Časopis Udruženja kardiologa Srbije

SRCE i krvni sudovi

Heart and Blood Vessels

Journal of the Cardiology Society of Serbia

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Ovaj broj je posvećen 100-godišnjici od rođenja Prof. dr Srećka Nedeljkovića (4.12.1923.-4.12.2023.)

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SRCE I KRVNI SUDOVI
HEART AND BLOOD VESSELS

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Email: srceikrvnisudovi.urednistvo@gmail.com
www.uksrb.org

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Primer za navođenje reference iz knjige: Nichols A, Rourke MH. Aging and hypertension. U knjizi: Hypertension. Urednici: Nichols A, Rourke MH. Lea and Febiger; London/Melbourne, 1990:257-299.

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Heart and Blood Vessels is the official journal of the Serbian Cardiology Society and publishes Original articles, Case reports, Cardiovascular images, Review articles and Special articles. It is mandatory to enclose, along with the manuscript, a letter to the Editor-in-chief stating that the manuscript:

- has not been previously published or is currently submitted for review to another journal
- was read and approved by all authors

The manuscript with all appendices should be addressed to:
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Editor-in-Chief, Heart and Blood Vessels
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The Editorial Board will send it to reviewers for evaluation. Reviewers' comments will be forwarded to the author to either correct the original manuscript in accord with the suggestions or to express their opinion with adequate arguments in a letter to the Editor-in-chief explaining why they refrained from doing as reviewers deemed appropriate. The final decision will be made by the Editor-in-Chief together with the Editorial Board whether to accept the manuscript for publishing or not. For published manuscripts authors don't get fees, while copyright is transferred to the publisher. The journal is published in Serbian with summaries in English. Foreign authors can submit their manuscripts entirely in English.
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The text should encompass: Introduction, Methods, Results, Discussion, Conclusions, and References. Subtitles should be typed in regular font and bold. Short and simple sentences are advised. For medication, it is recommended not to use trade names, but their generic names. Abbreviations can be used in the text, but only when necessary and properly introduced. All results should be cited in standard SI units.
An original paper should be up to 4000 words.
A Case Report consists of an Introduction, Case presentation, Discussion and References. A Case Report should be up to 1500 words. Cardiovascular Images shouldn't be structured and should be up to 500 words.
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Book citation example: Nichols A, Rourke MH. Aging and hypertension. In: Hypertension. Editors: Nichols A, Rourke MH. Lea and Febiger;London/Melbourne, 1990:257-299.

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Akademician, prof. dr Miodrag Ostojić

On the occasion of the 100th anniversary of the birth of Prof. Dr. Srećko I. Nedeljković, founder and first director of the Institute for Cardiovascular Diseases of the Clinical Center of Serbia

Professor Srećko I. Nedeljković, the founder and the first Head of the Institute of Cardiovascular Diseases of the Clinical Center of Serbia, former FESC and FACC, passed away on January 2nd 2011, in Belgrade, at the age of 88.

The career of Professor Nedeljkovic is an example of achieving the highest professional aims through hard work, sacrifice and diligence.

Srećko Nedeljković was born on December 4, 1923 in the village of Virovo in Dragačevo (municipality of Arilje) in a farmer's family as the third of nine children of Anka and Ilija Nedeljković. He completed high school in Cacak, and his graduation paper "Creativity is the essence of life" was awarded as the most successful project in his class. Taught by his elder brother Relja, Srecko learns to play chess at the age of 13, what he pursued throughout his High School years in Cacak. In 1946 he enters the School of Medicine of the University of Belgrade where he graduates top in his class, in 1952, with and average grade of 9.3 out of 10. Soon afterwards, he becomes the internal medicine resident at the main University teaching hospital, the Internal Medicine Division B and becomes board certified internal medicine specialist in 1958. Upon the public defense of the nowadays equivalent of Fellowship thesis in Cardiology in 1962, Dr Nedeljkovic got his first appointment as an Assistant Professor of Internal Medicine at the School of Medicine of the University of Belgrade. In 1961 he went to Washington D.C., USA, for further training in biostatistics that was of paramount importance, when in 1962, in cooperation with Academician Professor Božidar Đorđević, he started the Seven Countries Study. It was only three years later, in 1965 that he was the first one to work on experimental models and then application in humans in order to introduce transthoracic defibrillation into routine practice. In 1967 he successfully defended his master and in 1969 his PhD thesis. In 1975 he was the visiting professor at Baylor College of Medicine, whose President at the time was a renowned cardiac surgeon Michael E. DeBakey, but he also had established excellent relations with equally brilliant and internationally recognized cardiac surgeon Denton Cooley and his team. Professor Nedeljkovic became full time professor in 1980, and in 1985 the Head of Postgraduate Studies in Cardiology, as well as the president

of Cardiology Society of Yugoslavia. In 1986 he founded the Institute of Cardiovascular Diseases of the Clinical Center of Serbia, in Belgrade, and retired in 1989 as its first Head. In 1990 he became the vice-president of the Medical Academy of Serbian Medical Association and in 1999 the president of the Science Committee of the Yugoslav Association for Atherosclerosis. Despite his official retirement, Professor Srecko Nedeljkovic was active not only as a doctor, but also as researcher and educator of younger colleagues at the Postgraduate Cardiology Studies of the School of Medicine of the University of Belgrade. Along with numerous publications and three editions of postgraduate textbook "Cardiology", where he was the editor-in-chief, along with Academician Vladimir Kanjuh and Primarius Dr Milija Vukotic he continually worked and researched in the Seven Countries Study, as well as JUSAD study (Yugoslav study of atherosclerosis precussors in school children). He also worked in compiling material for Serbian Encyclopedia (editor for the medical section – Vladimir Kanjuh) literally until his very last days. Although he was deeply involved in the Seven Countries Study, as an epidemiology study, he was also

the founder of modern hemodynamics and functional diagnostics in Yugoslavia. This involved modern emergency cardiology, along with electrophysiology. After C. Plavsic and B. Djorjdevic, he was the first to introduce heart catheterization in routine practice, as well as left heart catheterization and trans-septal catheterization, followed by selective coronary arteriography. Many of our most distinguished cardiac surgeons, along with worldwide well known cardiac surgeons operated based on the findings of Professor Nedeljkovic's pre-op diagnostics. Selfless in transferring his knowledge to his younger associates, by directing them towards introduction of new methods, Professor Nedeljkovic also very well knew how to delegate responsibilities and how to channel his associates' energy in the right direction. For his work in cardiology, similar to his competitive achievements in chess, he was awarded numerous national and professional awards (Table 1). Factography of Professor Srecko Nedeljkovic's life path is tremendous and will be presented on the Internet site of the Cardiology Society of Serbia and Serbian Heart Foundation as a picture of perfect example of what selfless and dedicated work can achieve and how it can make you not only an exceptionally good cardiologist but one of the most frequently cited among peers (his manuscripts were cited more than 3500 times).

I was lucky enough to have met the international chess master Srecko Nedeljkovic back in 1960, when I was participating in the pioneer chess championship in Belgrade. This short encounter turned into friendship in 1965 when I was selected to play in the Yugoslav state team against USSR in Sochi. As luck would have it, the championship took place in June 1966, when I was supposed to sit exams in my first year of medical studies. I turned to the team captain of Yugoslav chess team, Dr Srecko Nedeljkovic and asked him to help me sit my exams earlier so that I could participate in the chess championship. He did his best to help me, but it was extremely difficult and it turned out that I had to give up the chess championship in order to take my exam. After I completed my studies in 1971, I reported to Academician Professor Božidar Đorđević and Assistant Professor Srećko Nedeljković who welcomed me to their team. I was assigned to Assistant Professor Srecko Nedeljkovic to help him with introduction of new methods.

