12 i preko 12 u odnosu na bolesnike sa logističkim euroskorom 12 ($p > 0,05$). Broj operisanih interpozicijom tubus grafta bio je statistički značajno veći u odnosu na sve ostale hirurške procedure ($p = 0,005$).

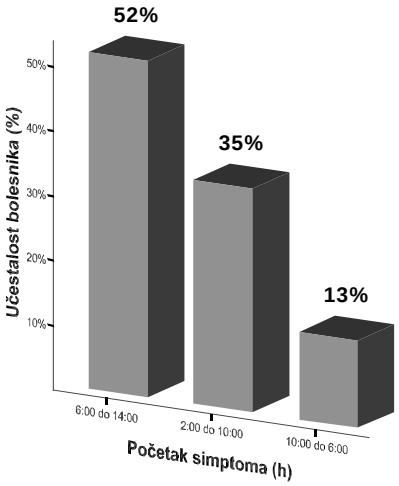
Arterijsku hipertenziju na prijemu imalo je 29 (52,7%) bolesnika ($p = 0,686$). Ukupno 23 (41,8%) bolesnika na prijemu je imalo sistolni krvni pritisak > 150 mmHg, kod 29 (52,7%) bolesnika iznosio je između 100 i 150 mmHg, dok je kod tri (5,5%) iznosio < 100 mmHg ($p < 0,01$). Dijastolni krvni pritisak < 80 mmHg na prijemu imalo je 24 (43,6%) bolesnika. Srednji arterijski krvni pritisak na prijemu iznosio je 104,9 ± 24,6 (56,7–163,3) mmHg.

Jedan (1,8%) bolesnik imao je prethodno dokumentovanu anginu pektoris, a kod devet (16,4%) bolesnika koronarografijom je ustanovljena hemodinamski značajna koronarna okluzivna bolest. Od bolesnika koji su imali hemodinamski značajnu koronarnu okluzivnu bolest umrla su tri (33,3%) bolesnika.

Prosečna vrednost maksimalnog prečnika ascendentne aorte iznosila je 4,09 ± 0,59 cm. Kod 16 (29,1%) bolesnika prečnik aorte iznosio je > 4,0 cm, dok je kod tri (5,5%) bole-

Nije bilo statistički značajne povezanosti između prečnika aorte i posmatranih faktora rizika od ishemijske bolesti ($p > 0,05$). Nije bilo statistički značajne povezanosti između prečnika aorte i prisustva hemodinamski značajnih stenoza koronarnih krvnih sudova ($p > 0,05$).

Početak simptoma kod 27 (52%) bolesnika registrovan je u toku prepodneva, što je bilo statistički značajno više u odnosu na broj bolesnika registrovanih noću [7 (13%); $p = 0,01$]. Takođe, statistički značajno više bolesnika registrovano je u toku popodneva 18 (35%) u odnosu na broj bolesnika registrovanih noću ($p = 0,028$) (slika 1). Nije bilo statistički značajne razlike u uče-




**Sl. 1 – Cirkadijalna varijacija početka simptoma kod bolesnika sa disekcijom aorte**

stalosti vremena nastanka simptoma kod bolesnika koji su u anamnezi imali arterijsku hipertenziju u odnosu na one koji nisu

($p = 0,301$). Kod 24 (43,6%) bolesnika bolest je registrovana u zimskom periodu, kod 12 (21,8%) u proleće, a kod 10 (18,2%) u jesen ($p = 0,015$). Veći broj bolesnika registrovan je zimi i to u odnosu na broj registrovanih i u proleće ($p = 0,046$) i u leto ($p = 0,009$), kao i u jesen ($p = 0,016$).

Nakon šest meseci praćenja smrtni ishod registrovan je kod 11 (20%) bolesnika, od čega je intrahospitalnih smrti bilo 8 (72%). Od 29 bolesnika koji su na prijemu imali arterijsku hipertenziju, šest meseci je preživelo njih 26 (89,7%), a od 26 bolesnika, koji su bili hipotenzivni na prijemu, preživelo je 18 (69,2%) ($p = 0,059$).

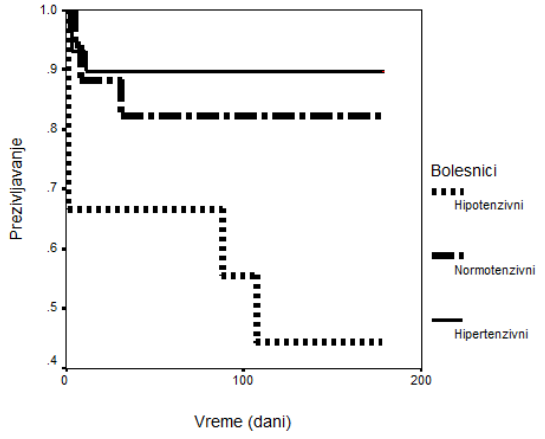
U cilju poređenja prediktivnih vrednosti ispitivane varijable testirane su logističkom regresionom analizom, pri čemu je zavisna varijabla bila 6-mesečni mortalitet. U univarijantnu logističku regresionu analizu bile su uključene sledeće varijable: godine starosti, pol, pušenje, dijabetes melitus, ukupni holesterol, angina, hronobiologija (doba dana i godine), srednji arterijski pritisak, sistolni krvni pritisak, dijastolni krvni pritisak, pulsni pritisak, arterijska hipertenzija u anamnezi, heriditet za arterijsku hipertenziju, hronična opstruktivna bolest pluća, maksimalni prečnik ascendentne aorte, prečnik interventrikularnog septuma, prečnik zadnjeg zida, enddijastolni i endsistolni prečnik leve komore, istisna frakcija, stepen aortne insuficijencije, hemodinamski značajna stenoza koronarnih arterija i logaritam euroskora. Pokazano je da postoji statistički značajna univarijantna povezanost samo srednjeg arterijskog krvnog pritiska, sistolnog krvnog pritiska i dijastolnog krvnog pritiska sa 6-mesečnim mortalitetom (tabela 2). Niži nivo srednjeg arterijskog krvnog pritiska na prijemu bio je nezavisni prediktor 6-mesečnog mortaliteta (0,956; 95%IP (0,918–0,994); $p = 0,024$). Kaplan-Meier-ovom krivom prikazano je preživljavanje bolesnika u odnosu na visinu arterijskog krvnog pritiska na prijemu (slika 3). Hipotenzivni bolesnici imali su lošije preživljavanje u odnosu na normotenzivne i hipertenzivne bolesnike u tri vremena analiziranja (Log Rank $p = 0,0057$, Breslow $p = 0,0050$, Tarone-Ware $p = 0,0053$).

**Tabela 2**

**Univarijantni prediktori 6-mesečnog mortaliteta (logistička regresiona analiza)**

| Varijabla | RR | 95% IP | *p* |
|---|---|---|---|
| Sistolni krvni pritisak | 0,971 | 0,945–0,997 | 0,030 |
| Dijastolni krvni pritisak | 0,948 | 0,905–0,994 | 0,026 |
| Srednji arterijski krvni pritisak | 0,956 | 0,918–0,994 | 0,024 |

**RR – relativni rizik, IP – interval poverenja**




**Sl. 2 – Kaplan-Meier-ova kriva preživljavanja bolesnika u zavisnosti od vrednosti arterijskog krvnog pritiska na prijemu**

## Diskusija

Hipertenzivno oboljenje srca i velikih krvnih sudova nastaje zbog dejstva sistemske arterijske hipertenzije, a sačinjavaju ga hipertrofija leve komore, srčana slabost, ishemijska bolest srca, disritmije, kao i bolesti aorte i drugih krvnih sudova. Arterijska hipertenzija je najčešće oboljenje koje povećava rizik od disekcije proksimalnog dela aorte, a smrtnost ovih bolesnika i danas je visoka, te je utvrđivanje bolesnika koji imaju povećan rizik od nastanka disekcije aorte veoma važno.

Prema IRAD, u kome su analizirani rezultati preko 1 000 obdukovanih osoba sa akutnom disekcijom aorte, prosečne starosti 63 godine, 72% bolesnika imalo je arterijsku hipertenziju tokom života, što je poredivo sa našim rezultatima, dok je samo 3% osoba tokom života imalo vrednosti krvnog pritiska ispod prosečnih [4]. Ateroskleroza je bila prisutna kod 31% bolesnika, dok je kardiohiruršku intervenciju ranije imalo 18% bolesnika sa disekcijom aorte [4]. Manji broj bolesnika sa aterosklerozom u našoj studiji može se objasniti mlađim životnim dobom naših bolesnika. U istom registru, sistolni krvni pritisak na prijemu kod 64% bolesnika sa tipom A disekcije bio je ispod 150 mmHg, što je registrovano i kod 42,8% naših bolesnika [4].

Iako se veći promer aorte smatra faktorom rizika od akutne disekciju aorte, nije jasno šta inicira razdvajanje slojeva zidova aorte, a sama patogeneza disekcije aorte je složena. Veći prečnik aorte je u vezi sa većim rizikom od njene rupture, ali izgleda nelinearno i od disekcije. Sve je više dokaza da se akutna disekcija aorte tipa A relativno retko dešava kod bolesnika sa pravom aneurizmom ascendentne aorte, a više od trećine bolesnika sa disekcijom aorte ovog tipa ima normalan ili gotovo normalan prečnik aorte ascendentne aorte [13]. Kod oko 10% disekcija aorte nema rascepa intime, a strukturne promene koje se vide u zidu aorte su degeneracija medije sa kidanjem elestičnih vlakana, promenjena distribucija proteina ekstraćelijskog matriksa i povećana ekspresija matriksnih metaloproteinaza [5–7]. Ranije sprovedene studije pokazale su da zidni stres leve komore ima ulogu u patogenezi disekcije, dok se novije studije usmeravaju na proučavanje biomehanike aorte, pokreta aortnog korena i sila koje deluju na zidove aorte [14]. Prema rezultatima Pape-a i sar. [15] 8,8% bolesnika koji su imali promer aorte ≥ 5,5 cm imalo je ranije hiruršku revaskularizaciju miokarda, u poređenju sa svega 2,8% bolesnika čiji je promer aorte manji od 5 cm, što postavlja pitanje

hirurške traume postojeće supkliničke slabosti u zidu aorte, kao etiološkog faktora disekcije.

Prečnik aorte u korenu kod 29,1% naših bolesnika iznosio bio je > 4,0 cm, dok je kod 5,5% bolesnika bio > 5,0 cm, što je u saglasnosti sa rezultatima drugih autora. Naime, u studiji Neri i sar. [13] prosečane vrednosti prečnika aorte kod bolesnika bez sistemskog oboljenja vezivnog tkiva bile su 41,3 mm, kod 57% bolesnika prečnik aorte bio je preko 40 mm, a svega 10% bolesnika imalo je pravu aneurizmu aorte. Prema podacima iz IRAD, 59% bolesnika sa akutnom disekcijom aorte tipa A imalo je prečnik aorte u korenu ispod 5,5 cm, a 40% ispod 5 cm, dok su nezavisni prediktori disekcije, kod prečnika aorte ispod 5,5 cm, bili arterijska hipertenzija u anamnezi, iradirajući bol i odmakla starost bolesnika, a nije zabeležena povezanost promera aorte sa mortalitetom [15].

Prema rezultatima velikih studija povezanost veličine aortnog korena sa prethodnim postojanjem arterijske hipertenzije slabija je nego što se očekivalo, dok je povezanost arterijske hipertenzije i disekcije aorte jača, te je potrebno više podataka radi boljeg razjašnjavanja ovih povezanosti [16, 17]. U Framinghamskoj studiji zabeležena je slaba, ali statistički značajna, pozitivna korelacija prečnika aortnog korena sa vrednostima srednjeg i dijastolnog krvnog pritiska, kao i negativna korelacija sa vrednostima sistolnog i pulsnog krvnog pritiska, dok su primarne determinante prečnika aortnog korena, određenog ultrazvukom, bile starost bolesnika, telesna visina, telesna masa i pol bolesnika [16]. Rezultati velike populacione LIFE studije govore u prilog tome da su kod bolesnika sa arterijskom hipertenzijom, koji imaju znakove hipertrofije leve komore na elektrokardiogramu, povećane vrednosti prečnika korena aorte povezane sa većom masom leve komore, ekscentričnom hipertrofijom i umanjenom sistolnom funkcijom leve komore, što bi moglo biti objašnjenje za veći kardiovaskularni rizik kod hipertenzivnih bolesnika [17, 18]. Međutim, u drugim studijama, kao i u našoj, nije pokazana povezanost prečnika aortnog korena sa arterijskom hipertenzijom, kao ni sa ostalim faktorima rizika od kardiovaskularne bolesti [19, 20]. Korelacija između prečnika aorte i antropometrijskih ili demografskih varijabli je slaba ili nije zabeležena [13]. Starost, muški pol i telesna površina glavne su odrednice dimenzije svih segmenata torakalne aorte. Prema rezultatima studije koju su izvršili Agmon i sar. [21] postoji samo slaba povezanost faktora rizika od ateroskleroze i aterosklerotskih plakova u aorti sa dilatacijom torakalne aorte, što govori u prilog tome da ateroskleroza ima minornu ulogu u nastanku dilatacije torakalne aorte.

Rezultati velikog broja studija pokazuju da se u jutarnjim časovima beleži veći broj neželjenih kardiovaskularnih događaja. Saglasno rezultatima IRAD, najveći broj naših bolesnika sa akutnom disekcijom aorte tipa A registrovan je tokom prepodneva i zimi [9]. Naime, prema IRAD, 37,2% bolesnika pokazuje simptome disekcije aorte u periodu od 6 h ujutru do podneva, 27,3% od podneva do 6 h po podne, 22,2% od 6 časova popodne do ponoći i 13,4% bolesnika pokazuje simptome ove bolesti od ponoći do 6 časova ujutru [10]. Prema godišnjem dobu, kod 19,4% bolesnika početak simptoma bio je leti, 25,6% u jesen, 28,8% zimi, a kod 26,2% bolesnika u proleće [10]. Međutim, varijacije prema godišnjem dobu zabeležene su češće kod bolesnika sa disekcijom aorte tipa B [8].

Arterijska hipertenzija je u osnovi više desetina miliona smrtnih slučajeva od neželjenih kardiovaskularnih događaja godišnje širom sveta, te i disekcije aorte, oboljenja koje i danas ima veliku smrtnost. Podaci savremenih studija pokazuju da je hospitalni mortalitet bolesnika sa akutnom disekcijom tipa A između 15% i 35%, a petogodišnje preživljavanje od 65% do 75% [22–25]. Prema rezultatima istraživanja Mehta i sar. [25] na 547 bolesnika sa disekcijom aorte tipa A uključenih u IRAD, ukupan intrahospitalni mortalitet iznosio je 32,5%, što je manje nego intrahospitalni mortalitet zabeležen u našoj studiji [25]. Intrahospitalni mortalitet pravovremeno i uspešno operisanih bolesnika sa tipom A akutne disekcije aorte iznosi 26,9%, dok je intrahospitalni mortalitet bolesnika lečenih medikamentno, bez ikakve hirurške procedure, 56,2% [25]. Neslaganje naših rezultata možda se može objasniti relativno malim uzorkom bolesnika u našoj studiji, što je i bio razlog da se ne određuju prediktori intrahospitalnog mortaliteta. U pomenutoj studiji Mehta i sar. [25] pokazano je da su neurološki deficit, poremećaj mentalnog statusa, miokardna i mezenterijalna ishemija, bubrežna insuficijencija, hipotenzija, tamponada srca i ishemija ekstremiteta bili značajno češći među bolesnicima koji su umrli, a prediktori smrtnosti bolesnika u bolnici bili su starost (70 godina ili više), iznenadni početak bolova u grudima, hipotenzija, šok ili tamponada srca, bubrežna insufcijencija, deficit pulsa i promene u elektrokardiogramu. Prema podacima istog registra, smrtnost hirurški lečenih bolesnika sa disekcijom aorte iznosi 10% u prva 24 h, 13% u prvih 7 dana, a čak 20% tokom mesec dana [4]. Većina bolesnika umire za 48 h od prijema ili 1,4% svakog sata, zbog rupture aorte, tamponade srca, akutne aortne insuficijencije ili cerebrovaskularnog akcidenta. Prema podacima većine sprovedenih studija nezavisni prediktori intrahospitalnog mortaliteta bolesnika sa akutnom disekcijom aorte su starost, ishemija visceralnih organa, arterijska hipotenzija, bubrežna slabost, tamponada srca, koma, deficit pulsa i sindromi malperfuzije, uopšte [25–28].

Treba istaći, međutim, da su dugoročni mortalitet ovih bolesnika, kao i njegovi prediktori manje poznati. Prema podacima u IRAD, u koji su između 1999. i 2003. godine bila uključena 303 bolesnika sa akutnom disekcijom aorte tipa A, jednogodišnje preživljavanje hirurški lečenih bolesnika bilo je 96,1%, trogodišnje 90,5%, a nezavisni prediktori bili su uznapredovala ateroskleroza i prethodna kardiohirurška intervencija [29]. Prema rezultatima retrospektivne studije koju su izvršili Chiappini i sar. [27] preoperativno postojanje dijabetesa tipa 2 bio je jedini prediktor dugoročnog mortaliteta, a postojeće oboljenje srca i prethodna kardiopulmonalnocerebralna reanimacija prediktori hospitalnog mortaliteta 487 bolesnika sa tipom A akutne disekcije aorte. U drugim istraživanjima prediktori dugoročnog mortaliteta bili su Marfanov sindrom, reoperacija, moždani udar, srčana slabost, hronična bubrežna insuficijencija [30, 31]. U retrospektivnoj studiji Forteza i sar. [32] analizirali su preživljavanje 103 hirurški lečena bolesnika sa akutnom disekcijom aorte tipa A, prosečne starosti 59 ± 8 godina, operisanih između 1990. i 2008.

godine [32]. Hospitalni mortalitet bio je 15%, a njegovi prediktori odmaklo životno doba i preoperativno šokno stanje, koje je kod naših bolesnika jedini nezavisni prediktor 6-mesečnog mortaliteta. Preživljavanje bolesnika nakon godinu dana praćenja bilo je 97,6%, a nakon 15 godina 57,1%, a jedini prediktor dugoročnog preživljavanja bila je anterogradna cerebralna perfuzija. U studiji Stevens-a i sar. [33], 195 hirurški lečenih bolesnika sa akutnom disekcijom ascendentne aorte, prosečne starosti 62 ± 15 godina, praćeno je do 26 godina. Ukupno 69% bolesnika imalo je u anamnezi arterijsku hipertenziju. Prema ovim autorima, intrahospitalni mortalitet pre 20 godina iznosio je oko 21%, a poslednjih pet godina sveden je na 4%, dok je jednogodišnji mortalitet bio 85%, a mortalitet nakon 20 godina praćenja 30% [33]. Nezavisni prediktori dugoročnog mortaliteta bili su starije životno doba, bubrežna disfunkcija, periferna arterijska bolest i sinkopa.

Prema rezultatima savremenijih studija dugoročno preživljavanje hirurški lečenih bolesnika sa akutnom proksimalnom disekcijom tipa A je veoma dobro, dok su danas nezavisni prediktori preživljavanja postojeći komorbiditeti, a manje rizici koji postoje tokom hospitalnog zbrinjavanja ovih bolesnika.

Retrospektivni karakter sprovedene studije, u koju je bio uključen relativno mali broj bolesnika jednog centra, predstavlja potencijalno ograničenje studije, zbog čega nije moguća direktna generalizacija naših zaključaka. Alternativno objašnjenje za dobijene rezultate moglo bi biti da su dobijeni rezultati posledica faktora koje nismo kontrolisali i/ili faktora koje nismo preciznije izmerili.

## Zaključak

U posmatranoj populaciji bolesnika, akutna disekcija ascendentne aorte registrovana je relativno retko kod bolesnika koji su imali pravu aneurizmu ascendentne aorte. Najveći broj bolesnika imao je u anamnezi arterijsku hipertenziju, dok nije zabeležena statistički značajna povezanost posmatranih faktora rizika i koronarne ateroskleroze sa prečnikom korena aorte. Srednji arterijski pritisak na prijemu bio je nezavisni prediktor šestomesečnog mortaliteta bolesnika sa akutnom disekcijom ascendentne aorte.

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# Multislice computed tomography urography in the diagnosis of urinary tract diseases

## Višeslojna kompjuterizovano-tomografska urografija u dijagnostici oboljenja urinarnog trakta

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**Abstract**

**Background/Aim.** Multislice computed tomography (MSCT) has triggered considerable changes in uroradiological imaging. The aim of this study was to establish the place of MSCT urography (MSCTU) in comparison with intravenous urography (IVU) and to determine the sensitivity and specificity of MSCT in the evaluation of urothelial abnormalities. **Methods.** This prospective study included 120 patients with a high clinical suspicion of urinary tract diseases divided into two groups. The group I consisted of 60 patients with macroscopic hematuria, bladder carcinoma and malignant pelvic tumors after radiotherapy or operation. They underwent both IVU and MSCTU. The group II included 60 patients (≥ 40 years old) with retroperitoneal and malignant pelvic tumors, complicated pyelonephritis, microscopic hematuria, acute urinary tract obstruction (without visible calculi on unenhanced scans), and they were submitted to computed tomography with additional scan phase enabling MSCTU. **Results.** Compared with IVU, MSCTU is more sensitive for the detection of urinary tract diseases (parenchymal changes, renal tumors, urolithiasis, fibrosis) and extraurinary processes. MSCTU is more specific than IVU for renal parenchymal abnormalities, tumors of the excretory system, urolithiasis, bladder tumors, fibrosis and extraurinary diseases. MSCTU is equally sensitive, but more specific for hydronephrosis compared to MSCT. The diagnosis made by the use of MSCTU in patients with macroscopic and microscopic hematuria and with obstruction not caused by stones, perfectly comply with operative findings and histological diagnosis. **Conclusion.** The obtained results support MSCTU to be the modality of choice in the diagnostic algorithm of patients with macroscopic hematuria and in the evaluation of microscopic hematuria and unexplained obstruction of the urinary tract. The only remaining role for IVU in our institution is imaging of the upper urinary tract in patients with hematuria under the age of 40.

**Key words:**
**urologic diseases; diagnosis; urography; tomography, x-ray computed; diagnostic techniques and procedures.**

**Apstrakt**

**Uvod/Cilj.** Uvođenje višeslojne kompjuterizovane tomografije (*multislice computed tomography* – MSCT) dovelo je do značajnih promena u uroradiološkom snimanju. Cilj ove studije bio je da se utvrdi mesto MSCT urografije (MSCTU) u odnosu na intravensku urografiju (IVU), kao i da se odredi senzitivnost i specifičnost MSCTU za određivanje patoloških promena urotela. **Metode.** U ovo prospektivno istraživanje bilo je uključeno 120 bolesnika sa visokom sumnjom na oboljenje urinarnog trakta. Bolesnici su bili podeljeni u dve grupe. U grupi I bilo je 60 bolesnika sa makroskopskom hematurijom, karcinomom mokraćne bešike i malignim tumorima u karlici nakon zračenja ili operacije i svima su urađeni IVU i MSCTU. U grupi II bilo je 60 bolesnika životnog doba ≥ 40 godina sa retroperitonealnim i malignim tumorima u karlici, komplikovanim pijelonefritisom, mikroskopskom hematurijom, akutnom opstrukcijom urinarnog trakta (bez prisustva konkrementa na nekontrastnim skenovima), a svima je urađen pregled kompjuterizovanom tomografijom i dodatna faza koja omogućava MSCTU. **Rezultati.** U odnosu na IVU, MSCTU je senzitivnija u detekciji oboljenja urinarnog trakta (parenhimske promene, tumori bubrega, urolitijaza, fibroza) i ekstra-urinarnih procesa. Tehnika MSCTU je specifičnija od IVU za parenhimske promene bubrega, tumore ekskretornog sistema, urolitijazu, tumore mokraćne bešike, fibrozu i ekstra-urinarna oboljenja. Tehnika MSCTU podjednako je senzitivna, ali specifičnija za hidronefrozu u odnosu na MSCT. Dijagnoze postavljene pomoću MSCTU kod bolesnika sa makroskopskom i mikroskopskom hematurijom, kao i opstrukcijom koja nije izazvana konkrementom, u visokoj su saglasnosti sa operativnim i patohistološkim nalazom. **Zaključak.** Dobijeni rezultati ukazuju na to da je MSCTU metoda izbora u dijagnostičkom algoritmu kod bolesnika sa makroskopskom i mikroskopskom hematurijom, ali i za analizu bolesnika sa nerazjašnjenom opstrukcijom urinarnog trakta. Jedina preostala primena za IVU u našoj ustanovi je vizualizacija gornjeg urinarnog trakta kod bolesnika sa hematurijom mlađih od 40 godina.

**Ključne reči:**
**urološke bolesti; dijagnoza; urografija; tomografija, kompjuterizovana, rengdenska; dijagnostičke tehnike i procedure.**

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## Introduction

Until the beginning of the 21st century, intravenous urography (IVU) was the initial method for urinary tract imaging in patients with hematuria, renal colic and other urological disorders. The introduction of multislice computed tomography (MSCT) had considerable impact on uroradiological imaging and imaging algorithms. The application of MSCT specifically designed for the evaluation of urinary tract diseases is called MSCT urography (MSCTU). MSCTU implies the examination of the complete urinary tract, as well as the surrounding anatomic structures, during a single examination, by multiple thin overlapping scans and 2D and 3D postprocessing with specific software packages. This procedure provides images with high spatial resolution similar to IVU [1, 2].

In literature, there are no data available on prospective surveys reporting that MSCTU possesses equal capacity in imaging morphological details as IVU [3]. Although clinical comparative studies are lacking, a complete shift from IVU to MSCTU is expected. Bearing this in mind, it is a challenge to make a scientific step-out in this field, which is likely to trigger further surveys in order to confirm the position and the value of MSCTU in modern uroradiological diagnostic algorithm.

## Methods

This single institution prospective analysis was performed on 120 patients with a high clinical suspicion of urinary tract disease. The patients were divided into two groups. Depending on the referring diagnosis the patients underwent both IVU and MSCTU or MSCTU as a single examination. The study was approved by the Ethical Committee of the hospital. The advantages of MSCTU in diagnosing urinary tract diseases were evaluated in comparison with IVU and a 'conventional' MSCT examination. In the group I of patients undergoing IVU and MSCTU the correlation of findings was focused on: renal parenchymal abnormalities, renal pelvis and calices, renal calculi, proximal ureter, middle ureter, distal ureter, bladder.

The analyses by segments listed for the group I was also performed in the group II of patients (scheduled for MSCTU only). MSCTU was performed according to the following protocol: plain unenhanced scan (low-dose scan) from the kidneys to the pubic symphysis; 10 mg of furosemide injected intravenously (*iv*) prior to *iv* administration of *iv* iodinated contrast medium; arterial phase of the kidneys (25 sec delay); venous phase 60 seconds (sec) after the arterial phase; the area from the kidneys to the symphysis scanning; ten min after the iodinated contrast was injected, a single control scan through the middle part of the kidney was performed to confirm appropriate filling of the renal pelvis. The appropriate filling of the renal pelvis initiated a scout topogram from the kidneys to the symphysis to evaluate appropriate ureteral opacification. If the scout topogram was satisfactory, the next phase was performed; excretory phase or 'urography' (low-dose scan).

The patients were given to drink 600 mL of water 20 min prior to the examination to distend bowel loops and to increase diuresis and distension of the collecting system. A quantity of 120 mL of iodinated contrast medium (300 mg I/mL) was injected at a rate of 4 mL/sec. All examinations were performed in the Institute of Radiology, Clinical Center, Novi Sad. Computed tomography (CT) and MSCTU were performed by a Siemens Somatom Sensation Cardiac 64 scanner and IVU by Telestatix Ei Nis X ray machine, a control unit Innomed TOP-X HF. Examinations were independently interpreted by the two radiologists with equal expertise in uroradiology and the results were analyzed statistically.

### *Sample selection*

The prospective study included 120 patients with a high clinical suspicion of urinary tract disease – 1) patients with macroscopic hematuria scheduled for IVU: both IVU and MSCTU were performed; 2) patients with bladder cancer discovered by cystoscopy or ultrasonography (US) planned for IVU: both IVU and MSCTU were performed; 3) patients with malignant pelvic tumors, after radiation and/or operation, having signs of urinary tract obstruction: both IVU and MSCTU were performed; 4) patients with a suspicion of acute obstruction of the urinary tract (renal colic): MSCTU was performed when no visible calculi on unenhanced scans were detected; 5) patients with retroperitoneal and malignant pelvic tumors planned for CT examination before operation and/or radiation therapy: CT examination + additional phase enabling MSCTU examination were performed; 6) patients with complicated pyelonephritis planned for CT examination: CT examination + 1 phase enabling MSCTU examination were performed; 7) patients (older than 40) with microscopic hemauria: CT examination + additional phase enabling MSCTU were performed.

The group I consisted of 60 patients who underwent IVU + MSCTU. The group II consisted of 60 patients who underwent a CT examination + additional phase enabling MSCTU examination. All the patients included in the study had urea and creatinine levels within normal limits. The exclusion criteria used in the selection of the subjects were low suspicion of urinary tract disease, and patients with microscopic hematuria below the age of 40.

The aim of this study was to examine the place of MSCTU in comparison with IVU as well as to determine the sensitivity and specificity of MSCTU in the evaluation of urothelial abnormalities.

## Results

### *Visualization of urinary tract abnormalities*

The Wilcoxon signed rank test *p*-values (the patients from the group I, the first and the second radiologist) for the quality of urinary tract abnormalities visualization (intraluminal defects, urinary tract without excretory function, intraluminal soft tissue abnormalities, calculi, extraurinary abnormalities) by IVU and MSCTU were statistically significant (Table 1). Comparing the *p*-values for urinary tract abnormalities visualization (the patients from the group I) in-

**Table 1**
**Wilcoxon signed rank test *p*-values for visualization of urinary tract abnormalities in the group I of patients**

| Matched pairs of variables | No. | *Z* | *p* |
|---|---|---|---|
| Intraluminal defect by IVU & MSCTU | 21 | 3.723555 | 0.000196* |
| No. excretory function by IVU & MSCTU | 15 | 3.179797 | 0.001474* |
| Intralum. soft tissue abnormal. by IVU & MSCTU | 17 | 3.621365 | 0.000293* |
| Calculosis by IVU & MSCTU | 14 | 2.934058 | 0.003346* |
| Extra-urinary abnormalities by IVU & MSCTU | 38 | 5.373093 | 0.000000* |

***statistically significant differences**
**IVU – intravenous urography; MSCTU – multislice computed tomography urography**

dependently interpreted by the two radiologists, there were no statistically significant differences found.

The Wilcoxon signed rank test *p*-values (the patients from the group II, the first and the second radiologists) for the quality of urinary tract abnormalities visualization (urinary tract without excretory function, calculi, extraurinary abnormalities) by MSCT and MSCTU were not statistically significant. Comparing the *p*-values for urinary tract abnormalities visualization (MSCT and MSCTU) independently interpreted by the two radiologists, there were no statistically significant differences found.

*Sensitivity*

The *p*-values for the matched pairs sensitivity (patients from the group I) of IVU and MSCTU for parenchymal abnormalities, renal tumors, hydronephrosis, urolithiasis, extraurinary abnormalities and fibrosis were statistically significant. The *p*-values for the matched pairs sensitivity (the patients from the group I) of IVU and MSCTU for pelvicaliceal and bladder tumors were not statistically significant (Table 2).

The Wilcoxon signed rank test *p*-values for the comparison of the diagnosis based on MSCTU and operative findings and those based on MSCTU and histological findings (the patients from the group I) were not statistically significant.

The Wilcoxon signed rank test *p*-values (the patients from the group II) for the sensitivity of MSCT and MSCTU for pyelonephritis, renal tumors, hydronephrosis, pelvic tumors, renal calculi, extrarenal lithiasis, extra-urinary abnormalities, fibrosis, spontaneous rupture and bleeding were not significant.

The *p*-value for the matched pairs diagnosis based on MSCTU and operative findings and the diagnosis based on MSCTU and histological findings (the patients from the group II) were not significant.

*Specificity*

The Wilcoxon signed rank test *p*-values (the patients from the group I) for the specificity of urinary tract abnormalities (parenchymal abnormalities, renal tumors, hydronephrosis, pelvicaliceal tumors, urolithiasis, bladder tumors, extraurinary abnormalities and fibrosis) by IVU and MSCTU were statistically significant (Table 3).

**Table 2**
**Wilcoxon signed rank test *p*-values for the sensitivity of intravenous urography (IVU) and multislice computed tomography urography (MSCTU) for urinary tract abnormalities in the group I of patients**

| Matched pairs of variables | No. | Z | *p* |
|---|---|---|---|
| Parenchymal abnormalities by IVU & MSCTU | 9 | 2.665570 | 0.007686* |
| Renal tumors by IVU & MSCTU | 4 | 2.665570 | 0.007686* |
| Hydronephrosis by IVU & MSCTU | 21 | 2.934058 | 0.003346* |
| Pyelocaliceal tumors by IVU & MSCTU | 6 | 1.000000 | 0.316983 |
| Urolithiasis by IVU & MSCTU | 14 | 2.665570 | 0.007686* |
| Bladder tumors by IVU & MSCTU | 15 | 2.022600 | 0.043115 |
| Extra-urinary abnormalities IVU & MSCTU | 11 | 2.934058 | 0.003346* |
| Fibrosis by IVU & MSCTU | 10 | 2.803060 | 0.005062* |

***statistically significant differences**

**Table 3**
**Wilcoxon signed rank test *p*-values for the specificity of urinary tract abnormalities in the group I of patients**

| Matched pairs of variables | No. | Z | *p* |
|---|---|---|---|
| Parenchymal abnormalities by IVU & MSCTU | 9 | 2.665570 | 0.007686* |
| Renal tumors by IVU & MSCTU | 4 | 2.665570 | 0.007686* |
| Hydronephrosis by IVU & MSCTU | 21 | 2.934058 | 0.003346* |
| Pyelocaliceal tumors by IVU & MSCTU | 6 | 2.665570 | 0.007686* |
| Urolithiasis by IVU & MSCTU | 11 | 2.665570 | 0.007686* |
| Bladder tumors by IVU & MSCTU | 15 | 3.295765 | 0.000982* |
| Extraurinary abnormalities IVU & MSCTU | 11 | 2.934058 | 0.003346* |
| Fibrosis by IVU & MSCTU | 10 | 2.803060 | 0.005062* |

***statistically significant differences**
**IVU – intravenous urography; MSCTU – multislice computed tomography urography**

The Wilcoxon signed rank test *p*-values (the patients from the group II) for the specificity of urinary tract abnormalities (pyelonephritis, renal tumors, pelvic tumors, renal lithiasis, extrarenal lithiasis, extraurinary abnormalities and fibrosis) by MSCT and MSCTU were not statistically significant.

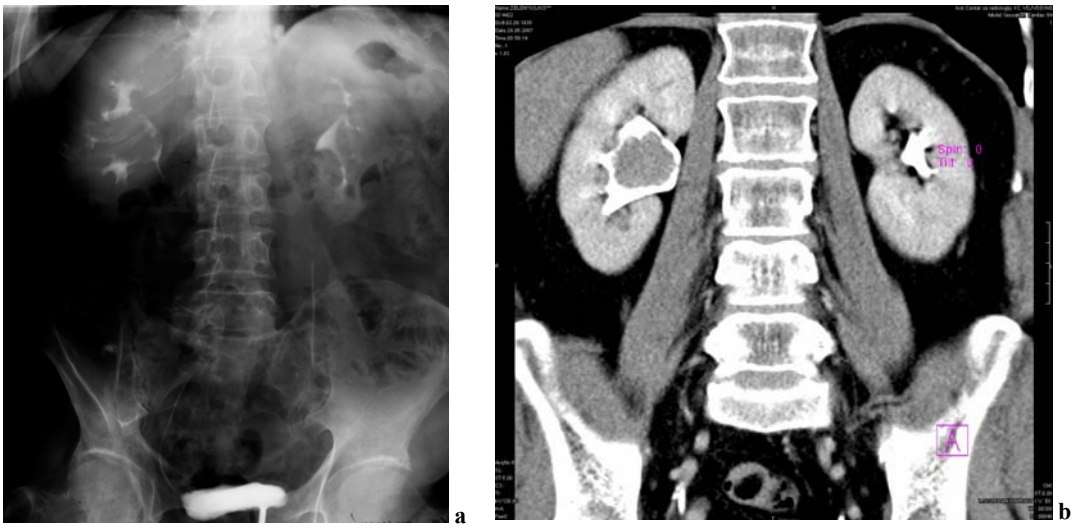
The *p*-value for the matched pairs specificity of hydronephrosis by MSCT and MSCTU was statistically significant.

Figure 1 (a and b) shows the right-sided tumor of the renal pelvis detected by intravenous urography and multiplanar reformated coronal image. The maximum intensity projection and multiplanar reformated axial images, revealed the left-sidedy hydronephrosis as a consequences of fibrous changes caused by Morbus Crohn (Figures 2, a and b).

**Discussion**

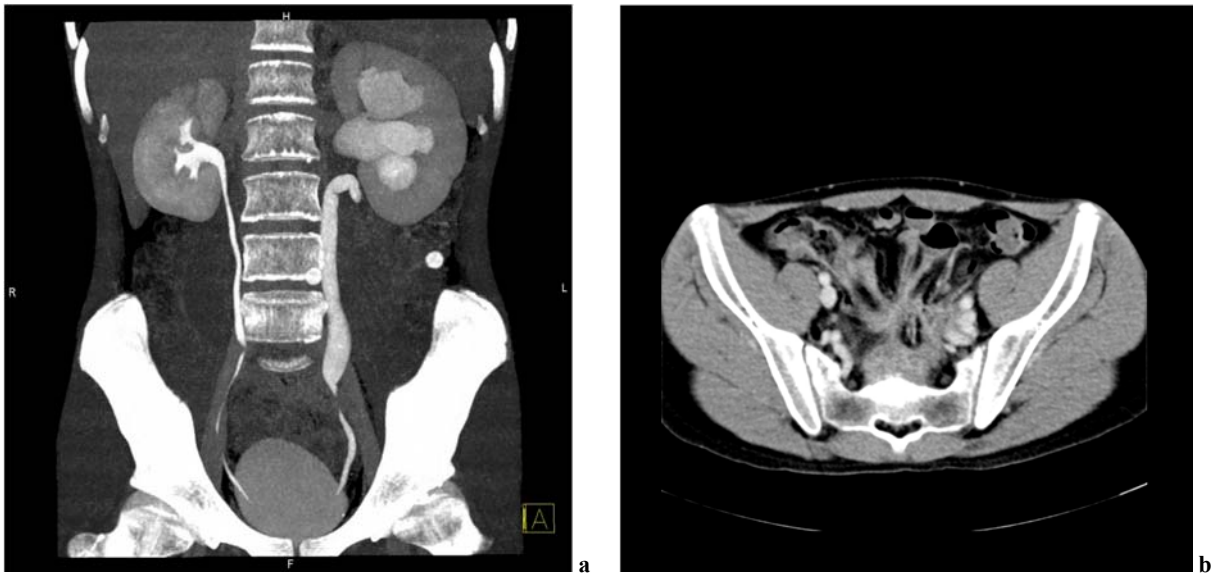
Visualization of the excretory system was better by the MSCTU method due to a dedicated protocol, including routine administration of diuretic, oral hydration (facilitating distension of excretory system and urinary bladder) and scout topogram (at the level of iliac crests). In some cases there were problems with optimal opacification of distal ureter by the MSCTU. That result was similar to the results of the studies performed by Kawamoto et al. [4] and Ernsting et al. [5].

MSCTU was more precise in the visualization of the urinary tract pathologies in the group I of patients. The differential diagnosis for intraluminal defect at IVU included non-calcified concrement, tumor, clot, mycetoma or



**a** **b**

**Fig. 1 – Right-sided tumor of the renal pelvis intravenous urography (a) and multiplanar reformated coronal image (b)**



**a** **b**

**Fig. 2 – Left-sided hydronephrosis as a consequence of fibrous changes caused by Morbus Crohn – maximum-intensity projection (a) and multiplanar reformated axial images (b)**

sloughed renal papilla. In our study, like in the majority of the reported studies, the defect could be clearly defined on MSCTU [6].

In the cases of adequate renal function, IVU and MSCTU were equally sensitive for hydronephrosis [7]. However, in our survey, there were patients with impaired kidney function or even with preserved renal function (renal and multifocal transitonal cell carcinoma – TCC, bladder TCC with infiltration of ureteral orifice and subsequent hydronephrosis, postirradiation fibrosis and obstruction by cervical cancer) where the pelvicaliceal system and ureter was not opacified at IVU, while the excretory system was clearly outlined at MSCTU [7].

This survey confirmed that MSCTU was superior to IVU in the visualization of urinary calculi and other causes of acute lumbar pain, including extraurinary disorders. The cited authors reported that unenhanced CT was 100% sensitive for calculi [8]. Contrary to IVU, MSCTU was reported to visualize extraurinary pathologies, considered as a major advantage [9].

As in the previous studies [7–9], this study confirmed that MSCTU and MSCT were more sensitive in detecting renal parenchymal disorders than IVU. MSCTU was more sensitive for kidney tumors than IVU in our prospective study, which was proved in the cited literature [10, 11].

IVU and MSCTU were equally sensitive in detecting tumors in the renal pelvis in 5 of 6 patients from the group I. In one case they were different (the patient with multifocal TCC), as IVU had not visualized the pelvicaliceal system (the absence of renal function due to hydronephrosis).

In our study MSCTU was more sensitive and specific in detecting urolithiasis than IVU. Such results were confirmed in the literature [12–14].

There were no statistically significant differences in sensitivity between MSCTU and IVU for bladder tumors in our survey. IVU was insufficient in displaying focal thickening of the bladder wall in patients who previously underwent transurethral resection (TUR) of bladder tumor. Thickening of the bladder wall was observed on MSCTU, and recurrence was suspected, but cystoscopy showed fibrous changes after TUR. IVU and MSCTU were equally sensitive for larger polypoid bladder tumors. Infiltrative tumors of the urinary bladder on IVU were presented as finger-like filling defects, while MSCTU visualized thickening of the wall, as well as perivesical changes (fat tissue infiltration, locoregional lymphadenopathy, infiltration of surrounding organs – seminal vesicles and prostate) for which IVU was insufficient. In a patient with retroperitoneal infiltration, spreading to the anterior-upper wall of the urinary bladder, IVU presented normal findings, while MSCTU displayed the disease. In general, MSCTU was more sensitive for urinary bladder tumors with a preserved bladder shape and with minimal wall thickening [9], but in our survey bigger polypoid bladder tumors were detected, for which IVU and MSCTU were equally sensitive.

When analyzing the diagnosis set by MSCTU compared to the operative findings and histological diagnosis, there were no statistically significant differences, which indicated that MSCTU enabled the correct diagnosis for the majority of patients in our study. MSCTU diagnosis was not correct in the two patients from the group I. One patient had massive hematuria, with the presence of soft tissue structure in the region of ureteropelvic junction (UPJ) and upper pole calyces, with attenuation numbers suggesting the presence of clots. The suspicion of underlying malignancy was not confirmed on imaging studies. However, the clinicians decided to perform total nephrectomy, as hematuria was long-lasting and massive. Histological diagnosis showed chronic pyelonephritis, with areas of dysplastic epithelium. In another patient with massive hematuria from the group I, intraluminal clots and discrete irregularities of several calices were seen on MSCTU, raising suspicion of papillary necrosis. After the surgery, histological analysis showed the presence of TCC.

MSCTU was superior to IVU when comparing the specificity for parenchymal abnormalities in the group I of patients. In our survey, the superiority of MSCTU for parenchymal abnormalities related to the changes in pyelonephritis and parenchymal tumors was obviated. Such results have already been reported [7, 9, 15]. MSCTU was more specific for hydronephrosis than IVU in the group I of patients, because it could determine the cause of hydronephrosis even in the patients with the absence of renal excretory function. MSCTU was more specific compared to IVU for tumors of the excretory system (Figure 1) and bladder in the group I of patients. IVU visualized defects, but IVU alone did not enable the final diagnosis, as the same appearance might be mimicked by neoplasm, coagulum, noncalcified concrement or sloughed papillas. MSCTU provides information on lesion charactaterization and on tumor stage. Cystoscopy is still considered the gold standard in the diagnosis of urinary bladder tumors, but MSCTU is a challenging competitor.

MSCTU was more specific than MSCT for hydronephrosis in the group II of patients, i.e. defining the cause of hydronephrosis. This result was obtained because of the superiority of MSCTU to MSCT in patients with obstruction without visible concrement on plain, unenhanced scans (in 7 patients). The causes of hydronephrosis were rectosigmoidal cancer with extraluminal spread and infiltration of the distal ureter, aberrant arteries, stenosis of UPJ, Crohn's disease with fibrous alterations involving the ureter (Figure 2) and fibrous postoperative changes in the pelvis. The findings were equivocal in all the listed cases (with the exception of fibrous changes) because of the wall thickening, which could also indicate infiltration. Despite the equivocality, MSCTU provided an accurate diagnosis. MSCTU was performed according to the special protocol which enabled better visualization of the urinary tract compared to the standard MSCT examination, and, therefore, the level of obstruction can be evaluated appropriately. The integral part of MSCTU protocol is the arterial phase, which can clearly show aberrant arteries and maximum-intensity projection (MIP) reconstructions in postprocessing can show stenosis. MSCT findings suspected hydronephrosis without a visible concrement, but MSCTU in excretory phase clearly showed peripelvic cysts in one patient from the group II.

**Conclusion**

The obtained results support MSCTU to be the modality of choice in the diagnostic algorithm of patients with macroscopic hematuria and in evaluation of microscopic hematuria and unexplained obstruction of the urinary tract. The only remaining role for IVU in our institution is imaging of the upper urinary tract in patients with hematuria under the age of 40.

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# Color Doppler ultrasonography and multislice computer tomography angiography in carotid plaque detection and characterization

## Primena kolor dopler ultrasonografije i višeslojne kompjuterizovane tomografske angiografije u otkrivanju i karakterizaciji karotidnog plaka

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**Abstract**

**Beckground/Aim.** Cerebrovascular diseases are the third leading cause of mortality in the world, following malignant and cardiovascular diseases. Therefore, their timely and precise diagnostics is of great importance. The aim of this study was to compare duplex scan Color Doppler ultrasonography (CDU) with multislice computed tomography angiography (MSCTA) in detection of morphological and functional disorders at extracranial level of carotid arteries. **Methods.** The study included 75 patients with 150 carotid arteries examined in the period from January 2008 to April 2009. The patients were firstly examined by CDU, then MSCTA, followed by the surgery of extracranial segment of carotid arteries. In 10 patients, the obtained material was referred for histopathological (HP) examination. We used both CDU and MSCT in the analysis of: plaque surface, plaque structure, degree of stenosis, and the presence of intraplaque hemorrhage. **Results.** The results obtained by CDU and MSCTA were first compared between themselves, and then to intraoperative findings. Retrospective analysis showed that MSCTA is more sensitive than CDU in assessment of plaque surface (for smooth plaques CDU 89% : MSCTA 97%; for plaques with irregular surface CDU 75% : MSCTA 87%; for ulcerations CDU 54% : MSCTA 87%). Regarding determination of plaque structure (mixed plaque CDU 66% : MSCTA 70%; correlation with HP findings CDU 94% : MSCTA 96%) and localization (CDU 63% : MSCTA 65%), and in terms of sensitivity and specificity, both methods showed almost the same results. Also, there is no statistical difference between these two methods for the degree of stenosis (CDU 96% : MSCTA 98%). **Conclusion.** Atherosclerotic disease of extracranial part of carotid arteries primarily affects population of middle-aged and elderly, showing more associated risk factors. Sensitivity and specificity of CDU and MSCTA regarding plaque composition, the degree of stenosis and plaque localization are almost the same. These results and the fact that there are no adverse effects (high radiation dose) compared to MSCTA indicate that CDU should be the initial method in diagnostic algorythm for carotid arteries.

**Key words:**
**ultrasonography, doppler, color; cerebral angiography; carotid artery diseases; carotid stenosis; tomography, x ray computed.**

**Apstrakt**

**Uvod/Cilj.** Cerebrovaskularne bolesti posle malignih i kardiovaskularnih oboljenja najčešći su uzrok mortaliteta u svetu. Zbog toga, pravovremena i tačna dijagnostika oboljenja na ekstrakranijalnom segmentu karotidnih arterija, kao jednog od osnovnih činilaca u nastanku cerebrovaskularnih bolesti, od velikog je značaja. Cilj ove studije bio je da se uporede rezultati kolor dopler ultrasonografije (CDU) i višeslojne kompjuterizovane tomografske angiografije (MSCTA) u određivanju postojanja morfoloških i funkcionalnih poremećaja na ekstrakranijalnom segmentu karotidnih arterija. **Metode.** Studija je obuhvatala 75 bolesnika kod kojih je pregledano 150 karotidnih arterija, od januara 2008. do aprila 2009. Bolesnicima je prvo urađen CDU i MSCTA, a zatim operacija karotidnih arterija. Kod 10 bolesnika uzet je materijal za patohistološku (PH) analizu. Analizirani su sledeći parametri : površina plaka, sastav plaka, stepen stenoze ekstrakranijalnog dela karotidne arterije i postojanje intraplakalne hemoragije. **Rezultati.** Rezultati CDU i MSCTA upoređeni su međusobno, a zatim i sa intraoperativnim nalazom. Utvrđeno je da je MSCTA senzitivnija nego CDU u vizulizaciji površine plaka (kod glatkih plakova CDU 89% : MSCTA 97%; kod plakova neravne površine CDU 75% : MSCTA 87%; kod ulkusa CDU 54% : MSCTA 87%). U odnosu na sastav plaka MSCTA je senzitivnija u odnosu na CDU (mešoviti plak CDU 66% : MSCTA 70%; korelacija sa PH nalazom CDU 94% : MSCTA 96%), dok su u odnosu na lokalizaciju plaka (CDU 63% : MSCTA 65%) senzitivnost i specifičnost obe metode približno isti.