Ever since I was a medical student, Associate Professor Srecko Nedeljkovic impressed me with his attitude towards patients and his bedside manners. He always had the time to see all the patients, whether they had appointments or not, he always thought that the most important thing was to offer your help when it was most needed. Dr Nedeljkovic was also my doctor of choice when it came to my father's medical care; I was always taken by his energy, warm welcoming manner and altruism that he emanated. Later, when we worked together, my impressions had only grown bigger. A witty character, he also had a particular sense of humor, so he would often comment when his office phone rang: "Ok, let's see who set his mind do get me busy now!" And he never even once refused to help anyone. His office was always unlocked and all of his associates were welcomed. But it was not his office only that Srecko shared with his associates. I can remember the time, when, soon after I got my first job and was on a rather limited income, he gave me the keys and directed me to the Nedeljkovic family flat in Herceg Novi, resort at the Adriatic sea, where I spent two weeks with my son and wife. He was all consumed with worry about his associates, and when soon after I started working he told me: "From now on, we'll have a lot to write about each other in our careers", I didn't immediately understand what he meant. However, pretty soon, it dawned on me that professional endeavors entail a lot of traps too, and that teacher-student loyalty is the key element in overcoming some difficult situations that all of us encounter. As an illustration of his care about his students, it suffices to mention that in 1994, without telling me anything, he recommended to Medical Academy of the Serbian Medical Association that I become a correspondent member of Serbian Academy of Sciences and Arts on behalf of Serbian Medical Association. It is with his persistent engagement and with invaluable contribution of Academicians Vladimir Kanjuh and Isidor Papo that this proposal was accepted. I have often said, in chess terms, that by pushing the pawn to the front he managed to turn it into a queen. That was how Srecko taught us that everybody should be given a chance to achieve a successful career, but also that not everyone responds the same way when presented with this opportunity ("Everyone deserves to live", and "I'll write a book –Hippocrates and all his students"). His key postulate was, and he used to say it in English: "Hard working-soft speaking". This was his Gandhi-like understanding of how to overcome obstacles that would often appear on his way. I remember the time when he worked hard to secure the funds for the new catheterization room. He called me and said: "Ostojic, do you know how president Tito led the IV offensive during the second World War? He said-we'll go through Prozor (Prozor is the name of the city which means "window" in English)." And our new catheterization room did go through the window and was built as an additional part of the existing building.

I could write about Srecko as a man, mentor, friend, doctor, instructor, scientist, chess player, head of family, but all these roles blend together into one person as colors do when forming a unique rainbow. Whichever role I decide to set aside, it wouldn't do justice to a man that Srecko really was. He appreciated and loved others, and it seems that they returned his affection and care. He was always satisfied and happy with what he achieved; he was modest, but never defensive. He recovered from his heart surgery (CABG) quicker than some would recover from a common cold, he only remained at hospital for 72 hours, and just before his serious leg surgery only several days before he died, when we told him that a radical procedure will be inevitable, he replied in his witty way: "That's just fine, we did it to our patients, too!". Srecko Nedeljkovic lived bravely and honorably and when he left us, he did it the same way again. A pessimist would say it's a pity that we lost him, I – however – as one of his students whom he supported and gave a chance to form one of the biggest world known cardiol-

Srećko I. Nedeljković: Awards and recognition

1.	Government of Serbia Award for best graduation essay "Work and creation is the meaning of life"	1943
2.	International chess master (first place at first international tournament in Belgrade and international tournament in Vienna)	1950
3.	Gold medal at the Olympics in Dubrovnik	1950
4.	Ranked as 43 on a world chess list	1955
5.	Yugoslav Exceptional Sportsman	1957
6.	October Award by the City of Belgrade for scientific achievements	1970 and 1981
7.	7th of July Award for improvements in Serbia development	1979
8.	Order of Achievement with gold wreath	1986
9.	Gold medal of Yugoslav Association of Cardiologists	1989
10.	Two gold medals of the Faculty of Medicine, Belgrade University, for improvements in post graduation cardiology curriculum	1985 and 1995
11.	Serbian Medical Association Life Achievement Award	1993
12.	Editor of chess section of Viva magazine	1996
13.	Serbian Patriarch Pavle's Award	2000 and 2004
14.	Grand Seal of Serbian Medical Association	2003
15.	Plaque of Serbian Academy of Sciences and Art	2000
16.	National sport award for special contribution to development and affirmation of sports by the Government of Republic of Serbia	2007
17.	Patron of the students' final chess tournament of University of Belgrade (Verica and Srecko Nedeljkovic's Trophy)	2008

ogy team (performing about 2800 percutaneous coronary interventions per year) at Division of Cardiology, Clinical Center of Serbia, would like to preserve my Mentor's never ending optimism and say – we are happy to have had such a man for our teacher, mentor and friend. Ideas and standards that he set will remain alive for years to come. Srecko was not only a doctor, teacher, scientist, chess player; **he was an extraordinarily wise man**. The bar he set for us is so high that the hard work to make it, is only yet to come.

Akademik, prof. dr Miodrag Ostojić

Povodom 100 godina od rođenja Prof. dr Srećka I. Nedeljkovića, osnivača i prvog direktora Instituta za kardiovaskularne bolesti Kliničkog centra Srbije

Profesionalna karijera prof. dr Srećka I. Nedeljkovića je primer kako se velikim radom, samopožrtvovanjem i pregalaštvom mogu dostići i najviši ciljevi.

Srećko Nedeljković je rođen 4. decembra 1923. godine u selu Virovo u Dragačevu (danas opština Arilje) u seljačkoj porodici kao treće od devetoro dece Anke i Ilije Nedeljković. Gimnaziju je završio u Čačku, a njegov maturski rad „U radu i stvaralaštvu leži smisao života" je nagrađen kao najbolji. Šah je naučio u 13. godini od starijeg brata Relje. Kao đak gimnazije u Čačku afirmisao se i kao odličan šahista. Godine 1946. upisao je Medicinski fakultet, Univerziteta u Beogradu, koji je završio kao jedan od najboljih studenata u generaciji 1952. godine (prosečna ocena 9.3). Ubrzo je dobio specijalizaciju iz interne medicine na bivšoj Internoj B klinici koju je završio 1958. godine, a habilitacioni rad iz kardiologije je odbranio 1959. godine. Tada je postao i asistent na Medicinskom fakultetu Univerziteta u Beogradu. Godine 1961. odlazi na usavršavnje u Vašington, SAD, gde upotpunjava svoja znanja iz biostatistike. Sa akademikom prof. dr Božidarom Đorđevićem započinje „Studiju sedam zemalja" 1962. godine. 1965. radio je prvo na eksperimentalnim modelima, a onda i u humanoj medicini na uvođenju u rutinsku praksu transtorakalne defibrilacije. Godine 1967. je odbranio magistarsku, a 1969. doktorsku tezu. Godine 1975. bio je kao Visiting profesor na Baylor koledžu medicine čije je rektor bio čuvani kardiohirurg Majkl Debejki. Redovni profesor postaje 1980. godine, a 1985. godine postaje i šef poslediplomske Katedre iz kardiologije, kao i predsednik Udruženja kardiologa Jugoslavije. Godine 1986. osniva Institut za kardiovaskularne bolesti, Kliničkog centra Srbije, u Beogradu i sa tog položaja odlazi u penziju 1989. godine. Godine 1990. je postao potpredsednik Medicinske akademije Srpskog lekarskog društva, a 1999. i predsednik Naučnog saveta Udruženja za aterosklerozu Jugoslavije. Iako u penziji od 1989. godine, Prof. dr Srećko Nedeljković je aktivan ne samo kao zdravstveni radnik, već i u naučno-istraživačkom radu i edukaciji mlađih na Katedri za poslediplomsku nastavu iz kardiologije Medicinkog fakulteta, Univerziteta u Beogradu. Pored mnogobrojnih publikacija i tri izdanja poslediplomskog udžbenika „Kardiologija" gde je glavni urednik sa Akademikom Vladimirom Kanjuhom i primarijusom dr Milijom Vukotićem, kontinuirano radi i na polju istraživanja u „Studiji sedam zemalja", kao i u JUSAD studiji („Jugoslovenska studija prekusora ateroskleroze u školske dece"). Radi i na izradi Srpske enciklopedije (za medicinu urednik akademik Vladimir Kanjuh) praktično do poslednjeg dana svoga života. Iako se bavio „Studijom sedam zemlja", kao jednom epidemiološkom studijom, prof. dr Srećko Nedeljković je i osnivač modernih hemodinamskih i funkcionalnih ispitivanja srca u Jugoslaviji. To obuhvata i modernu interventnu kardiologiju, kao i elektrofiziologiju. Uveo je posle Plavšića, Đorđevića kateterizaciju desnog srca u rutinsku praksu, pa uvodi kateterizaciju levog srca, kao i trans-septalnu kateterizaciju, pa zatim selektivnu koronarnu arteriografiju. Na osnovu njegovih nalaza, operišu najbolji naši, kao i svetski kardiohirurzi. Tokom celog svog rada nesebično prenosi znanja na svoje mlađe saradnike koje usmerava ka uvođenju novih metoda. Znao je da delegira odgovornost i usmeri saradnike. Zbog svog rada u oblasti kardiologije, kao i takmičarskih zasluga u šahu dobija mnogobrojna najviša državno-društvena, kao i stručna priznanja (Tabela 1). Faktografija životnog puta prof. dr Srećka Nedeljkovića je impresivna i predstavlja primer šta se sve može postići nesebičnim i požrtvovanim radom, tj. biti u svemu odličan i još i najcitiraniji kardiolog svog vremena u Srbiji.