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Ne postoji statistički značajna razlika između metoda u odnosu na postojanje stepena stenoze ekstrakranijalnog dela karotidne arterije (CDU 96% : MSCTA 98%). **Zaključak.** Aterosklerotska bolest karotidnih arterija javlja se kod bolesnika srednjeg i starijeg životnog doba, često udružena sa faktorima rizika. Senzitivnost i specifičnost CDU i MSCTA u proceni sastava plaka, stepena stenoze i lokalizacije plaka karotidnih arterija približno je ista. Zbog dobijenih rezultata i činjenice da nema štetnog efekta (visoke doze zračenja) u odnosu na MSCTA, CDU treba da predstavlja inicijalnu metodu u dijagnostičkom algoritmu karotidnih arterija.

**Ključne reči:**
**ultrasonografija, dopler, kolor; angiografija mozga; a. carotis, bolesti; a carotis, stenoza; tomografija, kompjuterizovana, rendgenska.**

## Introduction

Carotid atherosclerotic disease is the cause of cerebrovascular insult in 20% of cases and is often associated with atherosclerotic changes in coronary and peripheral vessels. Carotid disease is determined by the level of arterial stenosis, morphology of plaque and present ulceration. Ulceration of plaque is defined as "intimal defect greater than 1000 μm in depth covered with necrotic atherosclerotic plaque [1].

The presence of ulceration in plaque is an important risk factor for the occurrance of neurological symptoms, while high-grade stenosis associated with ulceration carries high risk of developing cerebrovascular insult (CVI). The incidence of ulceration in the carotid artery varies from 14% to 68%, and is more often in symptomatic patients.

Conventional or digital subtractional angiography (DSA) is still considered to be the gold standard for assessing the level of stenosis, but is somewhat insufficient in determination of plaque morphology (sensitivity 46%, specificity 74%) [2].

In spite of constant improvement of angiographic technique, it is sometimes followed by some complications. There are local, general [3] and neurological complications [4]. These complications are the main reason for common use of non-invasive techniques, such as color Doppler ultrasonography (CDU), [5], magnetic resonance angiography (MRA) and multislice computed tomographic angiography (MSCTA) in the diagnostics and assessment of carotid disease, as well as in determination of plaque morphology.

Stenosis of carotid arteries is one of the main factors in defining further treatment of a patient [6]. Treatment modalities in a preventive programme of cerebrovascular insult are: carotid endarterectomy (CEA), stenting of the carotid artery (CAS) and medicamentous therapy. The NASCET (North American Symptomatic Carotid Endarterectomy Trial) [7, 8] and ACAS study (Asymptomatic Carotid Atherosclerotic Group) [7, 9] showed that carotid thrombendarterectomy (CEA) significantly decreases the risk of developing CVI, in comparison to medicamentous therapy, not only in symptomatic, but also in asymptomatic patients.

The aim of this study was to determine reliability of CDU and MSCTA in diagnostics of carotid artery stenosis and morphologic features of plaque, in comparison to the intraoperative findings.

## Methods

This randomized retrospective study included 75 patients with 150 arteries examined, in one-year period (May 2008 – May 2009). There were 24 female and 51 male patients, average age of 63.7 years (ranging from 37 to 86). All the patients were referred to examination by the vascular surgeon, with prior MRA findings.

The following symptoms were analyzed: headache, dizziness, vertigo, tingling in extremities, sight problems. The following risk factors were analyzed: smoking, diabetes, hypertension, chronic renal insufficiency, hyperlipoproteinemia, and associated pathology: cerebrovascular insult, coronary infarction and peripheral arterial occlusive disease. Prior vascular interventions, such as classical surgical interventon (TEA), coronary stenting, peripheral stenting (aortoiliac or femoropopliteal segment) or contralateral carotid stenting were also taken into account. Neurological status included history of prior CVI.

The patients were firstly subjected to CDU, and then to MSCTA of carotid arteries in the same day, and afterwards (with the maximum of two-days delay) operation of the extracranial segment of carotid arteries was performed. After thrombendarterectomy, plaque sample was referred to pathohistological analysis.

CDU was performed by the experienced radiologist on the GE LOGIC 7 sonographic unit, with a transducer of 12MHz. MSCTA was performed by the same radiologist at multislice spiral CT scanner Somatom Sensation 64 Siemens, using the bolus-triggering technique. After a short explanation of examination technique, all the patients signed the standard informed consent. No patients presented with contraindications to application of *iv* contrast agent (all the patients had normal values of urea and creatinine, and no history of allergic reactions to iodine).

Intravenous non-iodine contrast agent (iopromid – Ultravist 370, Bayer Shering) was applied *via* cubital vein in the dose of 100–120 mL, flow 4 mL, programme Carotid vascular. The contrast agent was applied using an automatic injector, followed by the bolus of 40 mL of physiologic solution (NaCl) *via* the same system.

The technical parameters were as follows: matrix 512 × 512; FOV 14–19 cm; tube voltage mA 180–200 kV 120; slice thickness 1.6 mm. The center of the window was placed at the level of 200 HU, and attenuation range of 750 HU.

Scanning was performed from the level of aortic arch with vizualization of the circle of Willis.

The total examination time (with a patient preparing) was 10–20 min. After the examination protocol, data processing was done using software packages: MIP, MPR and VRT. Time necessary for postprocessing as well as for the interpretation of the obtained information depends on the ra-

diologist's experience and software package and ranges from 20 to 30 min.

Ultrasound cross sectioning of the extracranial segment of carotid arteries in B mode using CDU transversal and longitudinal scans, was performed in order to assess: plaque localization, plaque structure, plaque surface, intraplaque hemorrhage, the degree of stenosis of carotid arteries. The same parameteres were analyzed using MSCTA.

*Plaque localization*

Plaques were divided in several groups according to localization: localized exclusively in the bulb, localized in the bulb and proximal part of ACI, in the bulb, proximal parts of ACI and ACE, localized in ACC, the bulb and proximal parts of ACI and ACE.

*Plaque structure*

According to the O'Donnel's [10] postulates, in B- mode (black-white scale) modified by Bluth [11], there are 5 different types of plaques depending on echogenicity: type 1 – anechogenic plaque with echogenic fibrous cap; type 2 – predominantly anechogenic plaque but with echogenic fields that takes up to 25% of plaque volume; type 3 – predominantly hyperechogenic plaque with hypoechogenic areas that take up to 25% of plaque; type 4 – echogenic and homogenous plaque and type 5 – non-classified plaques that are covered with calcium and have acoustic shadow which masks plaque morphologic structure. Plaques were classified as homogeous or inhomogenous according to their echogenicity (uniform echogenicity makes it homogenous).

Following the Shroeder et al. [12] MSCTA classification, plaques were divided into 3 groups on axial images: group I – "fatty" plaque (attenuation < 50 HU); group II – mixed plaque (attenuation 50–119 HU) and group III – calcific plaques (attenuation > 120 HU). Attenuation was measured in Hounsfield units using circular cursor placed in the plaque.

*Plaque surface – intraplaque hemorrhage*

According to Kardoulus et al. [13] plaque surface is defined as: smooth, irregular, ulcerated and all three types with intraplaque hemorrhage.

Ulceration followingf this definition is continuous contour with focal lesion greater than 1 mm in both depth and width, with well-defined posterior wall at the plaque base, and with anechogenic surface in the plaque which is more than 1 mm deep and wide.

In B- mode and CDU intraplaque hemorrhage is presented as focal, echolucent zone in the irregular plaque with heterogenous structure.

On MSCTA intraplaque hemorrhage is seen as hyperdense zone in the plaque on precontrast images. After contrast injection, demarcation of the hemorrhage contour is more clear inside the plaque (so-called inhomogenous imbibition – MIP, MPR).

*The degree of stenosis*

As recommended in NASCET and ESCET studies [14], the degree of carotid artery stenosis was defined using CDU and MSCTA. Hemodinamic criteria used in CDU were maximum sistolic velocity over 230 cm/s (aveage 50 to 100 cm/s) and sistolic velocity in internal and common carotid artery ratio over 2.5. The degree of stenosis was defined according to residual volume on transversal scans. Following these criteria, stenosis of the carotid artery is divided into following groups: stenosis lower than 50%, 50–69%, 70–89%, 90–99%, occlusion.

The results obtained on CDU and MSCTA were compared between each other, and both with intraoperative finding, while in a certain number of patients [20], the material obtained from endarterectomy was referred to histologicpatho (HP) evaluation.

All the patients were subjected to a form of classical surgical method (eversion technique or thrombendarterectomy with patch or Dacron). Macroscopic evaluation of the plaque surface was performed by two experienced surgeons after extirpation from carotid artery (smooth, irregular, ulcerated). Ulceration is defined as macroscopic loss of intimal integrity wider and deeper than 1 mm.

HP analysis was performed at the School of Medicine, Novi Sad, Pathology Department, using hematoxylin and eozin, Van Gieson stain and Masson trixrom with anilin blue. As fixative 4% formaline was used. For Van Giseon staining paraffin cuts of 6 μm were made, so that elastic fibres turned to purpur red to dark brown color, nuclei were brownish and connective tissue yellow. Collagen fibres were deep red. Plaque struture and surface were defined using HP analysis.

The data were analyzed and showed in tables and figures with discussion, depending on the nature of the observed feature. Description of numeric variables was performed using classical methods of descriptive statistics (aritmetic mean, median) and measures of variability (standard deviation, variability coefficient and standard error, as well as minimum and maximum values). Relative numbers were used in all the tables. The Pearson's chi-square test was used (congruence test and contigency tables) for comparison of frequency difference in non-parametric variables. The unpaired Student's *t*-test for two independent data groups and variance were used. For comparing three or more groups of data, we used analysis of variance (ANOVA) for parametric data and non-parametric analysis of variance for non-parametric data.

**Results**

Average age of the patients included in this study was 63.7 years (min 47.0, max. 82.0, SD 8.5 years). Most frequently reported symptoms were associated in 47 (60%), vertigo in 29 (38.7) and tinnitus in 23 (30.7%) of the patietns.

The leading risk factor was hyperlipoproteinemia (HLP) type IIb, found in 50 (67%) of the patients, while 25 (33%) had normal values of blood lipids. The obtained difference was statistically highly significant ($\chi^2 = 11.067$; df = 1; $p < 0.01$) as a result of widespread HLP IIb in the patients.

Cerebrovascular insult, together with myocardial infarction was the most frequent associated disease in patients with extracranial carotid disease, found in 46 (61%) of the patients. Peripheral arterial stenosis/occlusion was present in 4 (5.4%) of the patients. The difference between the two groups was statistically highly significant ($F = 13.449$; $df = 3$; $p < 0.01$).

Most patients, 55 (73%), included in the study had no prior history of vascular interventions, while in 12 (15%) patients coronary or peripheral/ iliac stent had been placed ($F = 17.679$; $df = 4$; $p < 0.01$).

Considering plaque localization the results obtained by CDU and MSCTA were almost identical. By both methods, plaque was most often located in the bulb of ACC and proximal part of ACI (CDU 63% : $F = 11.940$; $df = 5$, $p < 0.01$; MSCTA 65% : $F = 11.200$; $df = 6$, $p < 0.01$) (Figures 1 and 2).

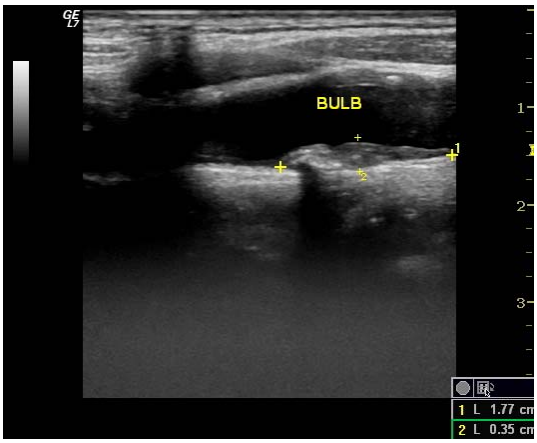


**Fig. 1 – Plaque localization: multislice computed tomographic angiography (MSCTA) finding – bulbus *a. carotis communis* (ACC)**

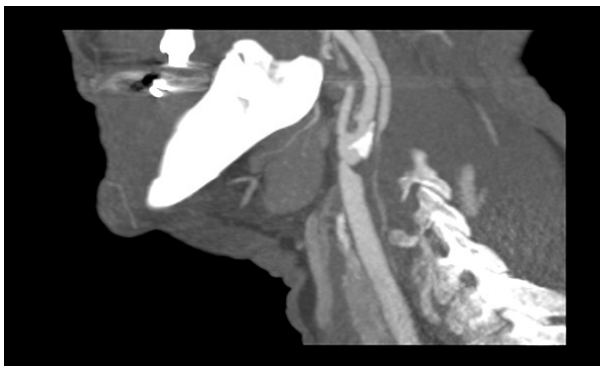

**Fig. 2 – Plaque localization: multislice computed tomographic angiography (MSCTA) finding – a. *carotis interna* (ACI) prox**

Analysis of plaque structure revealed that most plaques were of mixed type (fibrolipid and fibrous-calcificated) and the results of CDU and MSCTA were similar (CDU 55% : $F = 20.279$; $df = 4$, $p < 0.01$; MSCTA 54% : $F = 22.147$; $df = 4$; $p < 0.01$) (Tables 1 and 2).

**Table 1**

**Comparison of color Doppler ultrasonography (CDU) and multislice computed tomography angiography (MSCTA) plaque structure findings**

| Plaque structure | CDU (n) | CDU (%) | MSCTA (n) | MSCTA (%) |
|---|---|---|---|---|
| Normal | 6 | 8.0 | 10 | 13.3 |
| Lipid | 7 | 9.3 | 6 | 8.0 |
| Fibroous | 4 | 5.3 | 6 | 8.0 |
| Calcified | 3 | 4.0 | – | – |
| Mixed | 55 | 66.4 | 53 | 70.7 |
| Total | 75 | 100.0 | 75 | 100.0 |

**Table 2**

**Degree of stenosis determined by color Doppler ultrasonography (CDU) and multislice compute tomographic angiography (MSCTA)**

| Degree of stenosis (%) | Number of patients (n) | |
|---|---|---|
| | CDU | MSCTA |
| None | 7 | 6 |
| 0–49 | 12 | 12 |
| 50–69 | 3 | 4 |
| 70–89 | 34 | 33 |
| 90–99 | 16 | 17 |
| Occlusion | 3 | 3 |

This study showed that sensitivity of CDU and MSCTA was almost the same regarding plaque surface, which was later confirmed intraoperatively and histopathologically. Most often, the surface was irregular. Sensitivity of MSCTA was 100% and of CDU 95.2% (Figures 3 and 4).

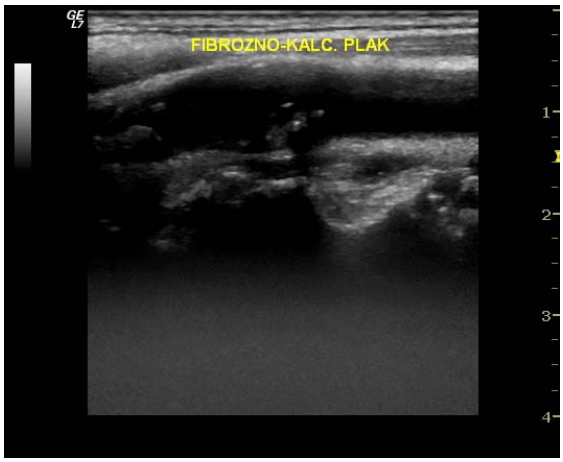


**Fig. 3 – Irregular surface of mixed plaque – color Doppler ultrasonography (CDU)**

There was no statistically significant difference considering visualization of the ulceration by using CDU and MSCTA.

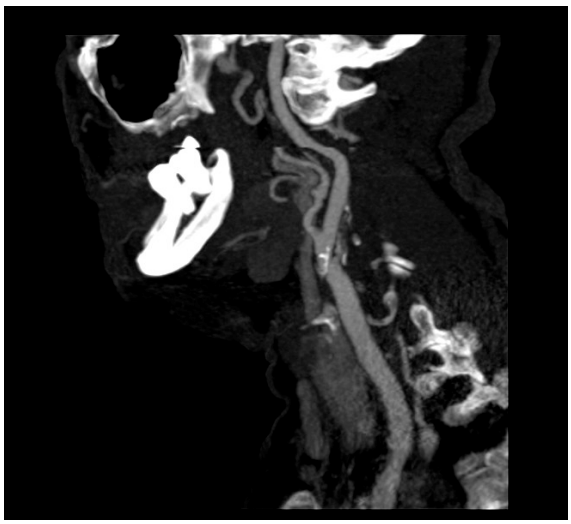

**Fig. 4 – Irregular surface of fibrous calcified plaque – multislice computed tomographic angiography (MSCTA)**

Furthermore, there was no statistically significant difference in determining the degree of stenosis between the two methods (Figures 5 and 6).

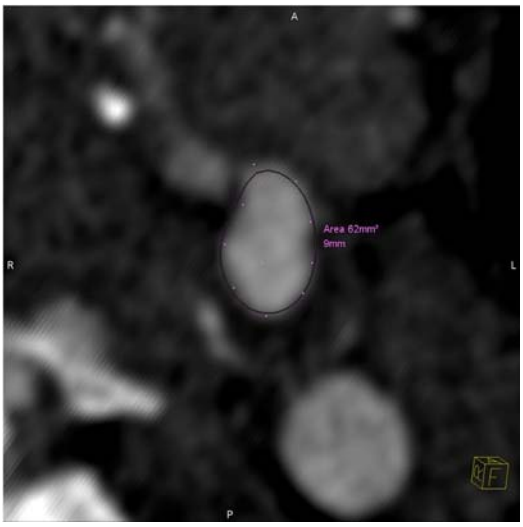

**Fig. 5 – Degree of stenosis measurement by multislice computed tomographic angiography (MSCTA)**

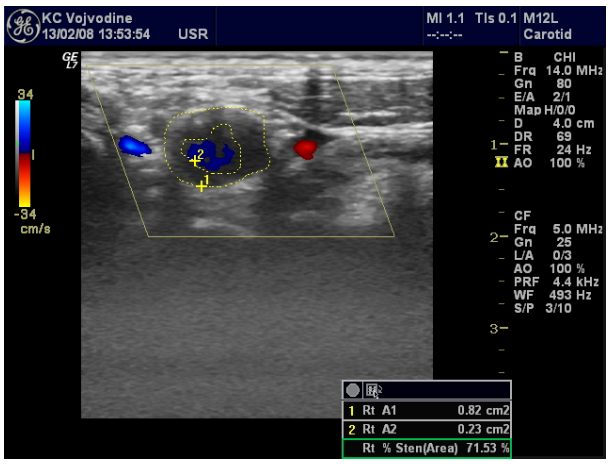


**Fig. 6 – Measurement the degree of stenosis – color Doppler ultrasonography (CDU)**

The study showed that most patients, 34 (45.3%), had stenosis of 70–89% confirmed by CDU and MSCTA (CDU: $F = 21.937$; $df = 5$; $p < 0.01$; MSCTA: $F = 23.322$, $df = 5$, $p < 0.01$). False negative findings in CDU were present in 4 (5.4%) of the patients in the group with low-grade stenosis (under 50%).

Sensitivity of CDU and MSCTA was proven to be the same (100%) in confirming occlusion of carotid arteries. Only in 1 (0.7%) patient there was a disagreement between CDU and MSCTA (false negative finding on CDU). Intraoperatively, occlusion of carotid artery was found (Figure 1).

## Discussion

Carotid disease, which is a part of generalized atherosclerotic vessel disease, is one of the causes of CVI. This fact has been confirmed in the literature, particularly in the USA where CVI represents the third most frequent death cause, following cardiovascular and malignant diseases. In the USA there is one CVI occuring every three minutes, and the costs of treatment are about 51 billion dollars per year. Therefore, it is understandable that CVI has an extreme improrttance in socioepidemic and economy aspects [15]. Consequently, adequate and timely diagnostics is important in treatment of carotid disease.

This study showed that plaque was most frequently localized in the bulb and proximal part of ACI: CDU – 41 (55.4%) patients, MSCTA – 48 (64%).

Analyzing the results obtained on CDU, we found 7 (10%) false negative results, compared to MSCTA and intraoperative findings. In those patients, plaque was not only seen in the bulb but could also be visualized in the proximal part of ACI. The explanation is, that in cases of highly positioned bulb or short neck, adequate visualization of the proximal part of ACI is not possible. In addition, visualization is problematic in circular proximal parietal calcifications both in the bulb and ACI.

Suboptimal visualization of plaque can occur on MSCTA examination due to atrifacts caused by the surrounding bone structures (shoulder region, teeth) but it is less pronounced. Anyway, there is no statistically significant difference between the results on CDU and MSCTA.

Numerous authors confirmed that plaque is most often localized in the bulb and the proximal part of ACI [16], for the reason of the bulb anatomy, its size and hemodinamic characteristics. The bulb is almost double as wide as the internal carotid artery which results in specific hemodinamic features. We presented similar results.

Analizing plaque surface in carotid arteries is one of the key questions in assessment of the risk of complications and for determining further treatment steps.

In this study, almost the same sensitivity was shown between two methods considering plaque surface, which was later confirmed intraoperatively and pathohistologically, and was in accordance with the literature [7]. Sensitivity of CDU was 87.2%, while of MSCTA 91.4%.

In some studies on plaque surface in the carotid arteries, the advantages of MSCTA were reported. Kagava et al. [8]

found the sensitivity of MSCTA to be 91.2% and specificity 91.4% on the sample of 68 carotid arteries, compared to intraoperative findings.

Niderkoorn et al. [17] reported that the sensitivity and specificity of MSCTA significantly correlate to the intraoperative and HP findings for plaque surface (MSCTA 92.5% compared to intraoperative findings and 89.7% compared to HP).

Link et al. [18] found the sensitivity of CDU to be low in detection of ulceration (37.6%) as compared to intraoperative findings. Low sensitivity of CDU is probably due to large calcificated areas that cover ulcerations, or misplacement of the transducer referring blood vessel and ulceration.

Our study, however, did not show a statistically significant difference in depicting the ulceration between CDU and MSCTA.

Data presented in this paper are in accordance with results found in the literature on MSCTA, but there is a certain disagreement regarding CDU examinations (95.2% : 37.4%) [18]. This disagreement could be explained by the fact that in this study examinations were performed by the same experienced radiologist in all the patients, on the same US unit, using the same hemodinamic and morphologic criteria for the degree of stenosis, plaque morphology and structure. A relatively small number of patients and a low number of calcificated plaques might also contribute to this difference to a certain degree.

The disadvantages of B-mode and CDU in plaque surface defining are that it is a subjective method depending on the radiologist's experience and sonography unit quality. Nevertheless, all the studies showed that MSCTA has high sensitivity and specificity in detection of plaques with irregular surface and ulcers as compared to CDU findings [8, 17, 18].

Analysis of plaque structure in this study showed that most plaques were mixed, fibrolipid and fibrous-calcific in 55 (66.4%) of the patients, and the results reported by CDU and MSCTA were similar (66% – CDU and 70% – MSCTA). Both methods highly correlated to intraoperative and HP findings (CDU 94% and MSCTA 96%).

The results showed that CDU is less reliable in patients with short neck, highly positioned bulb and rough calcifications, which as well degrade the quality of MSCTA examination.

Geroulakos et al. [19] indicate that fibrous plaque does not have thromboembolic potential, which is present in ulcerated mixed plaques and those with intraplaque hemorrhage.

Walker et al. [20] reported that ulcerations are more frequent in lipid plaques than in calcificated. Relationship between plaque structure and clinical manifestation of the disease is still not clearly defined, but it is shown that cerebrovascular insults more frequently occur in patients with lipid plaques.

Fisher et al. [21] reported that the number of "silent brain infarctions" is greater in patients with ulcerated and lipid plaques compared to calcific, and implied that the presence of calcium is important for plaque stability.

A group of authors [17, 19–21] showed that plaque calcification negatively affects visualization and precise definition of plaque morphology on CDU and MSCTA. Ulcerations smaller than 5 mm are hardly visualized with MSCTA, even more if there are artifacts from surrounding bone structures and movements of the patients during examinations. Shaalan et al. [22] analyzed 48 plaque samples after CEA, and reported that in patients without calcifications in plaque, cerebrovascular symptomatology occured more frequently.

The degree of stenosis in carotid disease directly correlates to size and structure of plaque. It is possible to evaluate stenosis as a hemodinamic feature in real time using CDU, while MSCTA enables only depiction of its morphologic aspect. The degree of stenosis and disrupted hemodinamic are the crucial parameters in extracranial carotid disease.

There are some limitations in determination of flow velocity in the carotid arteries using CDU, but most authors rely on the NASCET and ECST criteria [14]. Some authors recommend the following exclusively hemodynamic criteria (maximum sistolic and diastolic velocities, sistolic velocities ratio in ACI and ACC). Priorly, sistolic velocity over 130 m/s was considered as criterion for stenosis over 70% while Nederkoorn et al. [17] and Kagawa et al. [8,] imply that those velocities can go up to 300 m/s.

Meta-analyses [8, 14, 17] have shown that MSCTA is a diagnostic method of high sensitivity (97%) and specificity (99%) in cases where the degree of stenosis in carotid arteries is lower than 70%. On the contrary, when stenosis is higher than 70%, sensitivity and specificity decrease (sensitivity 85%, specificity 93%) [23]. It is pronounced in patients with calcified circular plaques in carotid arteries, because they are susceptible to artifacts which disable adequate evaluation, as confirmed in several studies [11, 18, 20]. The disadvantage of MSCTA is also a high radiation dose during the examination [24].

## Conclusion

Atherosclerotic carotid arteries disease affects mostly middle-aged and elderly patients, and is often associated with various risk factors. Sensitivity and specificity of CDU and MSCTA in determination of plaque composition, the level of stenosis and plaque localization in carotid arteries are almost the same. The results obtained in the study and the fact that there is no significant adverse effect (radiation dose level) compared to MSCTA, favour CDU as the initial method in diagnostics algorithm in carotid artery disease.

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# Primena supkutane paratibijalne fasciotomije u lečenju hroničnog venskog ulkusa

## Subcutaneous paratibial fasciotomy in the treatment of chronic venous ulcer

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**Apstrakt**

**Uvod/Cilj.** Hronični venski ulkus spada u oboljenja visoke incidencije i predstavlja jednu od najtežih komplikacija hroničnе venske insuficijencije. Procenjuje se da u odrasloj populaciji od hroničnog venskog ulkusa boluje 1–2% osoba, što ima veliki socijalno-ekonomski značaj. Cilj ove studije bio je da se kroz kliničko iskustvo utvrdi uticaj supkutane paratibijalne fasciotomije na tok i ishod lečenja hroničnog venskog ulkusa. **Metode.** Od februara 2006. do septembra 2009. godine, u okviru lečenja hroničnog venskog ulkusa, u grupi od 43 bolesnika primenjena je supkutana paratibijalna fasciotomija uz ostale klasične metode lečenja, a, potom, praćen je njen uticaj na klinički tok ulkusa krurisa u odnosu na drugu grupu od 43 bolesnika kod kojih su primenjene klasične metode lečenja bez paratibijalne fasciotomije. **Rezultati.** U grupi bolesnika u kojoj je primenjena supkutana paratibijalna fasciotomija došlo je do znatno povoljnijeg kliničkog toka zatvaranja ulkusa krurisa u odnosu na grupu bolesnika kod kojih ova metoda nije primenjena. Kod bolesnika iz grupe sa paratibijalnom fasciotomijom nije došlo do neprihvatanja kožnog transplantata po Tiršu, niti do recidiva ulkusa u periodu od šest meseci nakon operacije, dok je kod kontrolne grupe došlo do neprihvatanja transplantata po Tiršu kod 11 bolesnika, a kod devet do recidiva ulkusa u prvih šest meseci postoperativno. **Zaključak.** Supkutana paratibijalna fasciotomija predstavlja korisnu metodu koja utiče na bolji klinički tok zatvaranja ulkusa krurisa, smanjuje stopu recidiva i omogućava poboljšanje lokalne mikrocirkulacije u pogođenoj regiji. Sam operativni akt je bezbedan, ne zahteva posebnu aparaturu niti specijalnu obuku hirurškog tima, te kao takav primenjiv je kod najvećeg broja bolesnika sa ulkusom krurisom koji su kandidati za operativno lečenje.

**Ključne reči:**
**vene, varikozne; ulkus kruris; režnjevi, hirurški; fascija; disekcija; prognoza.**

**Abstract**

**Background/Aim.** Chronic venous ulcer (CVU), a disease of high incidence, is one of the most serious chronic venous insufficiency complications. It has been estimated that there are 1%–2% of adults with CVU deriving a high social significance. The aim of this study was to, using the clinical experience, determine the influence of subcutaneous paratibial fasciotomy (SPF) on the course and the treatment outcome of CVU. **Methods.** From February 2006 to September 2009 SPF was applied in a group of 43 patients treated for CVU along with other standard methods of treatment, and its influence on the course of ulcus cruris was followed up regarding the control group of another 43 patients treated with standard methods with no paratibial fasciotomy. **Results.** In the group of patients treated with SPF there was a significantly better clinical course of ulcus cruris closing as compared with the group of patients in which this method was not applied. In the group with paratibial fasaciotomy there was no Thiersch skin transplant rejection recorded nor ulcus recurrence within a 6-month after-surgery period, while in the control group there was Thiersch skeen transplant rejection in 11 patients, and ulcus recurrence in 9 patients within the same period. **Conclusion.** SPF is a useful method with a favorable influence on better clinical course of ulcus cruris closing, reducing recurrence rate and improving local microcirculation in the affected region. Operation act itself is safe, requires no specific equipment nor special training of the team of surgeons, thus being applicable to the majority of patients with ulcus cruris indicated for surgery.

**Key words:**
**varicose veins; varicose ulcer; surgical flaps; fascia; dissection; prognosis.**

### Uvod

Hronični venski ulkus (HVU) spada u oboljenja visoke incidencije i predstavlja jednu od najtežih komplikacija hroničnе venske insuficijencije. Procenjuje se da u odrasloj populaciji od hroničnog venskog ulkusa boluje 1–2% osoba, što ima veliki socijalno-ekonomski značaj. Najčešće obolevaju žene, i to 2 do 3 puta češće od muškaraca, a najveća učesta-

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lost obolevanja je između 40 i 45 godina, odnosno u populaciji radno sposobnog stanovništva. Lečenje ulkusne bolesti spada u najkompleksnija lečenja, uopšte, često sa veoma neizvesnim uspehom. Preko 40% bolesnika sa hroničnim venskim ulkusom leči se duže od 20 godina, a oko 10% bolesnika duže od 30 godina [1–4]. U lečenju se primenjuju brojne metode, kako konzervativne, tako i operativne, shodno etiologiji i lokalnom nalazu. Do danas nije utvrđena univerzalna metoda lečenja, a kao najsvrsishodnija pokazala se multidisciplinarnost u lečenju [5–8].

**Metode**

U periodu od februara 2006. do septembra 2009. godine u Klinici za vaskularnu hirurgiju Vojnomedicinske akademije u Beogradu sprovedeno je ispitivanje uticaja i vrednosti supkutane paratibijalne fasciotomije na tok i ishod lečenja HVU. Praćene su dve grupe bolesnika. U eksperimentalnoj grupi bilo je 43 bolesnika sa HVU kod kojih je, pored primenjenog klasičnog lečenja, primenjena i supkutana paratibijalna fasciotomija. Drugu, kontrolnu grupu, činilo je 43 bolesnika kod kojih su, takođe, primenjene klasične metode lečenja ulkusa kao i kod prve grupe, ali bez paratibijalne fasciotomije. Pod klasičnim lečenjem podrazumeva se primena konzervativnih mera za previjanje antiseptičnim rastvorima i korišćenje antibiotika prema brisu iz ulkusa. Operativno lečenje uzroka hronične venske insuficijencije sastojalo se od odstranjivanja insuficijentne *venae saphenae magnae* (*stripping*) sa parcijalnom varicektomijom, podvezivanja insuficijentnih perforatora metodom supfascijalne endoskopske ligature perforatora (SEPS), uz korišćenje kompresivne terapije i upotrebu venotonika i uz plasiranje transplantata po Tiršu na ulkusnu leziju kod jednog broja bolesnika. Izbor bolesnika izvršen je na osnovu anamneze, kliničkog pregleda, kolor dopler sonografskog nalaza površnog i dubokog venskog sistema, kao i upotrebom flebografije u specifičnim slučajevima. Kod obe grupe bolesnika kolor dopler sonografskim pregledom utvrđivano je stanje dubokog venskog sistema sa kompetentnošću valvularnog aparata, stanje površnog venskog sistema uz verifikaciju suficijentnosti safenofemoralnog ušća, kao i stanje perforatornih vena. U istom aktu vršeno je i markiranje insuficijentnih perforatornih vena kao priprema za buduće operativno lečenje. Kod obe grupe bolesnika primenjeno je operativno lečenje, striping *venae saphenae* sa varicektomijom, podvezivanje insuficijentnih perforatora SEPS metodom, kao i uzimanje transplantata kože po Tiršu u istom aktu i njegovo postavljanje na prethodno pripremljen ulkus. Kod eksperimentalne grupe rađena je u istom aktu supkutana paratibijalna fasciotomija incizijom kože od oko 2 cm, u njenom zdravom delu u proksimalnom delu potkolenice iznad ulkusne lezije, na 1 cm medijalno od unutrašnje ivice tibije (slike 1–3). Nakon otvaranja kože i potkože dolazilo se do fascije na kojoj se pravljen otvor skalpelom, a zatim se dugačkim makazama vršilo njeno uzdužno presecanje supkutano, paratibijalno, sve do iznad medijalnog maleolusa [11, 12]. Po ušivanju incizije kože postavljen je elastični zavoj u kontrolnoj grupi. Obe grupe bolesnika preoperativno i postoperativno dobijale su venotonike. Bolesnici su operisani primenom regionalne ili opšte anestezije. Prvi kontrolni pregled potkolenice i ulkusa vršen je 2. postoperativnog dana kod bolesnika kod kojih nije vršeno pokrivanje ulkusa Tiršovim transplantatom i 5. postoperativnog dana kod bolesnika sa Tiršovim transplantatom, a zatim svakodnevno do isteka 10. postoperativnog dana. Nakon šest nedelja vršen je novi kontrolni pregled, a zatim jednom mesečno do 6. postoperativnog meseca. Procenjivano je stanje lečenog ekstremiteta, brzina zaceljenja ulkusa, stanje Tiršovog transplantata na ulkusu nakon pokrivanja, kao i recidivi ulceracija u periodu do šest meseci postoperativno.

**Sl. 1 – Potkolenica pre početka fasciotomije sa markiranim insuficijentnim perforatorima**

**Sl. 2 – Makaze pokazuju pravac i dužinu supkutane paratibijalne fasciotomije**

**Sl. 3 – Paratibijalna fasciotomija kroz malu inciziju kože**

**Rezultati**

Ovo ispitivanje obuhvatilo je ukupno 86 bolesnika sa HVU kod kojih je zbog evolucije bolesti došlo do razvijanja hroničnog fasciokompresivnog sindroma potkolenice. Kod obe grupe bolesnika radilo se o HVU stadijuma C 5–6, a bila je prisutna lipodermatoskleroza potkolenice uz izraženu sklerozu fascijalnih omotača potkolenice, naročito u distalnoj trećini, dajući potkolenici izgled uske čizme zbog razvijenog hroničnog fasciokompresivnog sindroma (slika 4). Starost

**Sl. 4 – Izgled cirkularne lipodermofasciоskleroze u okolini ulkusa pre operacije**

bolesnika kretala se od 40 do 63 godine. Broj žena bio je 60, a muškaraca 26. Vreme perzistiranja venskog ulkusa krurisa kretao se od 10 do 23 godine. Kod 19 bolesnika iz grupe sa izvršenom paratibijalnom fasciotomijom plasiran je i slobodni transplantat po Tiršu, a iz druge grupe kod 25 bolesnika plasiran je Tiršov transplantat. U grupi bolesnika sa paratibijalnom fascijotomiom nije bilo neprihvatanja Tiršovog transplantata, a u drugoj grupi kod 11 od 25 bolesnika došlo je do neprihvatanja Tiršovog transplantata. Vreme potrebno za potpuno zarastanje ulkusa kod bolesnika sa paratibijalnom fasciotomiom kod kojih nije plasiran transplantat po Tiršu kretalo se od 3 do 10 nedelja, a u drugoj grupi od 7 do 22 nedelje (tabela 1). Kod dva bolesnika iz grupe bez paratibijalne fasciotomije nije došlo do potpunog zarastanja ulkusa ni nakon šest meseci. Nije se javio nijedan recidiv ulkusa u prvih šest meseci postoperativno u grupi bolesnika sa paratibijalnom fascijotomijom (slika 5), a u drugoj grupi javio se recidiv ulkusa kod devet bolesnika. Perzistirajući otok potkolenice zadržao se kod četiri bolesnika sa paratibijalnom fasciotomijom, a u drugoj grupi kod 28 bolesnika po isteku šest meseci postoperativno (tabela 1). Takođe, prisutnost lividne boje potkolenice, koja je preoperativno bila prisutna kod svih bolesnika, povukla se kod svih bolesnika sa paratibijalnom fasciotomijom, dok se u grupi bez fascijotomije održala kod 32 bolesnika. Kod naših ispitanika nije bilo intraoperativnih komplikacija vezanih za fasciotomiju, kao ni postoperativnih komplikacija.

**Sl. 5 – Stanje nakon supfascijalne endoskopske ligature perforatora i paratibijalne fasciotomije 7. postoperativnog dana**

**Tabela 1**

**Parametri praćenja bolesnika sa paratibijalnom fasciotomijom i vrste postoperativnih komplikacija**

| Parametri praćenja | Eksperimentalna grupa (n = 43) | Kontrolna grupa (n = 43) |
|---|---|---|
| Prosečna starost (godine) | 52 | 50 |
| Polna zastupljenost (n) | | |
| muškarci | 13 | 13 |
| žene | 30 | 30 |
| Broj plasiranih transplanatata po Tiršu (n) | 19 | 25 |
| Neprihvatanje transplantata po Tiršu (n) | 0 | 11 |
| Nezarastanje u prvih 6 meseci (n) | 0 | 2 |
| Trajanje zarastanja (nedelje) | 3 do 10 | 7 do 22 |
| Recidivi u prvih 6 meseci (n) | 0 | 9 |
| Perzistirajući otok nakon 6 meseci (n) | 4 | 28 |

**Diskusija**

Hronični venski ulkus najteža je forma hronične vense insuficijencije čije lečenje je dugotrajno i jako komplikovano, a izlečenje je neizvesno i uz česte recidive [1–4]. Sama hronična venska insuficijencija sa smetnjama u venskoj makrocirkulaciji pokreće čitav niz mehanizama koji za posledicu imaju proširenu sklerozu kože, potkožnog tkiva i, na kraju, fascije pogođenog ekstremiteta što sve vodi ka jednoj cirkularnoj lipodermatofasciosklerozi potkolenice sa ulkusom. Razvijena cirkularna lipodermatofasciоskleroza ima za posledicu razvijanje hroničnog fasciokompresivnog sindroma potkolenice uz posledičnu hroničnu ishemiju, što još više otežava zarastanje

ulkusa. Što je duža evolucija ulkusne bolesti, to su izraženije i teže promene okoline ulkusa sa stvaranjem kalcifikacija u potkožnom masnom tkivu i fasciji i posledičnim formiranjem zadebljalog sloja fascije i potkožnog tkiva u vidu oklopa u distalnoj trećini potkolenice. Usled ovoga dolazi do formiranja hroničnog fasciokompresivnog sindroma u potkolenici i povećanog pritiska u mišićnim odeljcima potkolenice koji onemogućavaju normalnu cirkulaciju, uz posledičnu ishemiju kako mišića, tako i nerava, potkože i kože [9–11]. Usled povećanog pritiska i skleroze otežana je i limfna drenaža, što dovodi do otoka i novog povećanja pritiska, čime se formira *circulus vitiosus*. Povezanost između HVU i hronično izmenjene kruralne fascije prvi su objavili Pflug i Davies [12]. Oni su saopštili da otežano zarastanje ulkusa direktno zavisi od stepena fibroze kruralne fascije i potkožnog tkiva kao i od zahvatanja dubljih struktura kao što su mišići. Pflug [13] je, takođe, saopštio da su koža, potkožno tkivo i mišićna fascija kod bolesnika sa HVU gradusa 1 zajednički zadebljali i da čine jako tvrd sloj u vidu oklopa koji dovodi do ogromnog povećanja pritiska u mišićnim odeljcima. Ove tvrdnje potvrdili su Langer i sar. [14] u svojim ispitivanjima vrednosti pritiska u mišićnim odeljcima potkolenice kod bolesnika sa HVU. Staubesand i Li [15] sproveli su analize kruralne fascije kod bolesnika sa HVU elektronskim mikroskopom i došli do zaključka da postoji jedna haotična orijentisanost kolagenih fibrila uz njihovu destrukciju i gubitak elasticiteta. Schmeller i sar. [16] u svom radu ispitali su promene na potkolenici sa HVU putem kompjuterizovane tomografije i magnetne rezonancije i, osim jako zadebljale fascije do, čak, 6 mm, našli su masnu degenaraciju muskulature potkolenice. To tumače kao posledicu ishemijske nekroze muskulature sa posledičnom masnom degeneracijom. Nemački autori na čelu sa prof. Hachom [9, 10] iz Frankfurta, u seriji radova o HVU, došli su do zaključka da je jedan od većine važnih problema u lečenju hroničnog ulkusa cirkularno zadebljala fascija i povećani pritisak u mišićnim odeljcima sa hroničnom ishemijom mišića i svih tkiva potkolenice. U sprovedenim merenjima pritiska u mišićnim odeljcima kod bolesnika sa HVU, ovi autori dobijali su vrednosti u ležećem stavu između 13,6 i 22 mmHg, a u stojećem od 29 do 65 mmHg. Ukoliko se ima u vidu činjenica da je kod normotenzivnih bolesnika bez HVU normalni pritisak u mišićnim odeljcima do 8 mmHg i da porast pritiska u mišićnim odeljcima između 20 i 40 mmHg dovodi do pojave akutnog kompartment sindroma, nameće se pitanje kako se kod bolesnika sa HVU i ovakvim pritiscima odvija cirkulacija u zahvaćenoj regiji. Hach i sar. [10] uveli su i metodu fasciektomije, to jest potpunu eksciziju promenjene fascije u predelu ulkusa, kao metodu lečenja. Patohistološkim analizama reseciranih tkiva potvrdili su nalaze prethodno pomenutih autora. Patofiziološki sve počinje sa promenama u venskoj makrocirkulaciji u vidu insuficijencije površnog ili dubokog venskog sistema koji dovode do refluksa venske krvi, otežanog toka ka srcu, a sve ovo dalje ka venskoj hipertoniji u donjim ekstremitetima. Venska hipertonija povećava transmuralni pritisak u kapilarnim i postkapilarnim krvnim sudovima i dovodi do njihovog oštećenja i povećanja propustljivosti, što ima za posledicu transudaciju i prolazak u tkiva aktivisanih leukocita i drugih zapaljenskih ćelija, proteina i eritrocita. Sve to izaziva hroničnu zapaljensku reakciju sa formiranjem ožiljnog tkiva u fasciji, potkoži i koži uz nastanak venskog ulkusa. Formiranje ožiljnog tkiva sve više ograničava prostor u mišićnim odeljcima potkolenice, uz porast pritiska u njima, što dovodi do mehaničke iritacije arterijskih sudova i njihovog spazma. Tako nastaje produžena ishemija tkiva koja dalje još više otežava zarastanje ulkusa. Christenson [17] je ispitivao uticaj paratibijalne fasciotomije na HVU i ishemiju merenjem parcijalnog pritiska kiseonika kože u okolini ulkusa pre i nakon paratibijalne fasciotomije i našao statistički značajni porast parcijalnog pritiska kiseonika nakon paratibijalne fasciotomije. Ovim se mogu objasniti povoljni klinički efekti fasciotomije na zarastanje ulkusa jer se njome snižava pritisak u potkolenici i poboljšava mikrocirkulacija uz održavanje dobre oksigenacije. Snižavanje pritiska nakon paratibijalne fasciotomije olakšava i limfnu drenažu, čime se smanjuje otok, a sve ukupno poboljšavaju se lokalni uslovi za mikrocirkulaciju i zarastanje ulkusa [18, 19]. Međutim, pitanje koje se samo nameće je kako onda primena kompresivne bandaže ima, takođe, povoljan efekat na zarastanje ulkus krurisa, kada se kompresivnom bandažom vrši suprotno od paratibijalne fasciotomije – pritiskom se deluje na regiju ulkusa sa već povećanim pritiskom u mišićnim odeljcima. Objašnjenje je dao 1985. godine Echtermeyer [20] koji je u svojim ispitivanjima došao do zaključka da elastična bandaža normalne potkolenice dovodi do porasta pritiska u prednjoj tibijalnoj loži do 60 mmHg i više, a da elastična bandaža kod potkolenica sa HVU dugotrajne evolucije nema značajnog uticaja na pritisak u mišićnim odeljcima, zbog jako zadebljale kože, potkože i fascije koji se ponašaju kao neka vrsta oklopa koji sprečava prenošenje pritiska na mišićne odeljke. Ovo pokazuje da elastična bandaža kod HVU utiče samo na sniženje povišenog pritiska u površnom venskom sistemu, da smanjuje proces transudacije u kapilarima kože i potkože čime se olakšava proces zarastanja ulkusa, a da paratibijalna fasciotomija deluje drugim mehanizmom – poboljšanjem arterijske cirkulacije snižavanjem pritiska u mišićnim odeljcima. Sve to govori u prilog činjenici da je u grupi bez fasciotomije mikrocirkulacija i dalje jako loša, iako su rešeni problemi vezani za hroničnu vensku insuficijenciju, jer sklerozirana fascija ostaje, kao i povišeni pritisak u mišićnim odeljcima uz lošu mikrocirkulaciju. Sa lošom mikrocirkulacijom jako je teško izlečiti i uvek prisutnu infekciju u ulkusima, a prisutna infekcija onemogućava zarastanje, kao i primanje Tiršovog transplantata.

Samo izvođenje supkutane paratibijalne fasciotomije ne produžava značajno trajanje operacije, a ne zahteva specijalnu aparaturu, niti posebne instrumente, jer se radi o običnim dugim makazama. U ustanovama koje imaju obučen kadar i aparaturu za izvođenje procedure SEPS, fasciotomija se može uraditi i u istom aktu pri podvezivanju perforantnih vena korišćenjem endoskopije, čime se ide jedan korak dalje jer se to radi pod kontrolom oka.

Do sada nije bilo objavljenih rezultata velikih studija koje su se bavile problemom vezanim za hroničnu ishemiju prouzrokovanu hroničnim fasciokompresivnim sindromom kod ulkusa krurisa, čime se otvara oblast za detaljnija istraživanja jedne, na prvi pogled, istražene oblasti.

**Zaključak**

Jedan od problema u lečenju ulkusa krurisa, pored hronične venske insuficijencije, je i hronična ishemija prouzrokovana hroničnim fasciokompresivnim sindromom, pa lečenje ulkusa bez rešavanja i ovog segmenta ne može biti uspešno. Naime, lečenje koje podrazumeva otklanjanje uzroka venske insuficijencije, kao što je podvezivanje insuficijentnih perforatora, striping *venae saphenae* i pokrivanje ulkusa Tiršovim transplantatom, nije dovoljno jer otklanja samo uzročni faktor – hroničnu vensku insuficijenciju, ali ostavlja posledice – hronični fasciokompresivni sindrom sa hroničnom ishemijom potkolenice. Samim tim, potrebno je lečenje upotpuniti izvođenjem supkutane paratibijalne fasciotomije čime se otvara sklerozirana fascija u predelu ulkusa i snižava pritisak u tkivima, što bi trebalo da poboljša mikrocirkulaciju u pogođenoj regiji i, samim tim, ubrza zarastanje ulkusa.

Supkutana paratibijalna fasciotomija predstavlja odavno poznatu metodu koja se koristila kod akutnog kompartment sindroma potkolenice. Našim ispitivanjem došli smo do zaključka da ona predstavlja korisnu dodatnu metodu kod lečenja ulkusa krurisa jer ubrzava zatvaranje ulkusa, snižava stopu recidiva i omogućava poboljšanje lokalne mikrocirkulacije u pogođenoj regiji. Sam operativni akt je bezbedan, ne zahteva posebnu aparaturu niti specijalnu obuku hirurškog tima, te kao takav primenjiv je kod najvećeg broja bolesnika sa ulkusom krurisom koji su kandidati za operativno lečenje. Primenom supkutane paratibijalne fasciotomije rešava se jedan od brojnih faktora otežanog zarastanja ulkusa – hronična ishemija usled hroničnog fasciokompresivnog sindroma, popravlja se mikrocirkulacija u pogođenoj regiji, što, sveukupno, povoljno utiče na njegovo zarastanje.

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# Cytokines in pathogenesis of peri-implantitis

## Uloga citokina u patogenezi periimplantitisa

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**Key words:**
**dental implants; inflammation; risk factors; inflammation mediators; cytokines.**

**Ključne reči:**
**implantati, stomatološki; zapaljenje; faktori rizika; zapaljenje, medijatori; citokini.**

### Implants and their interaction with organism

General term of implantation implies insertion of biomaterials of different designs into the tissues. Oral implantation is a surgical insertion of aloplastic materials (metals, alloys**,** ceramics, polymers, carbons as well as their combinations) into the hard and soft tissues of the upper and lower jaws [1].