Ja sam šahovskog internacionalnog majstora Srećka I. Nedeljkovića upoznao još 1960. godine igrajući na pionirskom prvenstvu Beograda u šahu. Kratkotrajan susret se pretvorio u poznanstvo 1965. godine, kada sam od strane Šahovskog saveza Jugoslavije određen da igram u državnoj reprezentaciji protiv reprezentacije SSSR u Sočiju na omladinskoj tabli. Te 1966. godine se meč održavao baš u junu kada je trebalo da polažem ispite na prvoj godini studija medicine na Medicinskom fakultetu u Beogradu. Obratio sam se tadašnjem saveznom kapitenu šahovske reprezentacije Jugoslavije Doc. dr Srećku Nedeljkoviću zamolivši ga da pomerim ispite unapred kako bi po njihovom polaganju otputovao na meč. Doc. S.

Nedeljković je sve učinio da se ispiti pomere unapred, ali to je bilo teško izvesti, jer je trebalo organizovati praktične delove ispita (hemije, fizike...) ranije samo za mene, tako da sam odustao od šahovskog meča i ostao da polažem ispite u redovnom postupku. Po završetku studija 1971. godine, javio sam se akademiku prof. dr Božidaru Đorđeviću i Doc. Dr Srećku Nedeljkoviću koji su me primili u u njihov tim. Odmah sam bio određen da radim sa doc. dr Srećkom Nedeljkovićem, da mu pomažem u uvođenju novih metoda.

Još kao studenta medicine, Doc. dr Srećko Nedeljković me je impresionirao svojim odnosom prema bolesnicima. Uvek je primao bolesnike, bili najavljeni ili ne, jer je smatrao da je najvažnije pomoći im u pravom trenutku. I svoga oca sam kao student dovodio kod Doc. dr Srećka Nedeljkovća sasvim iznenada, nenajavljen, i bio zadivljen energijom, toplim prijemom i altruizmom kojim je zračio. Kasnije, u toku zajedničkog rada, ti moji utisci divljenja su se samo povećavali. Znao je i on sam, kada mu pozvoni telefon u kancelariji, da kaže: „E, ko će me sada zaposliti?". Nikada nisam bio svedok da je nekome odbio pomoć. Njegova kancelarija je uvek bila otključana, i sve

Srećko I. Nedeljković: Nagrade i priznanja

1.	Nagrada Vlade Srbije za najbolji maturski rad iz srpskog jezika sa temom „U radu i stvaralaštvu leži smisao života”	1943. godina
2.	Internacionalni majstor (pobeda na prvom međunarodnom turniru Beogradu i na međunarodnom turniru u Beču)	1950. godina
3.	Zlatna medalja na Olimpijadi u Dubrovniku	1950. godina
4.	Na svetskoj šahovskoj rang listi zauzeo je 43. mesto (rejting 2546)	1955. godina
5.	Zaslužni sportista Jugoslavije	1957. godina
6.	Oktobarska nagrada grada Beograda za dostignuća u nauci	1970 i 1981. godina
7.	Sedmojulska nagrada Srbije za unapređenje u razvoju Srbije	1979. godina
8.	Orden zasluga za narod sa zlatnim vencem	1986. godina
9.	Zlatna medalja Udruženja kardiologa Jugoslavije	1989. godina
10.	Dve zlatne medalje Medicinskog fakulteta u Beogradu za unapređenje poslediplomske nastave iz kardiologije	1985 i 1995. godina
11.	Nagrada Srpskog lekarskog društva za životno delo	1993 godina
12.	Urednik Šahovske rubrike „Viva”,	1996. godina
13.	Gramata patrijarha Pavla	2000 i 2004. godina
14.	Veliki pečat Srpskog lekarskog društva	2003. godina
15.	Plaketa SANU	2000. godina
16.	Nacionalno sportsko priznanje za poseban doprinos razvoju i afirmaciji sporta od strane Vlade Republike Srbije	2007. godina
17.	Pokrovitelj finalnog šahovskog turnira za studente Beogradskog univerziteta (Trofej Verice i Srećka Nedeljkovića)	2008. godina

svoje saradnike je u nju smeštao tako da smo stalno, ako ne na radnom zadatku, bili u njoj. Ali, Srećko nije delio samo kancelariju sa saradnicima; sećam se da me je sa porodicom ,ubrzo po zaposlenju, ugostio u svom stanu u Herceg Novom. Zračio je brigom za saradnike, i kada mi je ubrzo po mom prijemu rekao

„E, od sada ćemo jedan o drugom u toku naših karijera imati prilike dosta da pišemo”, samo za kratko nisam odmah shvatio šta bi to trebalo da znači. Brzo sam shvatio da u radnom odnosu ima i dosta zamki, te da je lojalnost u odnosu učitelja i učenika jedan od ključnih elementa prevazilaženja i teških situacija sa kojima se svi susreću. Kao vrhunac njegove brige o učenicima navešću samo da me je 1994. godine, ne govoreći mi ništa, predložio u Medicinskoj akademiju SLD da kao predlog te akademije idem na Skupštinu SANU za dopisnog člana. Uz njegovo stalno angažovanje za taj predlog (potpisasli ga i Prof. Predrag Lalević i Prof. Dr Vera Kentera) i neprocenjiv doprinos akademika Kanjuha i Papa, taj predlog je i usvojen. Često sam govorio, šahovski rečeno, da je forsirajući pešaka na osnovnom redu, tog pešaka pretvorio u damu. To je bio Srećko koji nas je učio da svakome treba dati šansu za uspešnu karijeru, ali i da nisu svi isti kada im se ta šansa pruži („Svako treba da živi”, i „Napisaću knjigu, Hipokrat i svi njegovi učenici”). Njegov osnovni postulat je bio, i to je često naglašavao baš na engleskom jeziku „Hard working, soft speaking”. To je bilo u njegovom gandističkom poimanju savlađivanja prepreka koje su mu stalno iskrsavale na putu. Sećam se da me je, kada je teškom mukom obezbedio sredstva za novu salu za kateterizaciju, a niko nije želeo da ustupi prostor, pozvao i rekao: “Znate Ostojiću šta je Tito komandovao u IV ofanzivi? Idemo kroz Prozor!”. I zaista, naša nova kateterizacija je izašla kroz prozor i dozidana kao pupak uz postojeću zgradu. Samo šematski i zbog sistematizacije izlaganja, bi se o Srećku moglo pisati posebno kao čoveku, mentoru, prijatelju, lekaru, pedagogu, naučniku, glavi porodice, ali sve je to bilo sjedinjeno u jednoj osobi kao u kaledioskopu duginih boja. Šta god bi iz tih oblasti napisali, ne bi bilo dovoljno impresivno kakav je Srećko čovek bio. Mnogo je cenio i voleo druge, i čini mi se da mu je to bilo i uzvraćeno. Uvek je bio zadovoljan i srećan postignutim, skroman, ali nikada u nekoj defanzivi. Operaciju srca je prebrodio brže nego kijavicu, ležeći u bolnici samo 72 sata; a pred samu tešku operaciju noge, kada smo mu rekli da je potreban radikalni zahvat, onako duhovito je odgovorio: „U redu, pa, mi smo to i drugima priređivali!” Hrabro i čestito je živeo, hrabro nas je i napustio. Pesimista bi rekao šteta što smo ga izgubili, a ja, kao jedan od njegovih učenika kojima je svesrdno pružio šanse i dao mogućnost da formiram sada poznati svetski tim kardiologa, rekao bih, više optimistički, presrećni smo što smo imali jednog takvog čoveka za učitelja, mentora i prijatelja. Njegove ideje i standardi koje je postavio kao čovek i stručnjak ostatće večito da žive. Srećko nije bio samo doktor-lekar, pedagog, naučnik, šahista, on je bio, što sam i za njegovog života govorio, i njemu i drugima, **pravi narodni mudrac**. Dobro je što nam je lestvicu postavio tako visoko, jer ćemo svi morati vredno da radimo do kraja života ako želimo da ga dostignemo.

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Original article

15 Years of Zajecar Paceaker Center

Aleksandar Jolić[1], Vladimir Mitov[1], Tomislav Kostić[2], Dragana Adamović[1], Milan Nikolić[1], Marko Dimitrijević[1]

[1]Pacemaker center, Invasive Cardiology Department, Zajecar Health Center, [2]Pacemaker center, Cardiology Clinic, Clinical Center Nis,

Abstract The aim of this study is to present the results of the Pacemaker Center in Zaječar from 2008 to 2023. The analysis included 1849 patients with implanted CIED (Cardiac Implantable Electronic Device) with an average age of 73.30±1.16, comprising 1154 (62%) males and 696 (38%) females. There were 753 (36.35%) VVI, 964 (46.61%) DDD, 19 (1%) VDD, 26 (3.03%) ICD, and 16 (1%) CRT-P implants. Among the procedures, 234 (11.01%) were pulse generator replacements, while the rest were primary implants. Analysis of indications for CIED implantation revealed that 45.29% of patients had AV node disease, 23.24% had SA node disease, and 31.14% had atrial fibrillation with slow ventricular rate as the indication. The average duration of the intervention was 40.68 minutes, and the fluoroscopy time was 4.67 minutes. Conclusions: From 2008 to 2023, a total of 1849 implantations of various types of cardiac implantable electronic devices were performed. The number of implantations has been on consistent rise, with over one hundred procedures annually since 2010 and exceeding 150 implantations per year after 2019, reaching approximately 450 per million inhabitants. This is in line with the national and European averages for Eastern European countries.

Key words pacemakers, Zajecar Health Center

Introduction

The therapy with implantable electronic devices, known as Cardiac Implantable Electronic Devices (CIED), began its development in the 1950s as a method of implanting then-bulky and exclusively pulse generator devices for treating patients with severe bradycardic conduction disorders. These procedures were performed by highly trained and then and now still rare vascular and cardiothoracic surgeons. The development of this branch of medicine progressed rapidly alongside technological advancements, leading to today's devices that serve numerous therapeutic roles in both bradycardic and tachycardic heart rhythm and conduction disorders. They also play a crucial role in heart failure therapy and monitoring patients through various electrical and other parameters[1].

All CIED's can be broadly categorized into therapeutic-diagnostic and diagnostic devices. The first group includes devices for treating bradycardic and tachycardic disorders, as well as devices for heart failure therapy. In the group for treating bradycardic rhythm and conduction disorders, there are single-chamber (VVI), dual-chamber (DDD), and pacemaker with so called single pass electrodes (VDD) pacemakers. For treating tachycardic disorders, there are implantable cardioverter-defibrillators, both single-chamber (ICD VR), dual-chamber (ICD DR), and resynchronizers with defibrillator function (CRT-D). Devices for heart failure therapy include resynchronizers with pacemaker function (CRT-P) and those mentioned earlier with an added defibrillator function, as well as newer generation devices still in the development and research phase (baroreceptor stimulators, vagal stimulators).

To explain the type of device, it is necessary to briefly explain the international code table of pacemakers with corresponding letter groups in the code: 1. The first letter represents the stimulation site (V-ventricle, D-dual), 2. The second letter represents the site for registering electrical activity of the heart (V-ventricle, D-dual, O-no registration), 3. The third letter represents the reaction to the registered activity (I-Inhibition, D-dual, T-trigger, O-no response), and 4. The fourth letter represents the option for rate adaptability (R rate response) or none if not applicable.

Devices for monitoring include implantable loop recorders (ILR), which have the capability of directly monitoring various rhythm and conduction disorders. Today, they also have various telemetry options for sending collected data, allowing for almost instant alerting of doctors about significant events monitored in patients. The aim of this study is to present the results of the Pacemaker Center in Zaječar from 2008 to 2023.

Methods

In this study, an electronic database of patients with Cardiac Implantable Electronic Devices (CIED) from the

Address for correspondence: Alaksandar Jolic, MD; , Invasive Cardiology Department, Zajecar Health Center; Mail: jolical149@gmail.com

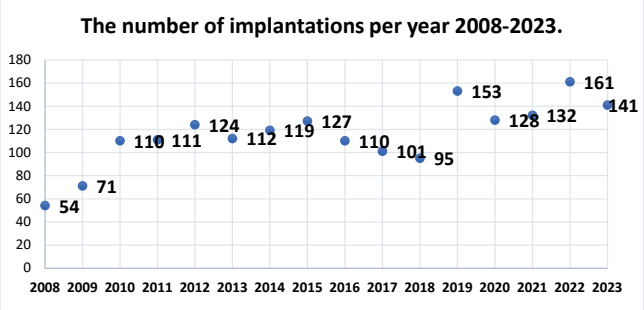

Figure 1. Number of implantations per year from 2008 to 2023

Out of the total number, 753 (36.35%) were VVI, 964 (46.61%) were DDD, 19 (1%) were VDD, 26 (3.03%) were ICD, and 16 (1%) were CRT-P (Graph 2). ICD implantations started in 2013, and CRT-P implantations began in 2018 (Graph 3).

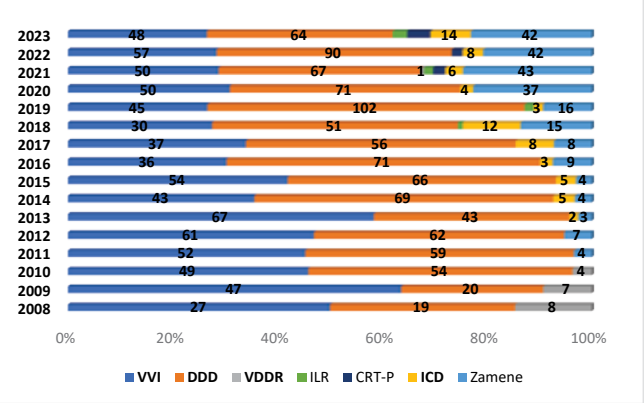

Figure 3. Types of pacemakers by year

Analysis of the indications for which CIEDs were implanted found that 45.29% of patients had AV node disease, 23.24% had SA node disease, while in 31.14% of cases, the indication was atrial fibrillation with slow ventricular rate (Graph 4 and 5).

Pacemaker Center in Zaječar, now part of the invasive cardiology department, was used. A retrospective analysis of data on the implantation of these devices was conducted for the period from 2008 to 2023. The analysis covered 1849 patients with implanted CIED, with an average age of 73.30±1.16, including 1154 (62%) males and 696 (38%) females. The implanted devices included 753 (36%) VVI, 964 (47%) DDD, 19 (1%) VDD, 26 (3%) ICD, and 16 (1%) CRT-P. There were 234 (11%) pulse generator replacements, while the remaining procedures were primary implantations.

Pacemaker implantations were performed in the Cath lab. Throughout the intervention, the patient's cardiac activity was monitored on the defibrillator monitor and since 2014, with the initiation of the new Cath lab, hemodynamics was monitored on the Cath lab hemodynamics monitor. The implantation was carried out by a trained team consisting of an operating physician, a medical technician-instrumentalist, and cardiovascular medical technicians (trained to work as instrumentals, in aseptic conditions, and to perform cardiopulmonary cerebral resuscitation). During the operation, the patient lies on their back. The operative field was prepared by disinfecting and isolating the field with sterile compresses, adhering to surgical principles of asepsis and antisepsis. Local infiltrative anesthesia was used, with a combination of Lidocaine, Bupivacaine, and bicarbonate. The implantation of the permanent antibradicardiac pacemaker was conducted using classical surgical techniques in the right pectoral region. An incision was made in the deltopectoral sulcus, approximately 5cm in length, starting 2cm below the clavicle. The cefalic vein was prepared as the primary vascular access. In cases where preparing the cefalic vein with adequate lumen and flow was not possible, the alternative approach involved puncturing the subclavian vein or axillary vein under the guidance of fluoroscopy in postero-anterior or 30-degree caudal projection, with or without venography (contrast application in the ipsilateral venous system) using the modified Seldinger technique. Electrodes were placed in the right cardiac chambers via the prepared or punctured vein. Electrode positioning was conducted under fluoroscopy control. The ventricular electrode was placed with passive fixation at the apex of the right ventricle or with active fixation, using a screw-in system, in the outflow tract of the right ventricle[2].

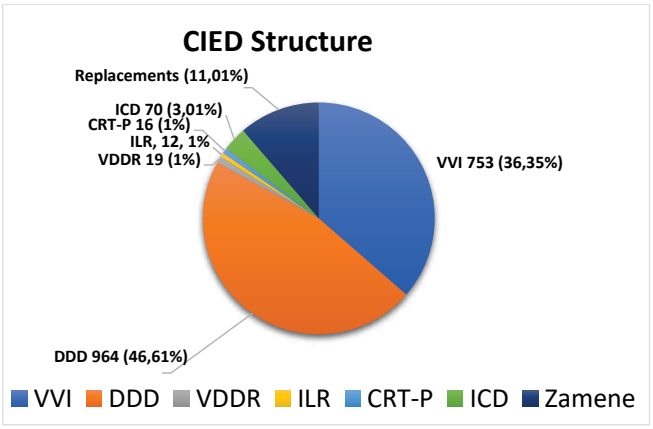

Figure 2. CIED structure from 2008-2023

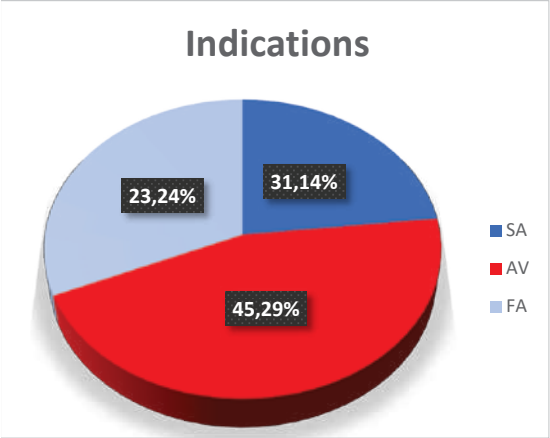

Figure 4. Indications in the total number

Results

In this time period, a total of 1849 CIED implantations were performed. Only in 2008, 2009, and 2018 were there fewer than 100 implantations annually; the data for 2023 is not fully presented (Graph 1).