The essence of implantology lies in favorable reaction of the organism to the presence of foreign body or favorable response of the bone tissue to implant material. The organism reaction is the development of inflammation resulting in a complete recovery of tissues and acceptance of implants or its loss. Implantation is a traumatic damage of the soft and hard tissues. Regardless of how much the procedure has been carefully conducted, tissue response is controlled by mechanisms of bone healing metabolism, as well as by other biomechanisms. As with every other tissue damage, the organism reacts with inflammation with the aim to limit the damage or to replace the lost or damaged tissue with the processes of regeneration or reparation [2]. Metabolic activities of the bone marrow and the constant process for bone remodeling are important prerequisites of the long-term implant stability. Successuful outcome of implant placement depends on: implant material, design, adequate patient selection and proper indicators, careful surgical technique used and creation of functional and esthetic prosthetic restoration.

Each implant material should be: biocompatible, bioinert, biofunctional and bioadhesive [1].

Biocompatibility means that implant material is not toxic, cancerogenic, allergenic, *i.e.* induces no immune reaction. In other words, histocompatibility is a "harmony" of implant material and living tissues that do not harm each other. Bioinertia primarily refers to material insolubility and stability, and resistence to corrosion, in tissue fluids. Biofunctionality includes implant design, its strenght and ability to withstand loading conditions. Bioadhesion is characterized by close intimate contact of implant surface and the surrounding tissuess. Ideal implant material which meet all the four-mentioned criteria has not yet been produced, but the common opinion is that it is sufficient that the human organism tolerates inserted material.

The condition of peri-implant soft and hard tisuess is highly significant for implant longevity and function [3]. The main role of soft tissue surrounding implants is to provide the hermetic seal and protective barrier between oral cavity and the internal peri-implant bone, thus preventing invasion of various pathogens. Bone tissue, on the other hand is responsible for implant osseointegration, stability, overtime and distribution of masticatory forces. There are many contradictory facts concerning peri-implant tissue. It is believed that hemidesmosome and basal membrane, similar to natural tooth, are the mediators for epithelial cell adhesion to the implant surface [4].

### Peri-implantitis

Peri-implantitis is defined as an inflammatory reaction with the loss of supporting bone in the tissues surrounding a functioning implant. Peri-implant diseases are classified according to the part of the oral tissue involved in the inflammatory process. If inflammation is located only the gingival

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tissue around the implant neck is defined as peri-implant mucositis. Progression of inflammation results in bone loss adjacent to the implant causing peri-implantitis. The onset of peri-implantitis is in the marginal bone adjacent to the coronary part of the implant while its apical part remains osseointegrated. The implant is clinically stable, while the last stadium where a complete loss of bone-to-implant contact occurs. If left untreated, it can result in implant loss. Numerous clinical studies have reported near 4% implant loss [4–6].

Risk factors that can lead to peri-implantitis are local (microbial plaque, parafunctions, smoking, poor oral hygiene) and general, *i.e.* susceptibility to peri-implantitis, is determined by genetic factors or the influence of some systemic diseases.

Two main etiological factors that significantly contribute to the onset of peri-implant mucositis and resorption of the marginal part of the bone tissue are bacterial infection and biomechanical factors resulting from the excessive loading the implants in function [7].

Excessive overload of implants can cause microfractures in marginal bone region and cause the loss of oseointegration around the neck of the implant.

Plaque accumulation and microbial contamination of peri-implant tissue cause inflammation of subepithelial connective tissue with massive inflammatory cell infiltrations. Epithelial seal is loosely fixed, suppuration can occur, clinical as well radiographical signs of tissue destruction can be observed.

A microbiological research has shown that subgingival bacterial flora, isolated in peri-implantitis, is completely different from the microbiological findings around implants with no signs of inflammation. Considering oral microflora as a possible risk factor for peri-implant tissue disease, the evidence suggest that no significant differences exist in the distribution of bacterial morphotypes around implants and teeth respectively.

Dominant microorganisms isolated from the subgingival plaque in the case of periimplantitis are Gram-negative bacilli and spirochetes. The number of spirochetes is in positive correlation with the quantity of plaque, pockets depth around the implants and bone resorption. Apart from spirochetes, other isolated bacilli are: *Prevotella intermedia, Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis, Fusobacterium nucleatum, Actinomyces i Haemophilus* [8].

Mombeli and Lang [9] in 1994 were the first to report on the interaction of microbiological flora and implant failure. In cases of successful implants, *i.e.* osseointegrated cocci predominated, whereas in the cases of peri-implantitis a significant increase of spirochetes was observed. Progression to peri-implantitis from perimucositis does not always occur, just as every case if gingivitis does not progress to periodontitis. Microbial differences between partially and completely edentulous patients were explored [10].

Increase susceptibility to peri-implantitis was described in partially edentulous jaws [10].

The assessment of the degree of inflammation is based on clinical and radiographic findings. Clinical signs include the status of peri-implant soft tissue, implant stability and general signs of inflammation which are evident in the advanced stages of peri-implantitis: peri-implant soft tissue oedema, redness, bleeding on probing, increased probing depth, suppuration, pain.

Radiographic findings reveal increased bone resorption which is presented on the mesial and distal aspects of the implant neck as a V – shaped radiolucency. Although standard radiographic examination is the most common method used, it is not completely precise, because the buccal and oral aspects of the peri-implant bone tissue cannot be evaluated.

**Cytokines in inflammation**

Cytokines comprise a group of soluble, low molecular proteins, unspecific mediators of an inflammatory reaction that transfer various intercell signals necessary for the integrated cell response to different exogenous stimuli both in physiological and pathological conditions. Cytokines are secreted by lymfocytes**,** by the cells of the monocyte macrophage systems, by thrombocytes and many other non-circulating cells. They modulate inflammation and immune reactions by regulating the growth, mobility and differentiation of leukocytes and other cells, and all together are important in pathophysiology of numerous diseases [11].

Cytokines can be classified according to their similarity in dominant biological activities related to the target cells, similarities in their origin, structural similarity and similitary of the receptors through which they act.

Most of cytokines show biological effects through specific receptors on the membranes of target cells. Linking of cytokines to receptors triggers the intercell signals that result in specific changes in genetic expression of the target cells.

Some of cytokines express chemotactic effect, whereas the other express direct cytotoxic or antiviral effect.

Cytokines play an important role in pathogenesis of almost all of systemic and local diseases. They represent important mediators of physiological and pathological activities in the tissues of orofacial region [12]. One of the most spread out diseases of orofacial region is periodontal disease which when left untreated results in the loss of teeth, when dental implants can be used as a one of treatment modalities. Detection of cytokines in clinical laboratories is important because it can provide following of progression and activity of numerous disesase. In research laboratories, evaluation of cytokine gene expression has been investigeted expecting that this kind of research would provide better explanation of mechanisms of cytokine effect in the process of periodontal diseases.

**The role of cytokines in peri-implantitis**

Local response to peri-implant bacterial infection is in immunological and biochemical aspect very similar to the response in periodontal disease, which has been reported in many studies [13, 14].

Page et al. [15] set a hypothesis in 1997 that the progression of periodontal disease depends on: the presence and ac-

tivity of pathogenic bacteria; high local production of proinflammatory mediators (cytokines), extracellular matrix metalloproteinasis (MMP) and prostaglandin (PGE); low local production of inihibitors of inflammatory processes, particularly cytokines with immunosuppressive action, such as interleukin (IL) 10 (IL-10), factor of growth transformation beta 1 (TGF-β1) and MMP inhibitors.

Local balance of these mediators that reflects local activity of cells that produce them, determines the level of tissues destruction. Pathohistological substrate of disease consists of mononuclear cell infiltrate, the composition of which significantly transforms depending on the advancement of the process. Namely, predomination of T lympocytes in early lesions, is slowly replaced by B lymphocytes infiltrate in late, chronic or acute lesions.

Based on the determination of the produced cytokines profiles and types of cell infiltrates, there are at least three well – argumented and oppose theories of pathogenesis of the onset of periodontitis from the initial gingivitis.

Seymour et al. [16] in 1993 claim that the change of predominant T lymphocyte infiltrates in gingivitis into the dominant B lymphocyte infiltrate in periodontitis is mediated by the excessive local production of Th2 type cytokines. Th2 cytokines (IL-4, IL-5, IL-10, IL-13) cause local proliferation and differentation of B lymphocytes, local secretion of nonprotective antibodies specific for antigene bacteria determinants and hyperproduction of IL-1, which leads to the lesion progression.

This is not in agreement with Ebersole and Taubman [17] who claim that the local production of Th2 type cytokines is important for local immune response, because it stimulates the production of specific antibodies, as well as the production of anti-inflammatory cytokines: IL-4, IL-10, IL1 receptor antagonist (IL1-RA), which can stop the onset or delay the progression of periodontal lesion. According to the same authors, the onset, longevity and progression of the lesion is the consequence of specific $CD8^+$ T lymphocytes activities. Tissue damage caused by cytotoxic $CD8^+$ T lymphocytes, can be direct or is the result of production of proinflammatory cytokines (IFN-γ, IL-1) that stimulate destructive processes of local macrophages and osteoclasts.

Contrary to these hypotheses, Dennison and Van Dyke [18] claim that macrophages and their altered functions are mainly responsible for the pathogenesis of a periodontal lesion. Namely, according to them macrophages represent the effectory cells that manage the activities of osteoclasts and osteoblasts. An adequate production of one of the key Th2 cytokines, IL-4, inhibits the activation of macrophages, the presence of antigenes, production of proinflammatory cytokines necessary for triggering an adaptive immune response and increases the apoptosis of macrophage, resulting in the delay in onset of periodontal lesion. Interferon (IFN)-γ key Th1 cytokine has the opposite effect.

Peri-implantitis is a result of an unregulated inflammatory response of the host to antigene bacterial determinants from dental plaque. The basis of peri-implantitis consists of an interactions complex that is established between bacterial products, host cells and locally produced biological active factors. The degree and outcome of the destructive processes is determined by the nature of inflammatory response at the local level.

The capability of immune effectory cells to produce and release cytokines in response to stimulation of biological agents is a good strategy for monitoring the condition of peri-implant tissues. Because of this, the research of cytokines local production on the region of inflammation gives relevant data on the state of peri-implant tissues in relation to the monitoring of production of cytokines in peripheral blood. The balance between stimulatory and inhibitory cytokines, together with the regulation of expression of their receptors and signal cascades determine the level of peri-imiplant tissues destruction. Namely, the local balance of these mediators, which reflects the local activity of cells that produce them, determine the level of tissue destruction.

Cytokines that are present in peri-implant tissues can be diagnosed by measuring their concentrations in peri-implant fluid (PICF). This fluid fills the peri-implant sulkus and cytokines present in it, reflecting physiological interaction of gingival epithelium and local leukocytes on the microorganisms of dental plaque and oral flora [19]. Microorganisms are capable of synthesizing detrimental products that damage epithelium and connecting tissue cells and extracellular content.

Periotron is a device that precisely collects and determines the volume of peri-impant fluid. Cytokines are mostly detected by commercial cytokine kits (ELISA test). However, some other immunological essays for simultaneous detection of multiple cytokines from small samples have recently been developed.

Over the last ten years, the role of cytokines as useful diagnostical indicators that might represent an important addition to clinical parameters has been considered, and which might indicate the presence or absence of peri-implant disease, or indicate the treatment result that, in same cases may include the need for additional medical procedures.

Increased level of proinflammatory cytokines and chemokines significantly correlates with the level of inflammation [20, 21].

Local production of cytokines can depend on the interaction of specific microorganisms with gingival tissue, but also on the function of residential and infiltrating cells. In these complex events, one of the earliest one is the increase in production of IL-1β by gingival macrophages, which then induces, among other things, the secretion of IL-8. These two cytokines direct the selective migration of polymorphonuclear and monocytes from the gingival blood vessels, which are locally activated by the action of bacterial lipopolysacharide. Activated cells further produce different mediators, out of which the most impotrant are IL-1β, IL-6 and IL-8. The progression of gingival inflammation is probably the consequence of IL-1β and IL-6 activities, which cause an important tissue damage by the activation of osteoclasts and induction of collagen synthesis and fibroblasts [22]. In Figure 1 cells involved in the inflammatory response are presented.

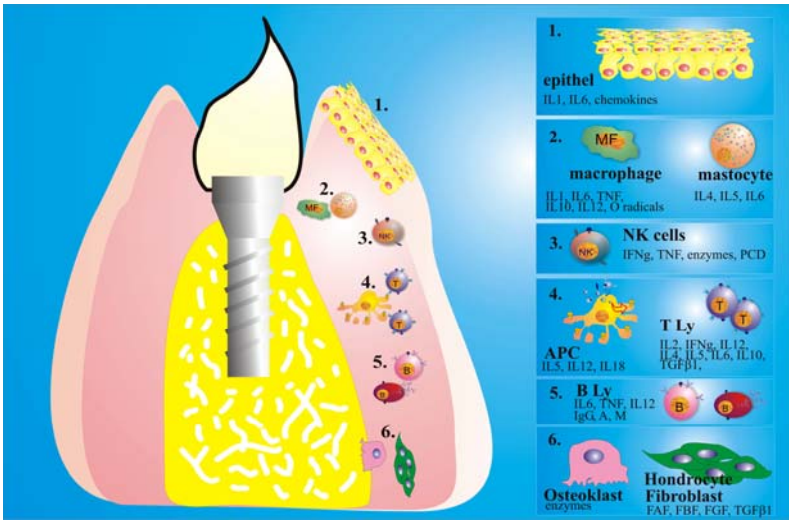


**Fig. 1 – Cells involved in the inflammatory response**

Proinflammatory cytokines and chemokines are very expressed in the peri-implant tissue in the early stages of inflammation when an implant is inserted. Panagakos et al. [22] and Salcetti et al. [23], by determining the values of IL-1β in the fluid of peri-impant sulkus, showed that concentration of this cytokine is increased by the progression of peri-implantitis. Most of the authors showed that tissue inflammation is proportionally connected with the increased level of different inflammatory mediators, which are, therefore, considered as adequate markers of inflammation. The results of Curtis et al. [24] show that there is a significantly lower level of concentration of proinflammatory cytokines in healthy tissue around implant compared to the advanced stage of peri-implantitis.

Chemokines and cytokines provide a complex network of signals that can activate or suprime an inflammatory response.

The clinical study performed in the Military Medical Academy monitored the levels of the following 4 cytokines: IL-1β, IL-8, tumor necrosis factor (TNF)-α and macrophage inflammatory protein-1 alpha (MIP-1α) [21]. Proinflammatory cytokines IL-1β and TNF-α are significant in immune response to microbial antigenes, whereas different levels of concentration of chemokines IL-8 and MIP-1α, can affect the migration of leukocites and together with TNF-α and IL1-β regulate the onset, course and outcome of inflmammation.

The research showed that the concentrations of proinflammatory cytokines and chemokines were singificantly higher in the patients with peri-implantitis in relation to the ones with perimucositis and the healthy ones. With the progression of peri-implantitis, the concentrations of all the researched cytokines in PICF were increased, but there were also individual differences in the level of the increase production of mediators of the inflammation. There has been a positive and statistically significant correlation between the levels of IL-1β and MIP-1α, TNF-α and MIP-1α as well as MIP-1α and IL-8 in PICF.

Proinflammatory cytokines (IL-1β, TNF-α) are important mediators of inflammatory host responses to the infection and other inflammatory stimuli and therefore have an important role in natural immunity and inflammation. IL-1β is a proinflammatory cytokine in certain concentration present in healthy peri-implant tissue and its value shows the real level of inflammation of peri-implant tissues. This local parameter of immune reactivity can be used for evaluation of the states of peri-implant tissues. It regulates degradation of the connective tissue and modulates the reparative activity by the induction of the endothel cells by proliferation of fibroblasts and hemotaxis of neutrophils in inflammated gingiva. Concentrations of IL-1β in PICF are increased in the early stages of peri-implantitis with the tendency of further increase with the progression of the disease [22, 25, 26].

IL-1β and TNF-α act synergically including stimulation of bone resorption [27].

The levels of IL-1β in PICF were approximately three times higher in patients with the evident peri-implantitis compared to healthy controls [25]. Also, the values of IL-1β showed a positive correlation with clinical parameters of the disease.

A significantly increased level of IL-1β in PICF have been detected in regions with failed dental implants compared to the level of this cytokine in PICF with successful control implants [23, 24, 28].

Murata et al. [29] have analysed the levels of osteocalcin, deoxipiridinolin and IL-1 β as the markers of bone metabolism in PICF in patients with peri-implantitis. The volume of PICF as well as the levels of IL-1ß in regions with peri-implantitis were significantly higher than in regions with mucositis or with helthy gingiva. The conclusion of this study is that IL-1β was an effective marker for evaluation of periimplant inflammation.

Curtis et al. [24] after their extensive research, come to a conclusion that the measurement of IL-1β in PICF as local parameter of immune reactivity, can be an important addition to clinical results in the diagnosis of peri-implantitis. Average values of cytokines of PICF were three times higher in relation to the values in the initial stage.

Many studies [22–24] have shown that IL-1β is present in: small, but detectable concentrations in gingival fluids around

clinically heatlhy implants; moderately high concentrations in samples of PICF of patients with early stages of peri-imiplantitis and high concentrations in the samples of PICF of patients with advanced peri-implantitis.

Based on the numerous studies it is possible to summarize the role of proinflammatory cytokines (IL-1β, TNF-α) in peri-implantitis: they enable migration of inflammatory cells into the tissue (they are included in the acute-phase response against the infection and pathogenesis of peri-implant destruction); they stimulate the processes of inflammation and tissue destruction; they induce and increase bone resorption; they stimulate the release of MMP that cause degradation of proteins of extracellular matrix and, apart from the local, affect the systemic manifestation of inflammation.

Unlike proinflammatory cytokines, hemokines belong to the family of chemotactic cytokines that stimulate and regulate migration of leukocytes from the blood into the tissues.

Inflammatory cells can release different chemokines and there is a proof that infection of specific bacteria and viruses can stimulate the cells of hosts to produce characteristic sets of immune cells.

As it has previously been emphasized, Th1, Th2 and Th17 play a significant role in the pathogenesis of peri-implantitis, but that role is still not well-known.

Activation of Th1 subpopulation cells through IL12 result in the production of IL-2 and IFN-γ. These cytokines stimulate predominatly the cell immune response mediated by the cytotoxic T-cells, macrophages and natural killer (NK) cells. On the other hand, activation of Th2 subpopulation cells is followed by the production of IL-4, IL-5, IL-6 and IL-10, which stimulates a predominantly humoral immune response and inhibits the cells immune response. Th17 is a new subtype of $CD_4^+$ T cells that is significant for the immunity to bacteria, but also for the pathogenesis of autoimmune processes. The level of IL-17, the most important representative of this type of cytokine, is increased during gingivitis and periodontal diseases [30]. So far it has not been investigated in peri-implantitis.

The relation of bacteria in dental plaque determines the direction of pathological mechanisms. If plaque accumulates on implant surface, the subepithelial connective tissue is infiltrated by the inflammatory cells. According to numerous studies [21, 29, 30], together with the progression of peri-implantitis, concentrations of all the examined cytokines in PICF are increased, but also that there are individual differences in the rate of increase in the production of these inflammatory mediators. Therefore, there is a difference in concentration of cytokines of PICF depending on the stage of peri-implantitis, which indicates the interaction of cytokines concentration and clinical parameters.

Many researchers tried to modify pathological responses by manipulating cytokine interaction within the targeted peri-implant tissue [31, 32]. The discovery of new cytokines and identification of new activities for the existing cytokines have significantly contributed to understending immunopathogenesis of peri-implant disease.

The detection of cytokines as valid biomarkers of pathological process, can be very effective because it provides more precise explanation of patophysiological mechanism of the disease itself. Also, evaluation of cytokine production can be for the benefit of monitoring the immune status of the organism.

## Conclusion

The diagnosis and monitoring of many systemic diseases in medicine in most cases is based on laboratory analyses of biological fluids, secrets and tissues. Therefore, in the last ten years, research in the field of implantology have also been focused on the analysis of peri-implant fluids with the basic aim to identify potentially valid biochemical and immunological markers of the level of activity of inflammatory processes and/or to predict risk for the onset of peri-implant disease.

The results of the clinical research so far have shown that monitoring of the levels of proinflammatory cytokines and chemokines in peri-implant fluid can be used for monitoring of disease progression, as well as for its early detection.

The role and interaction of Th1, Th2 and Th17 cytokines in these processes are still less understood.

Monitoring of dynamics of local cytokine levels during peri-implantitis, together with research of gene polymorphism for these cytokines and other genes included in the inflammatory process, and the correlation with clinial parameteres can be valid means for the diagnosis, prognosis and application of new peri-implant treatment methods.

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# Nova modifikacija Bentall-ove procedure: primena aortoprotetskog hemostatskog šava

## A revised modified Bentall's procedure using aorto-prosthetic hemostatic suture

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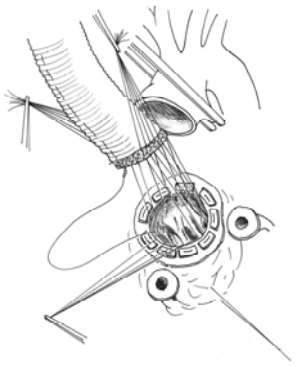
**Key words:**
**aortic rupture; therapeutics; cardiovascular surgical procedures; postoperative complications; treatment outcome; thoracic surgery.**

### Uvod

Posle objavljivanja 1968. godine Bentall-ova (Bentall-De Bono) operacija postala je standardna kardiohirurška procedura zamene aortnog korena [1, 2]. Operaciju čine implantacija kompozitnog grafta (aorta + aortni zalistak) i reimplantacija ostijuma koronarnih arterija u kompozitni graft. Novije operativne tehnike omogućile su rekonstrukciju aortnog korena uz očuvanje nativnog aortnog zaliska [3–6]. Međutim, Bentall-ova procedura i dalje se primenjuje u većini ustanova kao „zlatni standard“ u patologiji ascendentne aorte. Prikazali smo našu modifikaciju Bentall-ove procedure koja se sastoji u dodatku hemostatskog šava u nivou anuloprotetske suturne linije.

### Opis naše modifikacije Bentall-ove procedure

Pristup aortnom korenu radi se preko medijalne sternotomije. Operativni zahvat izvodi se upotrebom ekstrakorporalnog krvotoka koji se uspostavlja kaniliranjem femoralne arterije i desne pretkomore. Dekompresija plućne cirkulacije i levog srca postignuta je plasiranjem aspiracionog katetera u gornju desnu plućnu venu. Posle postavljanja totalne kleme na ascendentnu aortu, zaustavljanje srčane aktivnosti postiže se anterogradnom primenom kardioplegične solucije direktnom kanilacijom u ostijume obe koronarne arterije. Priprema za implantaciju kompozitnog grafta (St. Jude Medical Inc, St. Paul, MN) vrši se isecanjem dilatiranog i/ili diseciranog tkiva ascendentne aorte, pripremom koronarnih ostijuma za reimplantaciju i isecanjem kuspisa aortne valvule. Prilikom isecanja proksimalnog kraja aorte potrebno je osloboditi 3–5 mm aortnog tkiva iznad nivoa aortnog anulusa, neophodnog za hemostatski aortoprotetski šav. Implantacija kompozitnog grafta (slika 1) vrši se pojedinačnim 2-0 polifilamentnim šavovima, oslonjenim na pledžete koji se nalaze sa spoljne strane aortnog anulusa. Kompletna hemostaza i ojačanje proksimalne suturne linije postiže se kontinuiranim monofilamentnim 5-0 polipropilenskim šavom (slika 2). Hemostatski šav spaja ostatak reseciranog aortnog tkiva i slobodnu ivicu kompozitnog grafta oko pirolitkarbonskog prstena tako da u potpunosti prekriva prethodnu suturnu liniju sa postojećim pledžetima (slika 3). Koronarni ostijumi reimplantiraju se *button* tehnikom, a distalna anastomoza između kompozitnog grafta i distalne aorte kontinuiranim polipropilenskim 4-0 šavom, ojačanim teflon trakom (Bard Inc, Billerica, MA).