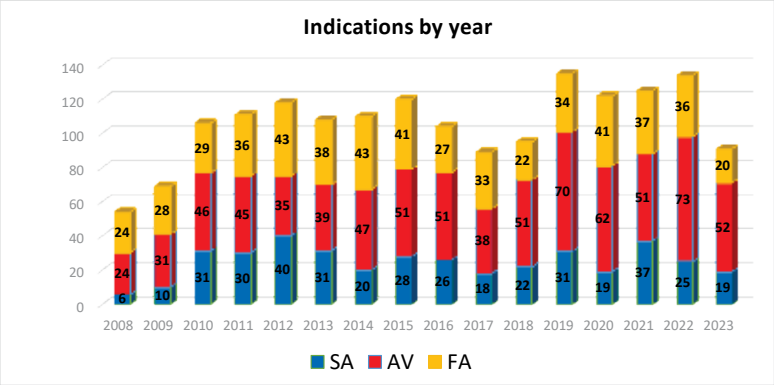

Figure 5. Indications by year

The average duration of the intervention was 44.93±6.38 minutes, and the fluoroscopy time was 5.37±2.24 minutes. Over the years, the longest average time was in 2008, with 54.35 minutes, and the shortest was in 2021, with 32.2 minutes. The average fluoroscopy time ranged from 3.14 minutes in 2010 to 12.8 minutes in 2020 (Graph 6).

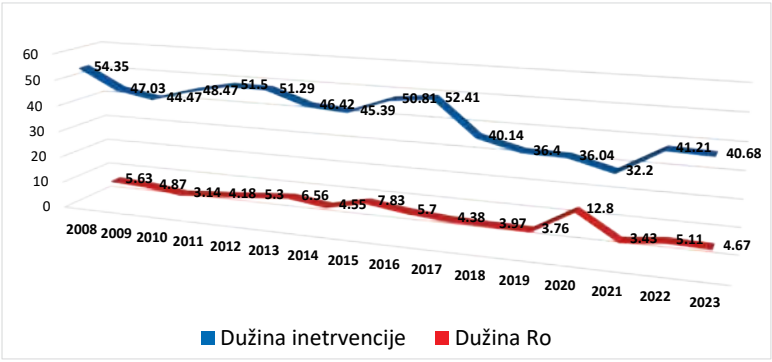

Figure 6. Total and fluoroscopy times from 2008 to 2023

Discussion

The Pacemaker Center in Zaječar began its operations in 2006, initially focusing on the implantation of temporary pacemaker electrodes as a life-saving measure until the patient could undergo permanent pacemaker implantation or until the resolution of the disorder. The era of permanent CIED implantation, including single-chamber pacemakers and VDDR pacemakers, commenced in 2008, followed by the implantation of dual-chamber pacemakers a month later. The implantation of single-chamber cardioverter-defibrillators started in 2013. From 2018 onwards, resynchronization CIED implantations began, completing the range of current devices. It's noteworthy to mention our center's participation in a study involving vagal stimulators as the next step in heart failure electrotherapy.

In recent years, there has been an increase in the number of pacemaker implantations. This is attributed to improved diagnostics, better education of medical professionals, and the overall increase in life expectancy in the general population. In Serbia, the number of implantations has also been on the rise, reaching 435 per million inhabitants or 3186 pacemakers in 2010 and 521 per million inhabitants or 3724 implantations in 2015. The number of implantations in our center is in line with the our national average, with 440 implantations per million inhabitants in 2010 and 508 implantations per million inhabitants in 2015. This is significantly better than Moldova with 79 implantations per million inhabitants but still far from Belgium, which had 1218 implantations per million inhabitants[3,4,5]. In our setting, the most common indication was AV node disease in 45.29% of patients, followed by atrial fibrillation in 31.14% of patients. This distribution of indications is expected given the average age of patients, which was 73.30 years[6]. As a result, the smallest number of patients, 23.24%, had SA node diseases, which are more common in younger age groups. Since SA and AV node diseases were the most prevalent, DDD and VDD pacemakers were also proportionally more prevalent at 47.61% compared to VVI at 36.35%. The average total time of implantations was 40.68 minutes, and the average fluoroscopy time was 4.67 minutes, with a trend showing a gradual decrease in intervention and fluoroscopy time each year.

Conclusion

During the period from 2008 to 2023, a total of 1849 implantations of all types of implantable cardiac electrical devices were performed. The number of implantations has been consistently on the rise, with over one hundred procedures annually since 2010 and exceeding 150 implantations per year after 2019, reaching approximately 450 per million inhabitants. This is in line with the national and European averages for Eastern European countries.

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Sažetak

15 godina pejsmejker centra u Zaječaru

Aleksandar Jolić[1], Vladimir Mitov[1], Tomislav Kostić[2], Dragana Adamović[1], Milan Nikolić[1], Marko Dimitrijević[1]

[1]Pejsmejker Centar, Odeljenje invazivne kardiologije Zdravstevni Centar Zaječar, [2]Pejsmejker Centar, Klinika za Kardiologiju, Klinički Centar Niš

Cilj rada je prikaz rezultata rada Pejsmejker centra u Zaječaru u periodu od 2008-2023. godine. Analizom je obuhvaćeno 1849 pacijenata sa implantiranim CIED-om prosečne starosti 73.30±1.16, od kojih je bilo 1154 (62%) muškaraca 696 (38%) žena. Bilo je implantirano 753 (36,35%) VVI, 964 (46,61%) DDD, 19 (1%) VDD i 26 (3,03%) ICD, i 16 (1%) CRT-P. Bilo je 234 (11,01%) zamena pulsnog generatora dok su ostale operacije bile primoimplantacije. Analizom indikacija zog kojih su implantirani CIED nađeno je da je 45,29% pacijenta imalo bolest AV čvora, 23,24% bolest SA čvora, dok je kod 31,14% razlog bila atrijalna fibrilacija sa sporom komorskom frekvencom. Prosečna dužina intervencije bila je 40,68 minuta, dužina rendgen skopije bila je 4,67 minuta.

***Zaključci:** U periodu rada od 2008 do 2023. bilo je 1849 implantacija svih tipova implantabilnih srčanih električnih uređaja. Broj implantacija je u konstatnom porastu, tako da od 2010. godišnje je bilo više od sto implantacija a nakon 2019. preko 150 implantacija ili oko 450 na milion stanovnika, što je u rangu nacionalnog i evropskog proseka za zemlje istočne Evrope.*

***Ključne reči**: pejsmejkeri, Zdravstveni centar Zaječar*

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Original article

Clinical and Pathological Characteristics of Pericardial Effusions: A Tertiary-Level Healthcare Center Experience

Aleksandra Matić[1], Isidora Milosavljević[1], Ivan Petrović[1], Milica Mandić[1], Miljana Miladinović[1], Sofija Mijović[1], Aleksandra Ilić[1,2], Aleksandra Milovančev[1,2], Dragana Dabović[1,2], Dragica Andrić [1,2], Milovan Petrović [1,2], Golub Samardžija[1,2], Aleksandar Redžek[1,2]

[1]Faculty of Medicine, University of Novi Sad, Novi Sad, Serbia, [2]Institute for Cardiovascular Diseases of Vojvodina, Sremska Kamenica, Serbia

Abstract

Introduction. Pericardial effusion represents a significant medical issue with diverse origins, often associated with malignant conditions. This study aims to comprehensively analyze the demographic, clinical, and cytological aspects of pericardial effusion in patients treated at a tertiary center.

Methods. This retrospective study included a four-year period and obtained fine needle aspiration cytology (FNAC) analysis results of pericardial effusion in 80 patients. Data covering demographics, reasons for hospitalization, and cytological analyses were collected and statistically evaluated.

Results. The average age of participants was 67±12 years, with a slight male predominance. The primary reasons for hospitalization were impending cardiac tamponade (41%), massive effusions (27%), and cardiac decompensation (9%). Hemorrhagic and malignant effusions were prevalent cytologically. Malignant effusions were noted in 20% of cases, primarily originating from lung adenocarcinoma, and in approximately 15% of cases, served as an initial indicator of hidden malignancy.

Conclusion. Understanding the demographic patterns, clinical presentations, and cytological types of pericardial effusion is crucial for timely diagnosis and treatment. This research highlights the significance of pericardial effusion as a potential indicator of an underlying malignancy and underscores the importance of early detection and intervention.

Kew words pericardial effusion, fine needle aspiration cytology (FNAC), malignant effusions

Introduction

Pericardial effusion is defined as an abnormal accumulation of liquid in the pericardial cavity. It represents a significant cause of mortality, and it can follow a wide spectrum of diseases.[1] In cases of a small pericardial effusion, typical symptoms are usually not present, although there may be a sensation of mild chest discomfort. When larger volumes of pericardial effusion occur, there is an increase in intrapericardial pressure, which leads to reduced filling of the heart's chambers on both sides, resulting in a progressive decrease in stroke volume and systemic blood pressure. It's important to note that the development of symptoms in pericardial effusion is influenced not only by the quantity of fluid but also by the rate at which it accumulates.[2] Pericardiocentesis is an invasive procedure involving the puncture of the pericardium for therapeutic evacuation of its contents, while simultaneously obtaining a sample of fluid for biochemical, cytological, microbiological, immunocytochemical, and cytogenetic analysis.[1] The analysis of pericardial effusion can represent a distinctive diagnostic challenge for cytologists,[3] as they can be sorted by different classification systems. The obtained effusion samples, following biochemical analysis, are clinically classified primarily into transudates and exudates.[4] Pericardial effusions can also be classified based on the predominance of certain cell populations into lymphocytic, macrophagic, neutrophilic-granulocytic, eosinophilic, hemorrhagic, mixed, suspicious for malignancy, malignant effusion, and transudate. Cytological analysis of pericardial effusion is a diagnostic procedure that is based on the examination of spontaneously shed cells into the pericardial cavity,[5] which entails two major groups: the first without atypical, neoplastic cells, predominantly consisting of mesothelial cells, histiocytes, and lymphocytes representing a benign type of effusion, and the second with the presence of malignant cells, indicating a malignant type. An uncertain finding, when rare abnormal cells are present, is labeled as a sample suspicious for malignancy. The main indication for performing FNAC (*Fine Needle Aspiration Cytology*) is to differentiate between benign and malignant effusions.[4]

Malignant or neoplastic findings in effusion are quite common, considering the tendency of certain tumors to metastasize to the pericardium. Most patients with malignant effusion already have knowledge of the primary neoplasm; however, in some cases, pericardial effusion is the initial manifestation of hidden malignancy, and

Address for correspondence: Assoc. Prof. Golub Samardžija, MD, PhD; golub.samardzija@mf.uns.ac.rs; Mobile:+381642131080

sometimes pericardial effusions are often observed as an incidental finding in patients with cancer.[6-8] Primary tumors of the pericardium occur less frequently compared to secondary tumors, and they include mesothelioma, and primary lymphoma which is more commonly accompanied by effusion.[4] Metastatic tumors account for the majority of malignant pericardial effusions,[9] and the most common are adenocarcinomas, followed by squamous cell and small cell carcinoma, while melanomas and lymphomas (both Hodgkin and non-Hodgkin) are rare.[4]

The objectives of this research were to analyze the age and gender distribution of patients with pericardial effusion, determine the most common reasons for admission of patients with pericardial effusion, identify the cytological types of pericardial effusions, and analyze the frequency of malignant types of pericardial effusions and the origin of malignant cells.

Methods

This retrospective study was approved by the Ethics Committee of the Institute for Cardiovascular Diseases of Vojvodina (Sremska Kamenica, Serbia), as it included 80 participants in which fine needle aspiration cytology (FNAC) of pericardial effusion was performed during a 4-year period (2018-2022). Demographic and clinical data were extracted from the hospital's information system and included sex, age, and reason for hospitalization. To obtain a better insight into the age distribution, patients were divided into 6 categories, each one including a 10-year period from the age of 35 until the age of 94.

Samples obtained by FNAC were stained with the *May Grunwald Giemsa* (MGG) method. Based on the cytological characteristics, pericardial effusions were classified into nine categories: lymphocytic, macrophagic, neutrophilic-granulocytic, eosinophilic, hemorrhagic, mixed, suspicious for malignancy, malignant effusion, and transudate. In patients with malignant effusion, the origin of malignant cells was determined.

Collected data were statistically assessed using Jamovi version 2.4.1, a freely available statistical software. We employed descriptive statistics to summarize and present the data.

Results

Demographic data

Sex distribution has shown that our sample mainly consisted of male participants (n = 46), while 34 were female. The mean age was 67±12.6, with the youngest participant being 35, and the oldest 90. The most abundant age group, in both sexes, was 65-74, without observed statistical significance between genders. Data are presented in Figure 1.

Clinical data

The most common reason for hospitalization was impending cardiac tamponade (41.3%), as well as massive pericardial effusion (27.5%). Pulmonary edema and aortic dissection weren't noted in male patients, while no female patient was hospitalized due to cardiac arrhythmias. Data regarding reasons for hospitalization are presented in Table 1.

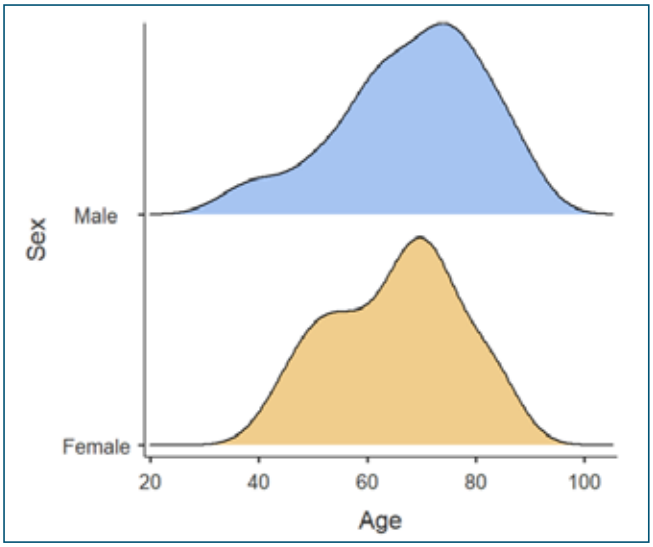

Figure 1. Age distribution based on participants' sex

Table 1. Reasons for hospitalization

Reason	Male		Female		Total	
	N	%	n	%	n	%
Impending cardiac tamponade	18	39.1	15	44.1	33	41.3
Massive pericardial effusion	14	30.4	8	23.5	22	27.5
Cardiac decompensation	2	4.3	5	14.7	7	8.8
Myocardial infarction	2	4.3	2	5.9	4	5.0
Elective admission	3	6.5	1	2.9	4	5.0
Pericarditis	3	6.5	1	2.9	4	5.0
Cardiac arrhythmias	4	8.7	0	0	4	5.0
Pulmonary edema	0	0	1	2.9	1	1.3
Aortic dissection	0	0	1	2.9	1	1.3

Type of pericardial effusion

In both sexes, the most prevalent type was hemorrhagic (33.8%) Image 1, followed by malignant (25.0%) Image 2, and mixed (13.8%) Image 3. There was not a single effusion that fulfilled the criteria of eosinophilic type (Table 2).

Table 2. Distribution of pericardial effusion types, based on cytological characteristics

Type	Male		Female		Total	
	N	%	n	%	n	%
Hemorrhagic	14	30.4	13	38.2	27	33.8
Malignant	11	23.9	9	26.5	20	25.0
Mixed	6	13.0	5	16.7	11	13.8
Transudate	5	10.9	1	5.9	6	7.5
Lymphocytic	3	6.5	2	5.9	5	6.3
Neutrophilic-granulocytic	3	6.5	2	5.9	5	6.3
Suspicious for malignancy	2	4.3	2	2.9	4	5.0
Macrophagic	2	4.3	0	0.0	2	2.5
Eosinophilic	0	0.0	0	0.0	0	0.0

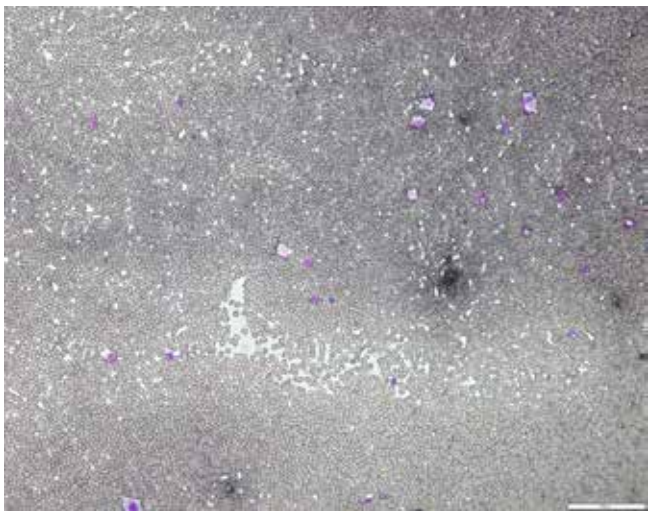

Figure 1. Hemorrhagic type pericardial effusion 20x MGG stained

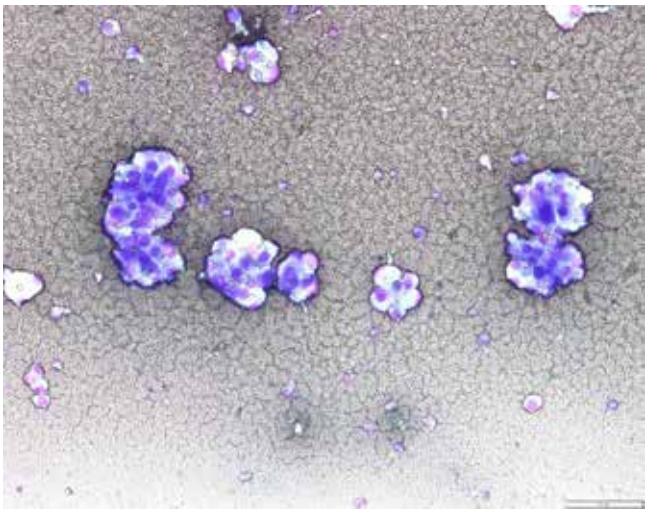

Figure 2. Malignant type pericardial effusion atypical epithel cells adenocarcinoma like 20x MGG stained