**Sl. 1 – Skica *button*-Bentall-ove procedure u fazi inkluzije kompozitnog grafta na postojeći aortni anulus**

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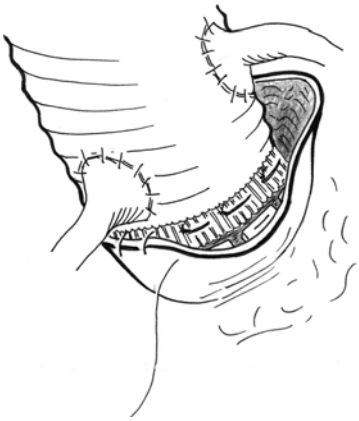
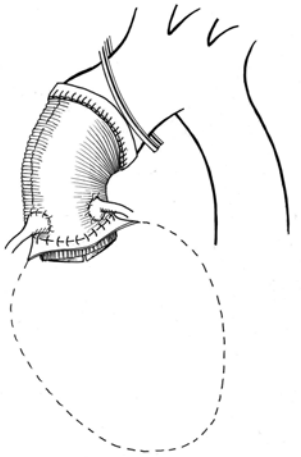


**Sl. 2 – Postavljanje hemostatskog anuloprotetskog šava (monofilamentni polipropilen 5-0) kojim se prekriva i ojačava prethodna suturna linija kreirana pojedinačnim, polifilamentnim 2-0 šavovima oslonjenim na pledžete**



**Sl. 3 – Završni izgled ojačane suturne linije na spoju kompozitnog grafta i nativnog aortnog anulusa**

### Poređenje naše modifikacije Bentall-ove procedure sa ranijim tehnikama

Akutna disekcija aorte smatra se najdramatičnijim stanjem u kardiohirurgiji. Visok inicijalni mortalitet i morbiditet uzrokovan je ne samo lokalnim patoanatomskim nalazom, već i multiorganskim komplikacijama nastalim kao posledica aortne disekcije [7–9]. Rana dijagnostika i promptno hirurško zbrinjavanje prihvaćeni su kao jedini moguć princip lečenja akutne disekcije aorte. U tom smislu, primena Bentall-De Bono procedure smatra se značajnim doprinosom uspešnom hirurškom zbrinjavanju disekcije aorte i rekonstrukcije aortnog korena. Operacija podrazumeva korišćenje kompozitnog grafta koji se sastoji od mehaničke aortne valvule i protetskog tubusa koji zamenjuju patološki izmenjen aortni koren i aortni zalistak [7, 10, 11].

Postoperativna hemoragija i iznenadna smrt posle izvođenja Bentall-De Bono procedure glavni su razlog visokog postoperativnog morbiditeta i mortaliteta, zbog čega je ta operacija pretrpela više modifikacija. Akcenat se stavlja na postizanje bolje hemostaze i sprečavanje nastanka pseudoaneurizmatskih formacija na suturnim linijama [5, 11–16]. Jedna od najprihvatljivijih modifikacija originalne Bentall-De Bono tehnike je *button*-Bentall-ova tehnika reimplantacije ostijuma koronarnih arterija po Kouchoukos-u i sar. [17]. Suština te modifikacije je u redizajniranju anastomoze koronarnih ostijuma u obliku dugmeta (*button*) i eliminacije inkluzione tehnike šivenja. Na taj način snižena je incidencija postoperativnih pseudoaneurizmatskih formacija koje su zbog sklonosti ka rupturi i kompromitovanju koronarnog protoka bile razlog za nastanak iznenadne srčane smrti. U poslednjih desetak godina rekonstrukcija aortnog korena uz očuvanje aortnih kuspisa postaja sve popularnija [10, 18]. Ova tehnika moguća je u slučajevima disfunkcije aortne valvule zbog dilatacije sinotubularnog spoja i/ili Valsalvinih sinusa. Međutim, upotreba kompozitnog grafta (sa mehaničkom ili biološkom protezom) i dalje predstavlja optimalno rešenje kod cepanja unutrašnjeg sloja Valsalvinih sinusa u disekciji aorte, Marfanovog sindroma, cistične medionekroze aorte (*annuloectasia*) i patologije aortnog zaliska sa širenjem promena na aortnom korenu.

Kritički osvrt na upotrebu kompozitnog grafta predstavlja česta disproporcija između aortnog anulusa i vaskularnog grafta, što otežava izbor optimalne proteze i bezbednost suturnih linija. S obzirom na to, lično iskustvo i podaci iz literature u ovoj oblasti navode nas na zaključak da su brižljiva hemostaza i operativna tehnika bez istezanja (*tension-free*) na šavnim linijama ključni deo hirurškog uspeha. Upotreba hemostatskog aortoprotetskog šava omogućila nam je ojačanje suturne linije između oslabljenog aortnog anulusa i slobodne ivice protetskog anulusa. Tim jednostavnim postupkom poništava se anuloprotetska disproporcija i obezbeđuje se ojačanje šavne linije koja spaja srce i kompozitni graft (mesto najvećeg opterećenja pritiskom). Na taj način formira se dvostruko ojačana anuloprotetska suturna linija, bolja hemostaza postojeće suturne linije a verovatnoća nastanka dehiscencije i pseudoaneurizmatskih formacija postaje manja. U našoj modifikaciji koristimo kontinuirani, polipropilenski monofilamentni 5-0 šav koji se, empirijski gledano, pokazao kao najpouzdaniji i najbrži.

Modifikaciju Bentall-ove procedure upotrebom hemostatskog anuloprotetskog šava započeli smo tokom 2006. godine. Ono što nedostaje je sprovođenje randominizirane, prospektivne studije čiju izradu planiramo u bliskoj budućnosti.

### Zaključak

Upotreba hemostatskog anuloprotetskog šava u Bentall-ovoj proceduri ojačava proksimalnu suturnu liniju između aorte i kompozitnog grafta čime se snižava rizik od dehiscencije i hemoragije i, samim tim, i ukupni postoperativni morbiditet i mortalitet. Ovaj operativni detalj ima veliki klinički značaj, naročito kod bolesnika sa disekcionim ili jatrogenim oštećenjem aortnog anulusa.

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CASE REPORTS

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# Response to cladribine in patient with systemic mastocytosis

## Primena kladribina u lečenju bolesnika sa sistemskom mastocitozom

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**Abstract**

**Introduction.** Systemic mastocytosis is a heterogeneous group of hematological disorders characterized by accumulation of mast cells in different organs. **Case report.** A 41-year-old woman presented with a three-year history of fatigue, occasional diarrhea, mild fever, skin rash and splenomegaly. Laboratory results showed severe anemia and thrombocytopenia. Cytological and histological investigation of bone marrow showed a marked increase of mast cells infiltration with following immunophenotype: CD117+, CD68+, CD34-, MPO-, CD15-. She was treated with cladribine 0.15 mg/kg body weight from day 1 to day 5, a total of six cycles, and achieved a good partial response, transfusion independency and normalization of spleen size. Although the patient responded to the treatment, the relapse with splenomegaly and bicytopenia was observed after 10 months. **Conclusion.** Cladribine therapy was efficient in the patient' with systemic mastocytosis but the response was transient, so there is the need to search for new therapeutic options and more effective strategies in the treatment of patients with aggressive mast cell disorders.

**Key words:**
**mastocytosis; cytodiagnosis; cladribine; remission induction; recurrence.**

**Apstrakt**

**Uvod.** Sistemska mastocitoza ubraja se u heterogenu grupu hematoloških oboljenja, a karakteriše je nagomilavanje mast ćelija u različitim organima. **Prikaz bolesnika.** Prikazana je bolesnica, stara 41 godinu, koja je u poslednje tri godine imala simptome malaksalosti, povremene prolive, povišenu temperaturu, osip po koži i splenomegaliju. Laboratorijski nalazi pokazali su tešku anemiju i trombocitopeniju. Citološko i histološko ispitivanje kostne srži pokazalo je izraženu infiltraciju mast ćelijama sa imunofenotipom: CD117+, CD68+, CD34-, MPO-, CD15-. Bolesnica je lečena kladribinom u dozi od 0,15 mg/kg telesne mase, od prvog do petog dana, ukupno šest ciklusa, i postignut je dobar parcijalni odgovor. Bolesnica nije zahtevala transfuzije i veličina slezine se normalizovala. Iako je bolesnica povoljno reagovala na primenjenu terapiju, nakon 10 meseci došlo je do relapsa sa splenomegalijom i bicitopenijom. **Zaključak.** Terapija kladribinom je efikasna kod bolesnika sa sistemskom mastocitozom, ali odgovor na lečenje je prolazan. Potrebno je istraživanje novih terapijskih agenasa i efikasnijih strategija u lečenju bolesnika sa agresivnim oblikom mastocitoze.

**Ključne reči:**
**mastocitoza; citodijagnostika; kladribin; remisija, indukcija; recidiv.**

### Introduction

Systemic mastocytosis (SM) is a clonal, extremely rare disorder characterized by abnormal mast cell proliferation in different organs, including bone marrow, skin, gastrointestinal tract, liver, spleen and lymph nodes [1]. After skin, bone marrow is the second most frequently involved organ, and its infiltration by mast cells can lead to bone pain, pancytopenia and pathologic fractures. The diagnosis of mastocytosis is based on histological and immunohistochemical examination of skin or bone marrow biopsy specimens [2]. Recommended therapy for aggressive forms of SM consists of cytoreductive agents and interferon-alpha (IFN-alpha) [3].

### Case report

A 40 year-old Caucasian woman presented with a two-year history of fatigue, occasional diarrhea, mild fever and rash. Physical examination and laboratory investigation revealed maculopapular rash (Figure 1), mild splenomegaly, with mild anemia (hemoglobin 103 g/L) and thrombocytopenia 129 × $10^9$/L. Skin biopsy showed mastocyte infiltration in the derm, and the diagnosis of cutaneous mastocytosis was established. The patient was treated with symptomatic therapy – histamine H1 and H2 receptor blockers. A year later the patient was admitted to the hospital with severe fatigue, diarrhea and rash. Clinical examination showed pale skin

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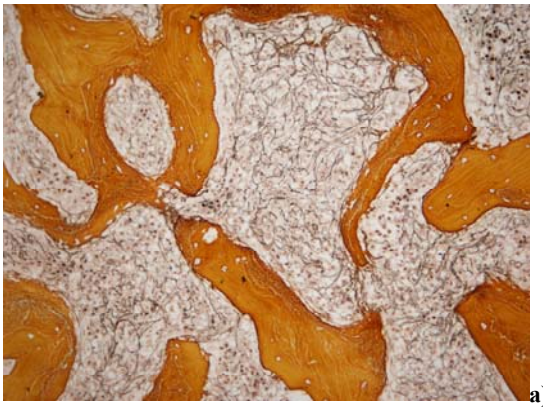
**Fig. 1 – Skin lesions (*urticaria pigmentosa*) on the leg of the patient**

with disseminated itching rash, splenomegaly 5 cm below the left costal margin. Ultrasonography and computed tomography (CT) scan showed splenomegaly 19 cm. Gastroduodenoscopy showed friable duodenal mucosa with multiple erosions. Laboratory data revealed severe anemia with hemoglobin concentration of 59 g/L, thrombocytopenia $18 \times 10^9$/L, white cell blood count $5.1 \times 10^9$/L (differential leukocyte formula: myelocytes 1%, bands 3%, segmented 29%, eosinophils 3%, lymphocytes 51%, monocytes 13%, erythroblasts 21/100). Erythrocyte sedimentation rate was elevated (134 mm/h). Coagulation parameters and serum immunoglobulin concentration (IgG 10.6 g/L; IgA 1.9 g/L; IgM 1.51 g/L) were normal. Serum C-reactive protein 11.34 g/L (normal range 0–5 g/L) and $\beta_2$ microglobulin level 2.45 mg/L (normal range 0.70–1.80 mg/L) were elevated. The level of serum histamine 0.79 μmoL (normal range 0.36–0.66 μmoL) and lactate dehydrogenase – LDH (786 U/L) were increased. Serum ferritin was elevated, 743.0 μg/L (normal range 5.00–170.00 μ/L). Cytological investigation of bone marrow revealed a marked increase of mast cells. A trephine biopsy showed infiltration of bone marrow by monomorphic, spindle shaped mast cells, and moderate fibrosis of the bone marrow (Figure 2). These cells were PAS negative. Their immunophenotype was c-kit/CD117+, CD68+, CD34-, MPO-, CD15-, which is consistent with mast cells. Cytogenetic analysis revealed normal female karyotype 46, XX. Cultures of hematopoietic progenitor cells showed the increased number of CFU-GM colonies (colony-foming unit granulocyte macrophage), spontaneous growth of BFU-E (burst forming unit erythroid) and increased number of erythropoietin stimulated BFU-E, comparing to the control and the absence of CFU-MK (megakaryocyte progenitors). Skeletal radiography did not show abnormalities on the bones. Clinical presentation and laboratory findings were consistent with the diagnosis of systemic mastocytosis. The patient was treated with cladribine 0.15 mg/kg body weight from day 1 to day 5, a total of six cycles. The cycles were repeated after 4 weeks. The response was assessed according to the proposed criteria by Valent et al. [4]. The patient achieved a good partial response with normalization of spleen size and a complete blood count (CBC). The response lasted 10 months, when relapse occurred, with splenomegaly and bicytopenia (anemia and thrombocytopenia). The patient was again transfusion-dependent, under treatment with H1 and H2 receptor blockers.

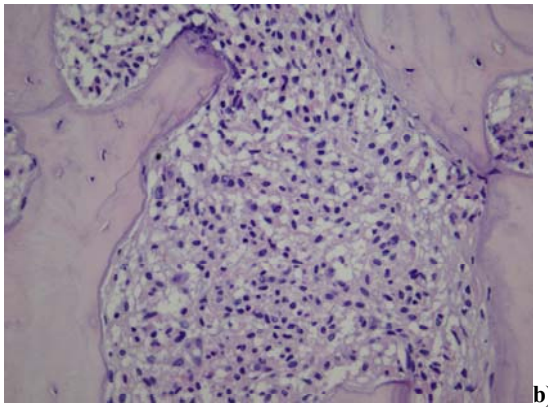
## Discussion

Clinical manifestations of SM are very heterogeneous, ranging from indolent to aggressive course with multisystem involvement and short survival. Systemic mastocytosis can coexist with other primary hematological disorders, such as myelodysplastic syndrome, myeloproliferative disorder or malignant lymphoma [5].

Bone marrow biopsy in patients with SM often indicates an increase in mast cells. Mast cells typically infiltrate bone marrow and consequently affect peripheral blood. Before bone marrow sampling, the pathologist must be informed about the possible diagnosis. A typical mast cell has a spindle – shaped nucleus and fine eosinophilic granules, and characteristic immunophenotype features (tryptase+, CD117+). The spleen, liver and gastrointestinal tract are also frequently involved [6]. In the presented patient cutaneus form of mastocytosis preceded systemic mastocytosis. The disease progressed, and aggressive course with multisystem involvement was developed. Bone marrow biopsy showed marked mast cell infiltration with specific immunophenotype (CD117+, CD68+), and bone marrow fibrosis grade II was found (Figure 2).



a)



b)

**Fig. 2 Bone marrow trephine biopsy speciments obtained in the 41-year-old patient with systemic mastocytosis**
**a) moderate fibrosis Gr II (Paraffin-embedded, HE ×100); b) spindle shaped mast-cells (paraffin-embedded, HE ×400)**

Until now there has been no curative treatment for SM. Patients with cutaneous or indolent systemic disease are treated symptomatically, using histamine H1 and H2 receptor blockers and disodium cromoglycate. Aggressive forms of SM are often associated with hematological disorder and are treated with cytoreductive therapy. Interpheron-alfa and cytostatic drugs have been applied [3], but relatively little is known about the quality of responses to IFN-alpha. Cladribine was effective in the patient with IFN-alpha resistant SM [7]. Cladribine eliminates mast cell growth factors, as cytokines interleukin (IL) 3 and IL-4. The response to cladribine in the presented patient was remarkably fast, after the first cycle of cladribine, the histamine-related symptoms vanished, and after a sixth cycle regression of splenomegaly and pancytopenia were observed. The drug was well tolerated, with no side effects. After a 10-month good response the patient developed relapse. Positive effect of cladribine treatment in 10 patients with systemic mastocytosis was published by Kluin-Nelemans et al. [8], but a complete remission was not achieved. Most patients treated with cladribine showed a rapid decrease of mast cell infiltration and very good clinical response, as we observed in the presented patient. In aggressive form of SM first line treatment with cladribine as single agent is effective, but disease often relapse.

Molecules targeting mutant kit tyrosine kinase are potential agents in treatment, and they are under investigation in clinical trials [9, 10].

## Conclusio

Cladribine therapy was efficient in the patient with systemic mastocytosis but the response was transient, so there is the need to search for new therapeutic options and more effective strategies in the treatment of patients with aggressive mast cell disorders.

So far there has not been established the standard therapy for SM, and treatment has to be adjusted to the needs of the individual patient. Advances in understanding the molecular pathogenesis of systemic mastocytosis will lead to development of new therapeutic options.

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# Familial aggregation of bladder cancer

## Familijarna agregacija raka mokraćne bešike

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**Abstract**

**Background.** Except for smoking and certain occupational exposures, the etiology of bladder cancer is largely unknown. Several case reports have described familial aggregation of transitional cell carcinoma of the bladder. Although the majority of patients with bladder cancer do not have family history of transitional cell carcinoma of the urinary tract, the study of familial transitional cell carcinoma may lead to the knowledge on the pathogenesis of this disease. The purpose of this study was to describe three cases of urinary bladder cancer in a single three-member family, i.e. in two generations (mother and son) and a family member related by marriage (the patient's wife). **Case report**. Three cases of urinary bladder cancer occurred in a three-member family within the interval of 5 years. The following common characteristics were detected in our patients: old age (over 60), working as farmers for more than 50 years, negative personal medical history on relevant health disorders, place of birth – village, place of residence – village, the same water supply, similar nutrition, positive family history on urinary bladder cancer or other malignant tumors, the first sign of illness was macroscopic hematuria in all the patients and the same pathohistological type of cancer – *carcinoma papillare transitiocellulare*. **Conclusion.** The stated common characteristics in our cases indicate, above all, the impact of exposure to external surrounding factors on the occurrence of urinary bladder cancer.

**Key words:**
**urinary bladder neoplasms; carcinoma, transitional cell; family; carcinoma, papillary.**

**Apstrakt**

**Uvod.** Osim značaja uticaja navike pušenja cigareta i profesionalne izloženosti nekim kancerogenima na nastanak karcinoma mokraćne bešike, etiologija tog malignog tumora nije sasvim razjašnjena. Nekoliko epidemioloških studija opisalo je familijarnu agregaciju raka mokraćne bešike – *carcinoma papillare transitiocellulare*. Mada se kod većine obolelih ne registruje pozitivna porodična istorija za tranziciocelularni rak mokraćne bešike, ispitivanje familijarne agregacije može doprineti sagledavanju patogeneze tog malignog tumora. U ovom radu prikazana su tri slučaja raka mokraćne bešike u jednoj porodici, kod dve generacije srodnika (majka i sin) i kod člana porodice koji nije krvni srodnik (supruga obolelog). **Prikaz slučaja.** Tri slučaja raka mokraćne bešike u troćlanoj porodici zabeleženi su u intervalu od pet godina. Oboleli od raka mokraćne bešike imali su sledeće zajedničke karakteristike: stariji uzrast (preko 60 godina), bavljenje poslom poljoprivrednika duže od 50 godina, negativnu ličnu zdravstvenu istoriju ozbiljnih poremećaja zdravlja, mesto rođenja – selo, mesto stalnog boravka – selo, isti način snabdevanja vodom za piće, sličan način ishrane, pozitivnu porodičnu istoriju raka mokraćne bešike i druge maligne tumore, hematuriju kao prvi znak bolesti, isti patohistološki tip malignog tumora – *carcinoma papillare transitiocellulare*. **Zaključak.** Karakteristike obolelih ukazuju na značaj izloženosti faktorima spoljašnje sredine u nastanku raka mokraćne bešike.

**Ključne reči:**
**mokraćna bešika, neoplazme; karcinom prelaznih ćelija; porodica; karcinom, papilarni.**

### Introduction

According to a large number of hypotheses on etiology, urinary bladder cancer is considered to be an illness with more possible causes [1–5]. Smoking is a single greatest risk factor for bladder cancer [3, 5–7]. Smokers have more than twice the risk of developing bladder cancer as nonsmokers [1, 2, 5, 7, 8]. Organic chemicals called aromatic amines are particularly linked with bladder cancer [3, 9]. Arsenic is a known bladder carcinogen and populations exposed to high arsenic levels in their water supply have reported elevated bladder cancer mortality and incidence rates [10, 11]. The reason for high incidence of urinary tract cancer in individuals suffering from Balkan nephropathy has yet to be determined [12].

Several epidemiological studies have indicated a possible familial component to bladder cancer [13–16]. Kiemeney and

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Schoenberg [14] mention familial aggregation of this neoplasm and possible genetic predisposition for its occurrence. Genealogical analysis of subjects up to the second degree of kinship indicated a considerably more frequent occurrence of urinary bladder benign tumors in the patients' families than in the families of the test group members (first-degree relatives). In the Spanish bladder cancer study, the odds ratios (OR) of bladder cancer among subjects reporting a family history of bladder cancer was 2.34 [95% confidence interval (95% CI) = 0.95–5.77] [17]. Plna and Hemminki [18] analyzed the risk of bladder cancer in offsprings according to parental and sibling cancer and founded that the highest familial risk of 7.26 (95% CI = 2.61–14.24) in brothers of bladder cancer probands diagnosed before the age of 45 years. Lin et al. [13] reported that a positive family history of bladder cancer may have interacted with smoking habits to increase the risk of bladder cancer. Recent metaanalyses of 31 case-control studies assessing the risk of bladder cancer conferred by N-acetyltransferase 2-slow acetylating genetic variants and of 28 case-control studies assessing the risk of bladder cancer conferred by glutathione S-transferase M1-null variants estimated OR of 1.4 (95% CI = 1.2–1.6) and 1.5 (95% CI = 1.3–1.6), respectively [19].

In epidemiologic studies, family history confers increase in bladder cancer risk, but it is uncertain whether this represents an evidence of genetic and/or shared environmental basis for familial aggregation [13, 15, 16].

The aim of this work was to describe three cases of urinary bladder cancer in a single rural family, i.e. in two generations (mother and son) and a family member related by marriage (the patient's wife).

**Cases report**

A 68-year-old man was admitted to the hospital at the beginning of 2003 because of the occurrence of blood in his urine and frequent urination. There was no evidence of several diseases in patient's personal medical history (urinary infections, lithiasis, bladder cancer, tumors of the kidney, diabetes mellitus, sexual diseases and any form of cancer). The patient was a farmer for more than 50 years. He smoked 1.5 packs of cigarettes a day for 50 years.

Family case-history showed that the patient's mother died in 2000 of bladder cancer. The patient's household was made of him and his wife diagnosed with bladder cancer in 2001. Our subjects had been married for 46 years. Thay had 4 children, 1 dead son (first-born child, lived for a week) and 3 daughters (the eldest daughter with myoma uteri from the age of 29 years, but now with no disease). The eldest daughter had one grandson, 13 years old. The family trees of our patient and his wife are given in Figure 1. According to family tree, the patient's mother died of bladder cancer at the age of 85. The patient's relative died of breast cancer at the age of 55. No other family members were affected by cancer.

The surgeon-urologist performed a partial cistectomy by the end of February in 2003, when the enlarged and immovable right ileal lymph glands were detected by an intraoperative and palpatory process. A biopsy specimen revealed *carcinoma papillare transitiocellulare*, a histological grade 3, with signs of muscle infiltration (Figure 2). Death occurred in June 2003.

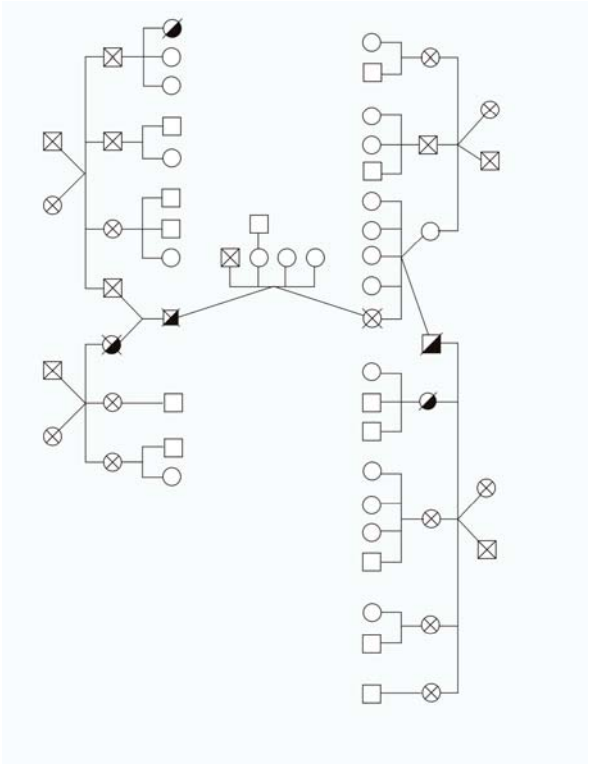

**Fig.1 –The affected family tree – alive relatives (male □, females ○); Dead relatives (male ⊠, female ⊗); bladder cancer (case: ⊠, ⊗; dead: ■, ●); other form of cancer (case: ◪, ◯; dead: ◪, ◯)**

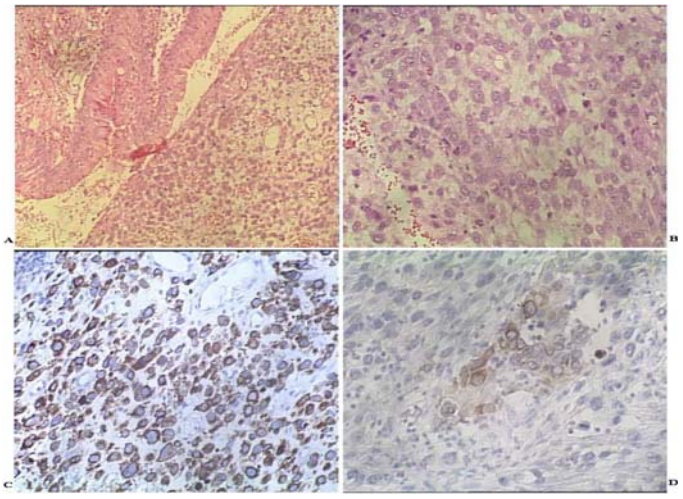

**Fig. 2 – Histologic analysis of bladder cancer in the reported patient – A) *carcinoma papillare transitiocellulare* (hematoxylin-eosin, original magnification x 40); B) *carcinoma papillare transitiocellulare* (hematoxylin-eosin, original magnification ×200); C) *carcinoma papillare transitiocellulare* (imunohistochemical analysis, strong expression of CK7, original magnification ×200); D) *carcinoma papillare transitiocellulare* (imunohistochemical analysis, focal expression of CK17, original magnification ×200)**

At the beginning of 1997, the patient's mother (born in 1915) was admitted to the hospital for hematuria and frequent urination. Transurethral resection was performed in January 1997, followed by radiation therapy. A biopsy specimen revealed *carcinoma papillare transitiocellulare*, histological grade 2, with signs of submucosa infiltration (Figure 3). In July 1997, recidive was diagnosed and cauterized. In August 1998, the second recidive was diagnosed, followed by another transurethral resection in January 1999. Death occurred in 2000.