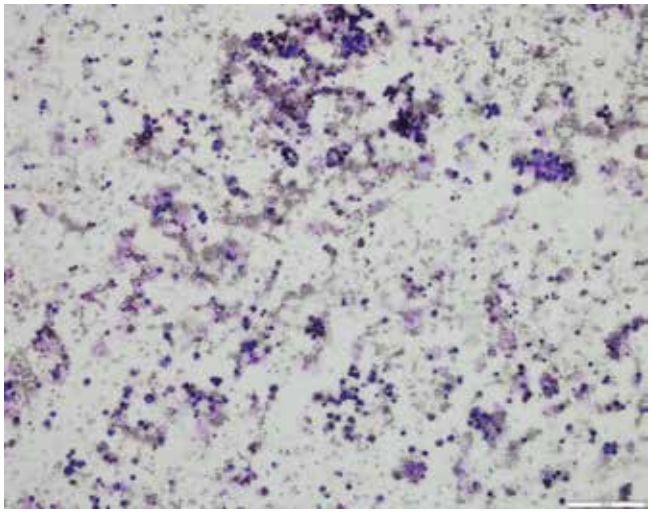

Figure 3. Mixed cellular type pericardial effusion 20x MGG stained

Origin of malignant cells

It was determined that every analyzed malignant type of effusion was a consequence of metastasis. The predominant source of malignant cells was pulmonary adenocarcinoma (n = 16), while malignant cells were much less frequently derived from diffuse gastric adenocarcinoma (n = 2), ductal breast carcinoma (n = 1), and renal cell carcinoma (n = 1). Out of 20 participants, diagnosed malignant pericardial effusion was a primary manifestation of the malignant disease in 10 of them. In each instance of pericardial effusion where the patient was unaware of an underlying tumor, the diagnosis revealed an adenocarcinoma.

Discussion

The incidence of pericardial effusions has been increasing over recent years, primarily due to prolonged survival rates among individuals with malignant diseases, chronic kidney disease patients undergoing hemodialysis, and increased use of anticoagulant therapy, and radiation therapy in tumor treatment, among other factors.[10] Cytological analysis of pericardial fluid samples represents a significant method that, in a considerable number of cases, allows for a definitive diagnosis, particularly when other standard clinical methods are insufficient and/or as support for other clinical and diagnostic approaches.[11]

Our study included 80 hospitalized patients diagnosed with pericardial effusion, and more than half of the participants were male. Although previous studies, conducted in India and in China,[10,12] have shown similar results indicating a predominance of male subjects, Kolte et al. observed a significantly higher number of women who underwent pericardiocentesis.[13] The average age of our participants was 67±12 years, with the highest number of patients aged between 65 and 74 years. The age distribution in our study is aligned with the research conducted by Gecman et al., where the average age of participants was 60±16 years.[14] In contrast, a study from India reported a much younger average age of their participants, which was 46±7 years with 25.8% of patients aged between 51 and 60 years.[12] In addition, Nataraja et al. observed that the majority of participants in their study were grouped in the range of 31 to 40 years,[15] and such significant differences could be explained by the age structure of the Indian population, where the median age is 28.7 compared to the population of Serbia, where the median age is 43.3 years.

In our study, more than a third of the participants underwent pericardiocentesis due to impending tamponade, after which they were hospitalized. The next most common reasons for admission were echocardiographically confirmed massive pericardial effusion and cardiac function disturbances such as heart failure, myocardial infarction, or severe arrhythmias. Research conducted in a tertiary care center to review pericardial effusion characteristics by Erkal et al. showed cardiac tamponade as the leading reason for admission in over 77.3% of participants, followed by massive pericardial effusions at 22.7%.[10] Similar results, with 70% of participants admitted due to impending cardiac tamponade, were observed by researchers at the Asian Medical Academic Center. Some studies, besides cardiac tamponade, cited heart diseases and arrhythmias as common reasons for admission.[16,17]

Regarding the predominance of specific cellular types, cytological findings can be categorized into several categories, and in our study, the predominant cytological findings, accounting for over 30%, corresponded to the hemorrhagic type, characterized by a multitude of red blood cells, followed by malignant and mixed types. The hemorrhagic type of effusion constituted half of the findings in studies conducted by Erkal et al., as well as Yadav and colleagues.[10,12] However, Kolte et al. in their research mentioned reactive mesothelial cells, histiocytes, and lymphocytes as the most common cellular components of pericardial effusion.[13]

Serous membranes are often sites of metastatic tumors, leading to the accumulation of fluid in the pericardial cavity.[3] According to studies conducted in Singapore, the most common cause of pericardial effusions was malignancy.[16] Cytological findings in our research are fundamentally divided into benign and malignant categories, a simple classification also used by other researchers in previous studies.[10] Malignant findings were less common in our study (20%). Similar frequencies of the malignant type of effusion were found in other studies.[6,12,17] Given that pericardium is frequently affected by metastases from malignant tumors, effusion formation is a common consequence of this process.[11] In our research, the origin of metastatic tumors resulting in pericardial effusion was primarily from lung adenocarcinoma (80%), with significantly rarer occurrences from diffuse gastric adenocarcinoma, ductal breast carcinoma, and clear cell renal carcinoma. He et al. also noted a dominant and nearly identical percentage of lung adenocarcinoma metastases in the cardiac sac, with breast carcinoma and lymphomas being other common causes of malignant effusions.[18] In their seventeen-year study encompassing 985 samples of pericardial effusion with cytological evidence of malignant cells, Dermawan et al. identified lung adenocarcinoma as the most prevalent metastatic tumor (61%), followed by infrequent occurrences from gastrointestinal tract tumors (most commonly gastric) and hematolymphoid origin (lymphomas).[9] In studies conducted by Kolte et al., lung adenocarcinoma and breast carcinoma were approximately equally responsible for pleural effusion, and a similar ratio was obtained in Saab et al.'s study.[7,13] The majority of patients who developed malignant pericardial effusion already had a diagnosed primary malignancy in their medical history. Our study observed a small percentage (4%) within the examined group, specifically 15% of participants with malignant effusion, where pericardial effusion, with or without signs of impending tamponade, was the initial manifestation of malignancy. In a study conducted by Dragoescu et al., 87% of patients with malignant pericardial effusion had a documented history of malignancy, while 13% of participants at the time of cytological examination of pericardial effusion did not have an established previous malignancy.[6] Last year's ESC guidelines on cardio-oncology recommend multimodality cardiovascular imaging (echocardiography, CMR and CT), ECG and measurement of cardiac biomarkers to confirm the diagnosis, assess the haemodynamic consequences of pericardial disease, and rule out associated myocarditis. Malignancy-related pericardial effusions caused by direct (lung, oesophageal, breast) or metastatic invasion (haematological malignancies, ovarian, melanoma) or by lymph node obstruction are generally associated with poor prognosis, and multidisciplinary discussion is needed before interrupting and restarting cancer treatment.[8]

Conclusion

The average age of participants with pericardial effusion was 67±12 years, showing no significant gender difference. The main reasons for admission were impending tamponade (41%), followed by massive effusions (27%) and cardiac decompensation (9%). Hemorrhagic and malignant types were most common in cytological findings. Malignant effusions were present in 20% of participants, primarily from lung adenocarcinoma. Notably, pericardial effusion can be an initial sign of an underlying malignancy, often marking the first manifestation of a malignant disease.