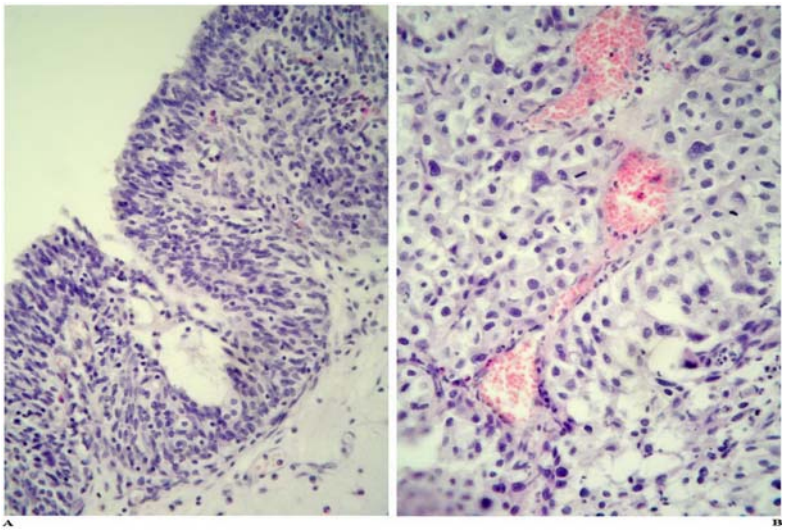

**Fig. 3 – Histologic analysis of bladder cancer in the patient's mother – A) *carcinoma papillare transitiocellulare* (hematoxilyn-eosin, original magnification ×100); *carcinoma papillare transitiocellulare* (hematoxilyn-eosin, original magnification ×400)**

The patient's wife (born in 1938) and got urinary bladder cancer at the age of 63. She was admitted to the hospital for hematuria and frequent urination in August 2001. A biopsy specimen revealed *carcinoma papillare transitiocellulare*, histological grade of 2 and nuclear grade 3 (Figure 4). The tumor was infiltrating submucosa and the fragments of the smooth muscle. Infiltration of lymph vessels and moderate necrosis points were detected. Transurethral resection was performed in August 2001, followed by radiation therapy. Twenty five months later the patient had no recidives. According to family tree (Figure 1), her father died at the age of 70 of lung cancer, and his relative died of stomach cancer at the age of 66. No other family members were affected by cancer.

The patient's mother and wife in their personal medical histories had no evidence of several diseases (urinary infections, lithiasis, bladder cancer, tumors of the kidney, diabetes mellitus, sexual diseases and of any form of cancer). They were both non-smokers.

Our subjects lived in a village about 10 kilometers away from Kragujevac. Kragujevac is a town with almost 200,000 people in the center of Šumadija Region in Central Serbia. In

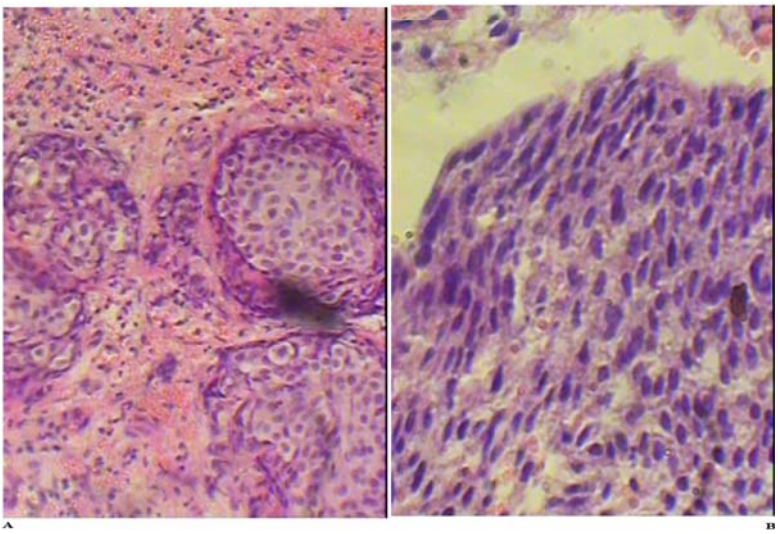

**Fig. 4 – Histologic analysis of bladder cancer in the patient's wife – A) *carcinoma papillare transitiocellulare* (hematoxilyn-eosin, original magnification ×100); B) *carcinoma papillare transitiocellulare* (hematoxilyn-eosin, original magnification ×400)**

the last few decades on the teritory of Šumadija Region it has been registered sporadic appearance of Balkan endemic nephropathy. The known seats of Balkan endemic nephropathy in Serbia are in other regions. In the neighbourhood of the reported cases there were no cases of Balkan endemic nephropathy.

Each family in the village is supplied with drinking water from its own well. Since there is no local water supply network in the village, our subject's father built one independent, about ten years ago. Drinking water from the water supply network has never been disinfected (that is, chlorinated) nor bacteriologically or chemically tested. To determine sanitery aspect of water for drink which was used by family members, we did the basic bacteriological and chemical analysis of water specimens from the water supply network and well water, and also did testing for heavy metals (arsenic, cadmium, lead, mercury). According to our results, water did not meet legally set criterions in drinking water, because of the presence of *Escherichia coli* in both the water supply network and well water. *Streptoccocus faecalis* was found in well water in the yard. In the water supply network specimen was found troubled water with sediments, excessive dose of ammonia ($NH_3$) and excessive use of $KMn0_4$, which can indicate for presence of organic substance in water. There were no heavy metals (arsenic, cadmium, lead, mercury) over the allowed concetrations maximum in the tested specimens.

## Discussion

Numerous studies have associated bladder cancer with exposure to carcinogens present in tobacco smoke and other environmental or occupational exposures. Nevertheless, familial aggregation of bladder cancer was described in several studies.

Few of anamnestic studies indicate family predisposition for urinary bladder cancer [1, 2, 13, 14]. Kantor et al. [20] detected exceptionally high risk of illness in case of joint hereditary and external factors. The risk of urinary bladder cancer was connected with the existing family history of urinary tract cancer (RR = 1.45), especially among patients under the age of 45, and confirmed smokers (RR = 10.7 those smoking 4 or more packets of cigarettes a day). In a study by Bermejo et al. [21] in Sweden that explored the sex-specific incidences and types of tumors in relatives of bladder cancer patients, among men older than 54 years were at an increased risk of bladder cancer only if their fathers or siblings were diagnosed after the age 65 years. A study by Kiemeney et al. [14] in Iceland, indicated an increase in the risk of urinary tract cancer in first-, second- and third-degree relatives suffering from urinary bladder cancer (RR = 1.24; 95% CI = 0.90–1.67). The finding that the prevalence of urinary tract cancer was 3% in first-degree relatives, and 10% in second- and third-degree relatives, suggests that there may not be a hereditary type of urinary bladder cancer. According to the findings of Petrovic [22], second- and third-degree relatives of the patients more frequently suffered from malignant tumors in comparison to relatives of the test group members of the same degree of kinship. According to the findings of Radosavljevic [23], the number of patients suffering from malignant tumors (except for urinary bladder tumor) in the second degree of kinship within the study group stood in positive correlation with the occurrence of the illness.

The stated common characteristics in our cases indicate above all the impact of exposure to external surrounding factors on the occurrence of urinary bladder cancer. Three cases of urinary bladder cancer occurred in this three-member family within a 5-year interval. The following common characteristics were detected in our subjects: old age (over 60), working as farmers for more than 50 years, negative personal medical history on relevant health disorders, place of birth – village, place of residence – village, the same manner of water supply, similar manner of nutrition, positive family history on urinary bladder cancer or other malignant tumors, the first sign of illness was macroscopic hematuria in all the patients and the same pathohistological type of cancer – *carcinoma papillare transitiocellulare*.

Namely, members of the same family are exposed to the same or at least similar environmental factors, with regard to nutrition, habits, degree of education, financial situation and the like. Numerous factors indicate that environmental factors interact with hereditary ones, thus determining the occurrence and form of illness. However, this interaction is difficult to examine and thus it is impossible to define accurately the degree of participation of hereditary and environmental factors in the etiopathogenesis of the illness, and hereditary factors perhaps only determine the general inclination to neoplasms.

## Conclusion

This report on unusual cases have contributed to our understading of the disease, especially with regard to cancer and familial aggregation of bladder cancer and exposure to suspected enviromental factors.

We propose that the etiology of familial bladder cancer may be complex, involving other possible associated malignant neoplasms in addition to specific carcinogenic exposures. There is a serious need for detailed reporting on families prone to bladder cancer wherein all of these potentially important associated factors are considered.

## Acknowledgements

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CASE REPORT

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# Hashimoto's encephalopathy: a long-lasting remission induced by intravenous immunoglobulins

## Hašimoto encefalopatija: dugotrajna remisija indukovana intravenskim imunoglobulinima

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**Abstract**

**Background.** Hashimoto's encephalopathy (HE) is a rare autoimmune syndrome characterized by various neuropsychiatric manifestations, responsive to steroid treatment and associated with Hashimoto's thyroiditis. There are only a few reports suggesting that intravenous immunoglobulins (IVIG) might represent an efficacious treatment modality for the severe steroid-resistant HE cases. We presented a patient with HE who developed a complete recovery after the IVIG therapy followed by a long-lasting remission. **Case report.** We described herien a female patient with the one-year history of autoimmune thyroiditis before the development of neuropsychiatric manifestations. In May 1999, a 38-year-old woman presented at the Institute of Neurology, Clinical Center of Serbia, Belgrade, with the brain-stem syndrome which responded well to steroid treatment. After detailed examinations, the diagnosis of Hashimoto's encephalopathy was established. Two years later, in June 2001, new manifestations (unsteadiness in gait, personality changes, seizures, and persistent headache) gradually developed during a 6-month period. Response to steroids was unsatisfactory and partial, since headaches and personality changes had continuously worsened. In January 2002, the patient received IVIG (0.4 g/kg body weight daily for 5 days). Gradual improvement was noticed and a complete recovery developed over the following weeks. Up to March 2009, during a 7-year follow-up period, remission persisted. **Conclusion.** To our best knowledge, this is the first report of a long-lasting remission of Hashimoto's encephalopathy after IVIG therapy. Therefore, this case further supports administration of IVIG, as a potentially beneficial treatment modality, in severe cases of Hashimoto's encephalopathy which are completely or partially resistant to steroids.

**Key words:**
**thyroiditis, autoimmune; brain diseases; therapeutics; immunoglobulins, intravenous; treatment outcome; remission induction.**

**Apstrakt**

**Uvod.** Hašimoto encefalopatija (HE) je redak autoimunski poremećaj koji se karakteriše pojavom različitih neuropsihijatrijskih manifestacija, dobrim odgovorom na terapiju steroidima i udruženošću sa autoimunskim tireoiditisom. Prikazali smo redak slučaj osobe sa HE kod koje je posle slabog odgovora na steroidnu terapiju, došlo do odličnog oporavka i dugotrajne remisije (tokom 7 godina praćenja) posle datih intravenskih imunoglobulina (IVIG). **Prikaz bolesnika.** Maja 1999. godine, 38-godišnja osoba ženskog pola sa jednogodišnjim trajanjem autoimunskog tiroiditisa u anamnezi, javila se u Institut za neurologiju Kliničkog centra Srbije zbog razvoja sindroma moždanog stabla, koji se povukao posle primene kortikosteroida. Postavljena je dijagnoza HE. Dve godine kasnije došlo je do postepenog razvoja novih tegoba (nestabilnost pri hodu, psihičke promene, epileptički napadi, glavobolje) koji su se održavali uprkos kontinuiranoj primeni kortikosteroida. Januara 2002. primenjeni su IVIG (0,4 g/kg telesne težine dnevno, 5 dana) koji su doveli do postepenog potpunog povlačenja tegoba. Praćenjem u toku sedam godina (do marta 2009) uočeno da se remisija održava. **Zaključak.** Prema našim saznanjima ovo je prvi izveštaj u dugotrajnoj remisiji HE posle primene IVIG. Ovaj slučaj predstavlja dodatnu podršku razmatranju davanja IVIG bolesnicima sa HE koji ne reaguju povoljno na terapiju steroidima.

**Ključne reči:**
**tireoiditis, autoimunski; mozak, bolesti; lečenje; imunoglobulini, intravenski; lečenje, ishod; remisija, indukcija.**

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## Introduction

Hashimoto's encephalopathy (HE) is a progressive and/or relapsing encephalopathy, associated with chronic autoimmune thyroiditis, and responsive to glucocorticoid therapy [1]. It has been reported that plasmapheresis [2, 3] and intravenous immunoglobulins (IVIG) [2, 4–6] might represent an alternative treatment modality for steroid-resistant HE patients.

We presented here a patient with HE who had developed a complete clinical recovery after the therapy with IVIG. To our best knowledge, this is the first report describing IVIG-induced recovery of HE with a long-lasting (7 years) remission.

## Case report

In May 1999, a 38-year old woman, complaining of subacute onset of dysarthria, dysphagia, and paresthesias in the left extremities, was admitted to the Institute of Neurology, Clinical Center of Serbia, Belgrade. She had the one-year history of Hashimoto's thyroiditis (HT) which was treated by administration of substitution therapy (100 μg levothyroxine, daily). The medical history was otherwise unremarkable. Neurological examination revealed hypomotility of both palatine vela (bulbar paralysis), hypesthesia and slight weakness of the left extremities, exaggerated deep tendon reflexes on the left, and diminished plantar response on the left. Apart from thyroid goitre, there was no other abnormality on general physical examination.

Trimodal evoked potentials, electroencephalography (EEG), brain computed tomography, and magnetic resonance imaging (MRI) findings were normal. Cerebrospinal fluid (CSF) examination disclosed the normal protein and glucose level, and normal number of lymphocyte cells; agarose isoelectric focusing with immunofixation did not reveal oligoclonal immunoglobulins. No abnormal findings were revealed regarding the routine blood hematology and biochemistry, infection serology and autoantibody screens, apart from the presence of antimitochondrial antibodies (AMA) in a titer of 1:160, as assessed by immunofluorescence. Thyroid profile showed euthyroidism: thyroid stimulating hormone (TSH) was 4.4 mU/L (normal, 0.6–4.7 mU/L) and free T4 12.7 pmol/L (normal, 10–25 pmol/L). However, the level of antithyroid peroxidase (TPO) antibodies was elevated, 584 IU/mL (normal, < 60 IU/mL), and antithyroglobulin antibodies were negative.

In June 1999, the treatment with oral prednisolone (60 mg, daily) was started. After two weeks, dosage of prednisolone was reduced by 10 mg daily, each month for 3 months, then from 20 to 10 mg daily over another six months, with slow tapering thereafter. A gradual improvement was noticed immediately and full neurological recovery occurred within 6 months. The diagnosis of HE was established. The steroid therapy was discontinued after 12 months. At that time, TPO antibody titer decreased to 262 IU/mL.

In June 2001, the patient became irritable and apathetic. The patient complained of excessive daytime sleepiness and headache. Two weeks later the patient developed unsteadiness in gait. Paresthesias in the left extremities appeared again. Neurological examination showed mild spastic left hemiparesis and hemihypesthesia, and ataxic gait. The patient was oriented, but her verbal responses were slow. EEG showed asynchronous slowed background rhythm with intermittent bitemporal theta slow waves. Carotid Doppler studies, brain MRI scans, and MRI angiography were normal. TPO antibody increased to 896 IU/mL. Methylprednisolone (1,000 mg daily) in intravenous infusion was administered for 5 days, followed by oral prednisolone in a daily dosage of 60 mg, with subsequent reducing a dose by 10 mg each 6 weeks. Up to January 2002, pyramidal deficit and ataxic gait gradually subsided, but the patient still complained of frequent, intense, disturbing headaches, irritability, and apathy. The patient also developed partial complex epileptic seizures. EEG disclosed independent sharp waves in theta range, bilaterally in temporal regions, on the mixed alpha-theta background activity. Therapy with carbamazepine was initiated. The steroid therapy was discontinued. The patient underwent a course of IVIG (400 mg/kg body weight, daily, for 5 days). Her clinical status began to improve three days after IVIG therapy and in the following weeks, headache, seizures and personality changes gradually disappeared.

Up to March 2009, during a 7-year follow-up period, the patient did not experience any neuropsychiatric symptom, and regular neurological examinations disclosed consistently normal finding. Concerning anti-TPO antibodies, their level was found to be repeatedly elevated in sera, with values ranging from 200–890 IU/mL, while the titer of AMA fluctuated from 1:40 to 1:160.

## Discussion

We presented a case of HE in a 48-year-old woman with the history of thyroid disease, whose clinical presentation was in accordance with previous descriptions of two types of HE presentations: vasculitic (stroke-like episodes) and diffuse progressive (with cognitive impairment, seizures, psychiatric symptoms and altered conciousness) [1, 7, 8]. Nonspecific EEG abnormalities, which occur frequently in HE, were detected. However, neither CSF abnormalities nor brain MRI lesions, which have been described in about half of the cases with HE, were found [8].

In the presented patient, serum concentration of anti-TPO antibodies was consistently elevated throughout the disease course. This serological abnormality is recorded in all patients with HE [8]. Antithyroid antibodies have been also found in CSF from patients with HE but not in all the tested [8, 9]. Up to now, their role in the pathogenesis of HE has not been fully elucidated yet [1].

The unique feature of our case was the complete clinical recovery after the IVIG therapy which lasted within a 7-year follow-up period. According to our best knowledge, until now, only a few patients with HE have been treated with IVIG [2, 4–6]. In two patients, no effect was observed [2, 4] and in one of them ataxia was partly reduced [5]. Recently, Jacob and

Rojabally [6] reported a case with initial steroid-responsive HE, which became steroid-resistant and then responded well to IVIG. Similarly, the patient was only initially steroid-responsive. Two years after the first steroid-responsive neurological episode, new neuropsychiatric features occurred. Steroids induced an incomplete remission, and severe behavioral changes persisted. However, the patient responded dramatically well to the consequently applied IVIG therapy. This treatment was followed by gradual disappearance of behavioral changes. The patient remained well during a 7-year follow-up period.

The reason for administration of IVIG in autoimmune diseases is based on their diverse mechanisms of action that include: reticuloendothelial cell blockage, complement inhibition, idiotype/antiidiotype antibodies, and modulation of cytokine production [10]. Additionally, IVIG may also prove useful in the treatment of these diseases due to Fas-mediated tissue destruction. Thus, it was shown that thyrocytes from HT glands expressed large amounts of Fas on their surface [11]. It is presumed that the Fas/FasL pathway is important for the progression of HT, most likely by the induction of apoptosis at the site of inflammation. Therefore, it might be assumed that apoptotic mechanisms involved in initiation of thyreoiditis could also result in the progression of encephalophathy in genetically susceptible host.

Patients with HE may have a wide variety of autoantibodies including antineuronal, antinuclear antibodies, AMA, those directed against cytoskeletons and liver membrane, which may be serological markers of polyclonal B-cell activation. Antibodies against amino terminal of alpha-enolase have been suggested to be a diagnostic marker for HE [12]. However, there is no evidence that these antibodies could have any pathogenic role in HE. In the presented patient we detected AMA without any evidence consistent with primary biliary cirrhosis (PBC). Patients with HT are considered as population at high risk for PBC, but up to now, only one case of HE associated with PBC was reported [13].

## Conclusion

Our report further supports a notion that therapy with IVIG should be considered in patients with HE, completely or partially resistant to steroids. Additionally, beneficial effect of this treatment would corroborate the immunopathological basis of this disease whose precise mechanisms remain to be elucidated.

## Acknowledgements

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C A S E R E P O R T

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# Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy

## Cerebralna autozomno dominantna arteriopatija sa supkortikalnim infarktima i leukoencefalopatijom

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**Abstract**

**Introduction.** Fast and precise diagnostics of the disease from the large group of adult leukoencephalopathy is difficult but responsible job, because the outcome of the disease is very often determined by its name. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is caused by the mutation of Notch 3 gene on chromosome locus 19p13. Beside the brain arterioles being the main disease targets, extracerebral small blood vessels are affected by the pathological process. Clinically present signs are recurrent ischemic strokes and vascular dementia. CADASIL in its progressive form shows a distinctive pattern of pathological changes on MRI of endocranium. The diagnosis is confirmed by the presence of granular osmiophilic material (GOM) in histopathological skin biopsies. **Case reports.** Two young adult patients manifested ischemic strokes of unknown etiology, cognitive deterioration, migraine and psychopathological phenomenology. MRI of endocranium pointed on CADASIL. Ultrastructural examination of skin biopsy proved the presence of GOM in the basal lamina and near smooth muscle cells of arteriole dermis leading to CADASIL diagnosis. The presence of GOM in histopathological preparation is 100% specific for CADASIL. The patients were not searched for mutation in Notch 3 gene on chromosome 19, because some other leukoencephalopathy was disregarded. **Conclusion.** Suggestive clinical picture, distinctive finding of endocranium MRI, the presence of GOM by ultrastructural examination of histopathological skin biopsies are sufficient to confirm CADASIL diagnosis.

**Key words:**
**cadasil; magnetic resonance imaging; immunohistochemistry; muscle, smooth, vascular; diagnosis; drug therapy.**

**Apstrakt**

**Uvod.** Brza i precizna dijagnostika bolesti iz velike grupe leukoencefalopatija kod odraslih težak je, ali odgovoran posao, jer je ishod oboljenja najčešće određen njegovim imenom. Cerebralna autozomno dominantna arteriopatija sa supkortikalnim infarktima i leukoencefalopatijom (CADASIL) uzrokovana je mutacijom u genu Notch3 na hromozomskom lokusu 19p13. Pored arteriola mozga, koje su glavna meta oboljenja, i ekstracerebralni mali krvni sudovi zahvaćeni su patološkim procesom. Klinički prisutni znaci su rekurentni ishemijski moždani udari i vaskularna demencija. U razvijenoj formi CADASIL ispoljava karakterističan obrazac patoloških promena na MR pregledu endokranijuma. Dijagnoza se potvrđuje prisustvom granuliranog osmiofilnog materijala (GOM) u patohistološkim preparatima biopsije kože. **Prikazi bolesnika.** Dvoje mladih, odraslih bolesnika ispoljavali su ishemijske moždane udare nejasne etiologije, kognitivnu deterioraciju, migrenu i psihopatološku fenomenologiju. Pregled MR endokranijuma ukazivao je na CADASIL. Ultrastrukturnim ispitivanjem biopsije kože dokazano je prisustvo GOM u bazalnoj lamini i u blizini glatkih mišićnih ćelija arteriola dermisa, te je utvrđena dijagnoza CADASIL. Prisustvo GOM u patohistološkom preparatu 100% je specifično za CADASIL. Kod bolesnika nije ispitivana mutacija u genu Notch3 na hromozomu 19, zato što je bila isključena mogućnost prisustva neke druge leukoencefalopatije. **Zaključak** Sugestivna klinička slika, karakterističan nalaz na MR pregledu endokranijuma, prisustvo GOM ultrastrukturnim ispitivanjem patohistoloških preparata biopsije kože dovoljni su za potvrdu dijagnoze CADASIL.

**Ključne reči:**
**cadasil; magnetna rezonanca, snimanje; imunohistohemija; mišići glatki, krvnih sudova; dijagnoza; lečenje lekovima.**

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**Introduction**

Complex and heterogeneous etiology of adult leukoencephalopathy introduces differentially and diagnostically a large number of diseases which are difficult to classify due to overlapping of clinical, histopathological, the gene or molecular criteria [1]. In etiology of adult leukoencephalopathy we can roughly distinguish hereditary diseases such as: cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL); leukodystrophies; mitochondrial miopathy, encephalopathy, lactic acidosis and stroke (MELAS); infective diseases – lyme disease, acquired immune deficiency syndrome (AIDS); intoxications – heroin abuse; tumors – gliomas, lymphomas; traumas; degenerative disease – Alzheimer's disease; vascular diseases – Binswagner disease; metabolism disorders – subacute combined degeneration; immunological diseases – multiple sclerosis, vasculitis [2].

A precise etiologic diagnosis is crucial because the outcome of leukoencephalopathy is conditioned by its true name. This paper showed how the diagnosis of CADASIL was set using indicative clinical picture, characteristic changes of endocranium magnetic resonance imaging (MRI) and determination of granular osmiophilic material (GOM) presence in histopathological preparation of a skin biopsy. CADASIL is a cerebral autosomal dominant hereditary arteriopathy caused by gene mutation of Notch 3 gene on chromosome locus 19 p13 coding transmembrane receptor Notch 3. This receptor is responsible for maturation of blood vessels in perinatal period and their homeostasis in adult period [2]. Clinical picture is dominated by repeated ischemic events, cognitive disorders leading to dementia, headache, psychopathological manifestations and a wide range of various pathologic events caused by vasculopathy which damages the central and peripheral nervous system, sceletal muscles, skin, heart and other organs [3–5]. Considering the availability of biopsy skin, it enables quite elegant solution of differential diagnostic dilemmas [6].

*Case report 1*

A patient, 36-year-old married woman with three children was admitted for hospital examination due to headache and vertigo. Headaches met the criteria for migraine; the patient has suffered since childhood. Vertiginous symptoms were suggestive for panic attacks. The patient negated the existence of vascular risk factors. Objectively, the patient was anxious, with sad mood and low intellectual capacities. Neurological status then registered slight weakness of the right arm, hypesthesia for superficial sensibility of the right half of the body, vibration sensibility shortened from the foot level towards distal, bilateral; tandem walking was performed with difficulties. MRI showed multifocal, confluent lesions of white matter on both cerebral hemispheres, lesion in pons paracentrally. Serum lab analyses (sedimentation, blood chemistry, B12, T3, T4, TSH, anti Tg ab, anti TPO ab, ANA, ANCA, anti DS DNA, anticardiolipin ab, immune complexes, cryoglobulin, ACE, Elisa on Borrelia Burgdorferi) were well. Liquor examination showed a slightly disturbed blood brain barrier with a little increased albumin coefficient (6.76, reference values are up to 5.7), normal IgG index finding and the absence of oligoclonal bands. Somatosensory and visual evoked potentials were in the physiological range. Brain-stem auditory evoked potentials (BAEP) showed discretely lower amplitude V wave left which was the only deviating from physiological values. MRI of cervical spine showed dorsomedial protrusion of C3 disc with a mild stenosis of the spinal channel and without myelopathy. Ultrasound of neck blood vessels registered slightly higher resistance index in the vertebral arteries whereas the finding of transcranial ultrasound blood vessels was normal. The patient was observed further and treated with symptomatic therapy. A slight cognitive disorder (Mini-Mental State Examination – MMSE 26/30), serious anxiety (Hamilton Anxeity Scale – HAM-A 25/30), severe depression (Hamilton Depression Rating Scale – HDRS 20) were noticed, whereas neurological status showed no significant dynamics. EEG examination showed epileptic focus temporal and frontal on the left side. The last control of EEG showed amplitude and frequently unbalanced basic activity of dominantly alfa type and the overall finding indicated an increased irritability of temporocentral regions of bilaterally milder expression. Due to the absence of clinical manifestation of epileptic attacks, antiepileptic therapy was cancelled. Repeated MRI due to the persistent signs of leukoencephalopathy, lacunar infarcts, intact blood brain barrier after paramagnetic application directed the radiologist to suggest it as CADASIL (Figure 1). A skin biopsy sample was taken for histopathological analysis and ultrastructural examination proved the presence of GOM in the basal lamina and near smooth muscle cells of arterioles in the dermis (Figure 2), thus confirming the diagnosis.

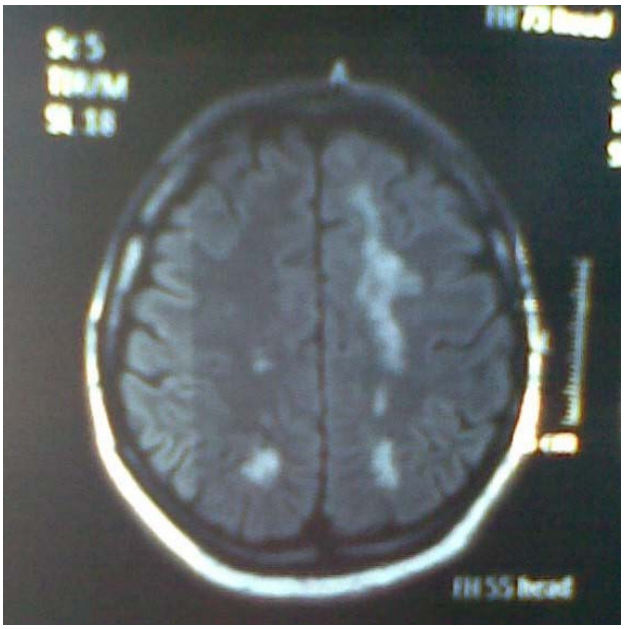

**Fig. 1 – Magnetic Resonance Imaging (MRI) of the endocranium of the patient 1 – multifocal and confluent lesions of the white matter of both hemispheres especially the left one**

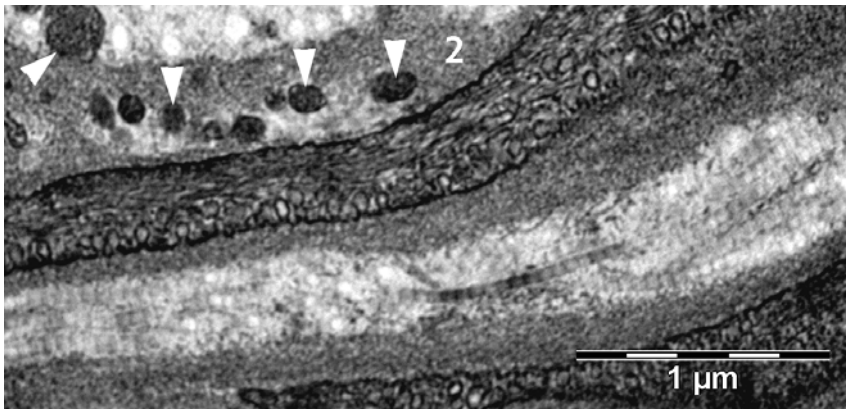


**Fig. 2 – Histopathological preparation of the arteriole of the patient 1 (Transmission Electron Microscopy – TEM) – a fragment of smooth muscle cell in the skin arteriole's *tunica media* with granular osmiophilic material (GOM) deposits (arrows)**

*Case report 2*

A patient, 31-year-old married male, father of two children, had strong vertigo, double vision, instability during walking few years ago. MRI of endocranium was done and some damages of brain mass in the area of *centrum semiovale* and *corona radiata* were detected bilaterally. BAEP easy dysfunction on the level of *pons-mesencephalon* right. Somatosensory evoked potentials (SSEP) from the level of *n. tibialis* showed disturbances in conducting from the level of Th12 to the sensitive cortex. Visual evoked potentials (VEP) revealed prechiasmatic subclinical lesion in the left optical tract. It was then assumed as multiple sclerosis and the patient was treated with pulse corticosteroid therapy in local regional medical center. Symptoms reduced afterwards but the feeling of weakness, fatigue during slight physical activities and lower mood persisted.

It was found out that the patient had tick bite in the area of head skin which has not been medically removed. His mother experienced frequent headaches. Clinical status was dominated by serious anxiety (HAM-A 25/30), moderate severe depression (HDRS 20), and mild instability during the Romberg test with eyes closed and insecurity during tandem walking were registered. Repeated MRI of endocranium showed signs of progressive changes indicative for microischemic lesions (Figure 3). Numerous examinations were performed (sedimentation, blood chemistry, basic biochemical analyses, APTT, INR, antithrombin III, D dimer, coagulation factors, immune complexes, cryoglobulin, immunoglobulin, protein electrophoresis, rheumatism factor, ACA, ANCA, ANA, anti ds DNA, Western blot on *Borellia Burgdoferi*, liquors examination – cytochemical, immunochemical analysis with albumin coefficient and immunoglobulin index, cardiac examination including heart ultrasound); vasculitis, neuroborreliosis, coagulation disorder, cardioembolic mechanism of brain ischemia were excluded. In search for the cause of ischemic lesions, the patient underwent skin biopsy and histopathological examination. CADASIL was confirmed as an etiological diagnosis (Figure 4).

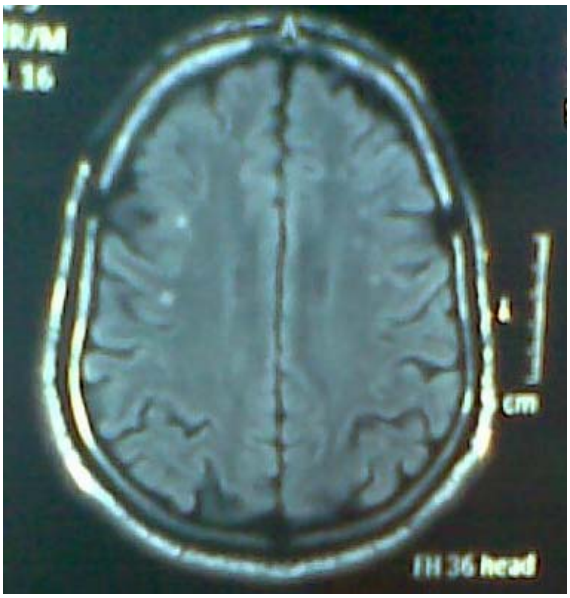


**Fig. 3 – The Magnetic Resonance Imaging (MRI) examination of the endocranium of the patient 2 – white matter lesions of both hemispheres**

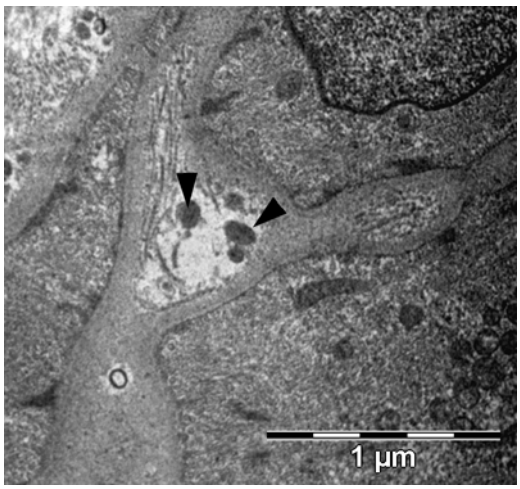


**Fig. 4 – Histopathological finding of the arteriole of the patient 2 – degenerated smooth muscular cells with granular osmiophilic material (GOM) deposits (arrows) in their proximity**

**Discussion**

We presented the two patients examined in the Military Medical Academy, Belgrade to etiologically clarify the signs of leukoencephalopathy. Clinical doubt in CADASIL was resolved by analysis of histopathological preparations of skin biopsy in the Institute of Histology and Embryology, School of Medicine, Belgrade.

The patient 1 demonstrated a wide spectrum of pathological manifestations typical for CADASIL: ischemic stroke (present in 85% of patients), cognitive deficit (present in 60% of patients), history of migraine (30% of patients), existence of epileptic focus during EEG examination (epileptic attacks in 10% of patients) [3].

MRI of the head imposed CADASIL as a differential diagnostic possibility. CADASIL in its developed form manifests a specific pattern of MRI abnormality with maximum distribution of lacunar infarcts and massive lesions of a white brain matter in frontal and temporal lobes, *insula* as well as external *capsule* and middle *pons* [7–9]. It helps in differential diagnosis but certain specific characteristics such as the involvement of frontotemporal polarity can be absent [9]. A total volume of T1 lesions on MRI is an important parameter useful for prediction of the course of the disease [7]. A relatively high difference in findings of the endocranium MRI of the patients is the consequence of a variable course of the disease. It can pass 3 to 43 years from the first manifestation of symptoms to lethal outcome [10].

The patient 2 was misdiagnosed with multiple sclerosis and was treated with corticosteroids. Persistent observation and consideration of differential diagnostic possibilities, histopathological examination of skin arteriole proved CADASIL. In spite of specific clinical and neuroimaging characteristics it often happens that a patient with CADASIL is misdiagnosed with multiple sclerosis [11]. Unilateral retrobulbar optic neuritis diagnosed with multiple sclerosis gives similar clinical picture as acute loss of visual acuity due to ischemia of optic nerve within CADASIL [12]. A total of 11% of patients showing radiological signs of leukoaraiosis and lacunar infarcts had CADASIL with clinical manifestation before 50 years of age, that is 2% of patients before 65 years of age [13]. Leukoencephalopathy in younger patients often leads to suspicious is multiple sclerosis. We find it important to point out that CADASIL is not as rare disease as it was considered earlier.

CADASIL leads to degeneration of smooth muscle cells of brain arterioles. Extracerebral blood vessels are also included in the pathological process. Expressed destruction of vascular smooth muscle cells leads to hypotony of cerebral arterioles and hemodynamic changes responsible for MRI changes and clinical symptoms [6]. Pathological signs of the disease are deposits of GOM in basal lamina of smooth muscle cells [10]. The nature of GOM is not completely clear. The latest results have shown that the largest part of GOM consists of accumulated extracellular domain of Notch3 receptor. There are opinions that GOM originates from degenerated smooth muscle cells of arteriole [6, 10]. Ultrastructural examination of skin biopsy preparation proved the presence of GOM in basal lamina of smooth muscle cells of arteriole dermis in the presented patients and therefore undoubtedly showed the diagnosis of CADASIL. In regard to molecular genetic results, skin biopsy is 100% specific and 57% sensitive for CADASIL [6]. Relatively low sensitivity of this method can be explained by difficulties in observation of sufficient number of arterioles and focal changes of vascular tissue.

In examination of a smaller number of patients with CADASIL, mean blood pressure was monitored in a course of 24 hours. It was noticed that the drop of values during the night is less than 10%. In the control group matched by age and gender the drop of mean blood pressure during the night measuring was more than 10% [14]. Monitoring of mean blood pressure might be an useful diagnostic method which could strengthen suspicion of CADASIL before skin biopsy [11].

The patients were not searched for mutations in Notch3 gene on 19th chromosome. Notch3 mutations can happen on any part of this big gene which has 33 exons [17]. Examination of 48 families in Great Britain showed approximately 90% of mutations on exons 3, 4, 5, 6 [13]. A research on 28 families in Italy with CADASIL showed only 18% of patients had mutations on exon 4, whereas the commonest mutation was on exon 11 with the frequency of 21%. All this supports the fact that distribution of mutation depends on the region of the country the family comes from [15]. Until today a great number of Notch3 mutations has been described. Searching for them is time-consuming and relatively expensive [13]. All patients with positive skin biopsy showed to have mutations on Notch3 gene [6]. It leads to a conclusion that the presence of GOM in histopathological skin preparations confirms the CADASIL diagnosis and therefore there is no need to do genetic examination due to diagnostic reasons. We must point out the importance of genetic counseling due to non-existence of specific treatment of CADASIL positive patients what was done in the presented patients [11].

A great clinical variability in patients with the confirmed diagnosis of CADASIL even within the same family members is considered to be caused by other genetic environmental factors [11].

Adult leukoencephalopathies belong to a large group of diseases. A completely different therapeutic approach demands fast diagnostics and correct therapeutic intervention in order to achieve favorable therapeutic outcome. The presented patients were given antiaggregation therapy. Considering a possibility that increased level of homocistein in blood or abnormality in metabolism of homocistein is significant in pathogenesis of the disease, we found it suitable to introduce folic acid in the therapy [16]. Bearing in mind a suggestion that a damage of cholinergic neurons in patients with CADASIL, the presented patients with the signs of cognitive disorders, *i.e.* vascular dementia were given cholinomimetic therapy [17]. Setting etiologic diagnosis in the shown patients is a crucial step for the most

adequate treatment. Indicative anamnesis, clinical picture, MRI results suggest the obligatory skin biopsy if there are doubts in CADASIL. The authors have been so far selecting patients successfully with no negative results in ultrastructural skin examination. Thus, there was no need to prove CADASIL with genetic analyses.

**Conclusion**

Suggestive clinical picture, distinctive finding of endocranium MRI, the presence of GOM by ultra-structural examination of histopathological skin biopsies are sufficient to confirm CADASIL diagnosis.

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## Poziv na reklamiranje u 2011. godini

U prilici smo da vam ponudimo mogućnost oglašavanja i reklamiranja proizvoda i usluga u časopisu „**Vojnosanitetski pregled**“ (VSP). To je sigurno najbolji vid i najzastupljeniji način upoznavanja eventualnih korisnika sa vašim uslugama i proizvodima.

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I N M E M O R I A M

# prof. dr NEDELJKO ROSIĆ pukovnik u penziji (1932–2011)

Dana 23. marta 2011. godine, u Beogradu je preminuo pukovnik u penziji, dr sc. med. Nedeljko Rosić, redovni profesor Vojnomedicinske akademije (VMA), jedan od vodećih srpskih farmakologa i toksikologa.

Pukovnik prof. dr Nedeljko Rosić rođen je 17. aprila 1932. godine u Beogradu. Medicinski fakultet u Beogradu završio je 1959. godine sa odličnim uspehom. Po završetku studija zaposlio su kao vojni lekar i u peridu 1960–1963. radio je u Splitu u garnizonskoj ambulanti. Od 1964. godine postaje član Vojnotehničkog instituta (VTI) u Beogradu gde i započinje njegova sjajna istraživačka karijera. Na Medicinskom fakultetu u Beogradu odbranio je magistarski rad („Uticaj atropina, skopolamina, JB-336 i takrina na pasivnu reakciju izbegavanja u pacova“) 1968. godine, a 1971. godine i doktorsku tezu („Uloga holinergičkih struktura u kontroli ponašanja eksperimentalnuih životinja“) koja je u najvećem delu urađena u laboratoriji čuvenog profesora Giorgia Bignami-ja (Instituto Superiore di Sanita, Rim, Italija), jednog od suosnivača evropske škole bihejvioralne farmakologije, u kojoj je prof. Rosić boravio kao stipendista tadašnje države.

U Vojnotehničkom institutu radio je do sredine 1980. godine, kada prelazi u Institut za bezbednost Saveznog sekretarijata za unutrašnje poslove, na mesto načelnika Odeljenja za toksikologiju. U VMA dolazi 1986. godine na mesto pomoćnika načelnika VMA za školovanje i naučnoistraživački rad, na kome ostaje do odlaska u penziju krajem 1996. godine.

Gotovo od samog početka profesionalne karijere, kao zaljubljenik u neuronauke i psihijatriju, počeo se baviti istraživanjima iz oblasti eksperimentalne bihejvioralne farmakologije. Plodno tlo za takav rad našao je u tadašnjem Medicinskom odeljenju VTI-a u Beogradu. U saradnji sa vodećim istraživačima Odeljenja, s velikim entuzijazmom i samopregorom formirao je laboratoriju za bihejvioralnu farmakologiju koja je po svojoj opremljenosti i znanju predstavljala sami vrh tadašnje jugoslovenske farmakologije. Prof. Rosić je veoma dobro uvideo da rad u ovoj, tada relativno nedovoljno razvijenoj disciplini, može da bude od velike koristi i za tzv. vojnu toksikologiju, posebno sa aspekta ispitivanja efekata nervnih i psihohemijskih bojnih otrova i antidota na ponašanje, čemu je tada u najrazvijenijim armijama sveta poklanjana izuzetna pažnja. Posebno je bio zainteresovan za proučavanje dejstava malih, subletalnih doza otrova, čiji su se efekti na ponašanje mogli otkriti i u odsustvu vidljivih, prepoznatljivih znakova trovanja. S obzirom na celokupni rad, prof. Rosić se može, bez imalo preterivanja, svrstati u malobrojne istraživače koji su pokrenuli i afirmisali oblast pretkliničke bihejvioralne farmakologije i toksikologije na našim prostorima. Upravo po publikacijama iz ovog domena prof. Rosić ubrajao se u vrhunske stručnjake u svetu.

U brojnim stručnim i naučnim telima vojnih i civilnih zdravstvenih, akademskih i regulatornih institucija u zemlji i inostranstvu radio je godinama kao vrhunski ekspert (član Komisije za lekove Saveznog ministarstva za rad, zdravlje i socijalnu politiku; aktivni član International College of Neuro-Psychopharmacology; član Saveta Medicinskog fakulteta u Beogradu; saradnik u Institutu za biologiju mora, Kotor, čiji je suosnivač bilo Medicinsko odeljenje Srpske akademije nauka, itd).

Bio je nastavnik u Školi rezervnih oficira sanitetske službe (oblast ABH zaštita), a, takođe, učestvovao je u pos-

lediplomskoj nastavi i na medicinskim fakultetima u Zagrebu, Rijeci i Tuzli.

Pored brojnih učešća na domaćim i međunarodnim simpozijumima i kongresima ističe se i njegova velika publicistička delatnost. Pored više stotina saopštenja i radova u domaćim i međunarodnim časopisima, sam ili u saradnji sa drugim, prvenstveno inostranim psihofarmakolozima, autor je brojnih poglavlja u knjigama iz oblasti bihejvioralne farmakologije i psihofarmakologije.

Profesor Rosić je svojim naučnim, stručnim i pedagoškim radom dao veliki doprinos razvoju i unapređenju naučnoistraživačke delatnosti na našim prostorima, ali i zdravstvene službe u celini. Njegovim prijateljima i saradnicima ostaće u pamćenju po trudu i plemenitosti koje je ugrađivao u svaki međuljudski odnos, a oni kojima je profesor Rosić krčio profesionalne puteve svesni su njegovog doprinosa tome i istrajni su da nastave putem koji je on trasirao.

Neka je večna slava i hvala pukovniku, prof. dr Nedeljku Rosiću!

prof. dr Dubravko Bokonjić,
načelnik Instituta za toksikologiju i farmakologiju,
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***Tabele***

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

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a) The title should be concise but informative. Subheadings should be avoided;

b) full name of each author;

c) name and place of department(s) and institution(s) of affiliation, clearly marked by standard footnote signs.

**2.** ***Abstract and key words***

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

**3.** ***Text***

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

In the **Introduction** repeat the title of the article, excluding the names of authors. State the purpose of the article and summarize the rationale for the study or observation. Give only strictly pertinent references and do not include data or conclusions from the work being reported.

**Methods.** Describe your selection of the observational or experimental subjects (patients or experimental animals, including controls) clearly. Identify the methods, apparatus (manufacturer's name and address in parentheses), and procedures in sufficient detail to allow other workers to reproduce the results. Give references to established methods, including statistical methods. Identify precisely all drugs and chemicals used, with generic name(s), dose(s), and route(s) of administration. State the approvement of the Ethnics Committe for the tests in humans and enimals.

**Results** should be presented in logical sequence in the text, tables and illustrations. Emphasize or summarize only important observations.

**Discussion** is to emphasize the new and important aspects of the study and the conclusions that result from them. Relate the observations to other relevant studies. Link the conclusions with the goals of the study, but avoid unqualified statements and conclusions not completely supported by your data.

### References

References should be superscripted and numbered consecutively in the order in which they are first mentioned in the text. **The references must be verified by the author(s) against the original document.** List all authors, but if the number exceeds 6, give 6 followed by et al. Do not use abstracts, secondary publications, oral communications, unpublished papers, official and classified documents. References to papers accepted but not yet published should be designated as "in press". Information from manuscripts not yet accepted should be cited in the text as "unpublished observations". References are cited according to the ***International Committee of Medical Journal Editors.*** *Uniform Requirements for Manuscripts Submitted to Biomedical Journals. Ann Intern Med 1997; 126: 36–47. Updated October 2001.*

Examples of references:

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

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

Blinder MA. Anemia and Transfusion Therapy. In: Ahya NS, Flood K, Paranjothi S, editors. The Washington Manual of Medical Therapeutics, 30th edition. Boston: Lippincot, Williams and Wilkins; 2001. p. 413-28.

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

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

### Tables

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

*Illustrations*

Figures are submitted in triplicate, and for the final version also on diskette/CD. Photos should be sharp, glossy black and white photographic prints, not larger than 203 × 254 mm. Letters, numbers, and symbols should be clear and even throughout and of sufficient size that when reduced for publication, each item will still be legible. Each figure should have a label on its back indicating the number of the figure, author's name, and top of the figure. If a figure has been published, acknowledge the original source.

Legends for illustrations are typed on a separate page, with arabic numerals corresponding to the illustrations. Identify and explain each one clearly in the legend symbols, arrows, numbers, or letters used to identify parts of the illustrations. Explain the internal scale and identify the method of staining in photomicrographs.

### Abbreviations and symbols

Use only standard abbreviations. Avoid abbreviations in the title and abstracts. The full term for which an abbreviation stands should precede its first use in the text.

Detailed Instructions are available at the web site: **www.vma.mod.gov.rs/vsp/download/instructions_to_authors.pdf.**

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