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Sažetak

Kliničko-patološke karakteritike perikardnih izliva: Iskustvo tercijarnog zdravstvenog centra

Aleksandra Matić[1], Isidora Milosavljević[1], Ivan Petrović[1], Milica Mandić[1], Miljana Miladinović[1], Sofija Mijović[1], Aleksandra Ilić[1,2], Aleksandra Milovančev[1,2], Dragana Dabović[1,2], Dragica Andrić [1,2], Milovan Petrović [1,2], Golub Samardžija[1,2], Aleksandar Redžek[1,2]

[1]Medicinski fakultet, Univerzitet u Novom Sadu, Novi Sad, Srbija, [2]Institut za kardiovaskualrne bolesti Vojvodina, Sremska Kamenica, Srbija

Uvod. *Perikardijalni izliv predstavlja značajan medicinski problem sa raznovrsnim uzrocima i često prati maligna oboljenja. Ova studija ima za cilj sveobuhvatnu analizu demografskih, kliničkih i citoloških aspekata perikardijalnog izliva kod pacijenata lečenih u tercijarnom centru.*
Metode. *Ova retrospektivna studija obuhvatala je četvorogodišnji period i uključivala je citološku analizu perikardijalnog izliva putem iglene biopsije (eng. Fine Needle Aspiration Cytology, FNAC) kod 80 pacijenata. Podaci koji obuhvataju demografiju, razloge hospitalizacije i citološke analize prikupljeni su i statistički evaluirani.*
Rezultati. *Prosečna starost učesnika bila je 67±12 godina, uz blagu predominaciju ispitanika muškog pola. Glavni razlozi hospitalizacije bili su preteća srčana tamponada (41%), masivni izlivi (27%) i srčana dekompenzacija (9%). Citološki su dominirali hemoragični i maligni izlivi. Maligni izlivi su zapaženi kod 20% slučajeva, uglavnom potičući od adenokarcinoma pluća i u oko 15% slučajeva je predstavljao inicijalni znak skrivenog maligniteta.*
Zaključak. *Razumevanje demografskih obrazaca, kliničkih prezentacija i citoloških tipova perikardijalnog izliva od suštinskog je značaja za pravovremenu dijagnozu i treatman. Ovo istraživanje ističe značaj perikardijalnog izliva kao potencijalnog indikatora skrivenog maligniteta i naglašava važnost ranog otkrivanja i intervencija.*

Ključne reči: *perikardijalni izliv, "Fine Needle" aspiracija (FNAC), maligni izlivi*

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Case Review

Approaches for the Treatment of Spontaneous Coronary Artery Dissection – a Case Review

Denis Nikolov[1], Oktaj Maksudov[2], Ivan Vasilev[1], Petar Uzov[2], Pavlin Pavlov[1], Iana Simova[1, 3], T. Vekov[3]

[1]MHAT Heart and Brain – Pleven, [2]MHAT Heart and Brain – Burgas, [3]Bulgarian Cardiac Institute

Abstract Spontaneous coronary artery dissection (SCAD) is a tear in the wall of the epicardial coronary artery that is not caused by trauma, coronary intervention, or atherosclerotic plaque rupture. Diagnosis is made by coronary angiography, computed tomography coronary angiography (CTCA), intravascular ultrasound (IVUS) and optical coherence tomography (OCT). SCAD has been shown to be a rare cause of acute coronary syndrome and sudden cardiac death. The usual clinical presentation is a picture of acute myocardial infarction. Young women represent about 70% of patients and 30% of such cases are related to the peripartum period, due to hormonal changes. Left anterior descending (LAD) is the most common site of dissection which represents 60% cases. Right coronary artery (RCA) is the second most common site (more common in men), followed by the left main coronary artery.

The treatment options for this event are conservative, interventional (PCI) or surgical (CABG). The conservative approach is suitable for low-risk stable patients, but in the presence of ongoing ischemia, cardiogenic shock or sustained ventricular tachycardia/fibrillation – an intervention should be performed.

In this current article we will present two cases of SCAD which took a completely different path in regards of the treatment approach that was chosen. The first case is a 48-years old female who was admitted in cardiology department due to the chest pain and dynamic ECG changes. The coronary angiography revealed a SCAD in LAD, but due to the stable state of the patient we decided to go with conservative treatment. However, after 12 hours, the patient reported another episode of chest pain with the ECG showing ST-elevations in precordial leads. Due to the high complexity of the intervention we decided to refer the patient for operation. CABG was performed (LIMA-LAD) and the patient was discharged five days post operation. Our second case as a 46-years-old man presenting with ECG changes for inferior AMI. The angiography revealed a SCAD in RCA. Due to ongoing chest pain we decided to go for an interventional treatment – PCI was successfully performed with implantation of four drug-eluting stents.

SCAD is a condition that can occur in everyday practice in patients with ACS and can be expected as the cause of ACS in young patients without significant risk factors. There is no universal principal regarding the treatment method, so rushing to perform an intervention (PCI or CABG) is not recommended, unless there is ongoing ischemia. In some of the cases, the dissection regenerates spontaneously, but in the acute phase, intervention or surgery is sometimes required.

Key words spontaneous coronary dissection, myocardial infarction, management

Introduction

Spontaneous coronary artery dissection (SCAD) is a tear in the wall of the epicardial coronary artery that is not caused by trauma, coronary intervention, or atherosclerotic plaque rupture. Diagnosis is made by coronary angiography, computed tomography coronary angiography (CTCA), intravascular ultrasound (IVUS) and optical coherence tomography (OCT). SCAD has been shown to be a rare cause of acute coronary syndrome and sudden cardiac death. The usual clinical presentation is a picture of acute myocardial infarction. Young women represent about 70% of patients and 30% of such cases are related to the peripartum period, due to hormonal changes [1, 2]. LAD is the most common site of dissection which represents 60% cases. RCA is the second most common site (more common in men), followed by the LM coronary artery.[3] The treatment options for this event are conservative, interventional (PCI) or sugical (CABG). The conservative approach is suitable for low-risk stable patients[4], but in the presence of ongoing ischemia, cardiogenic shock or sustained ventricular tachycardia/fibrillation – an intervention should be performed. Weather by percutaneous coronary intervention (PCI) or by a coronary artery bypass graft (CABG), it is up to the heart team to decide based on the complexity of the lesion and the patinet's condition.

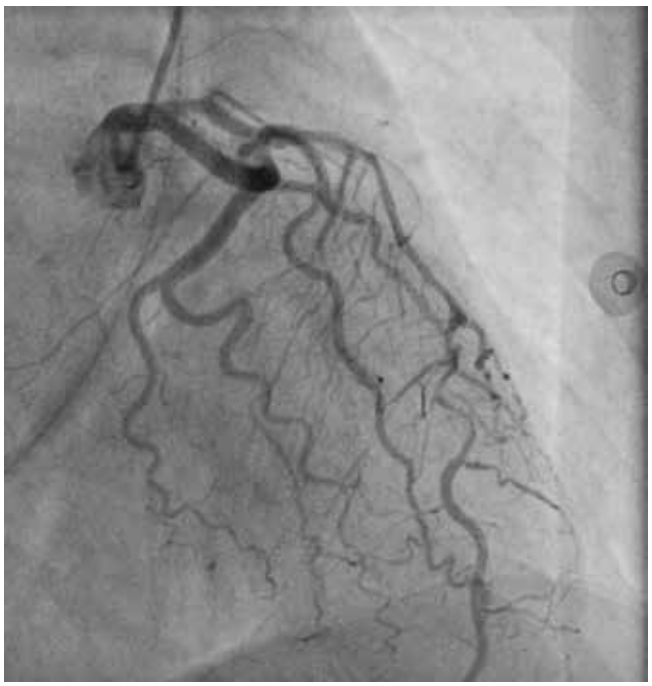

Fig. 1 LAD dissection

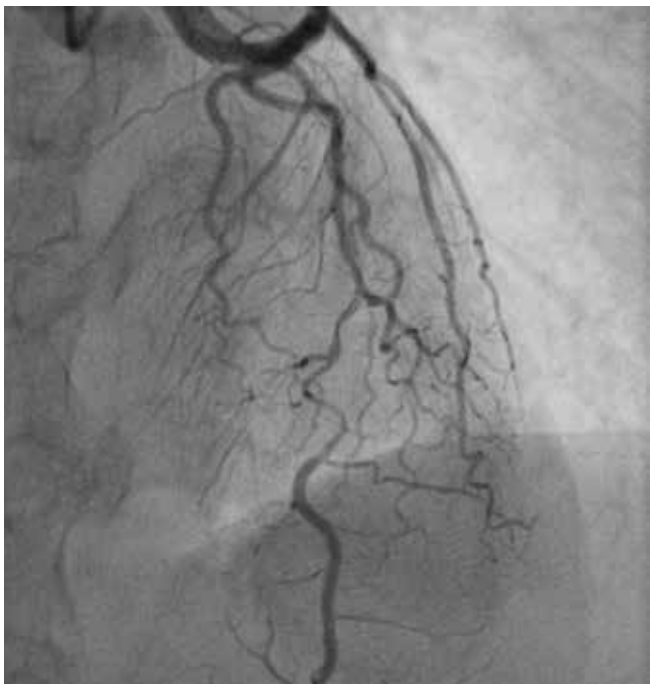

Fig. 2 LAD dissection

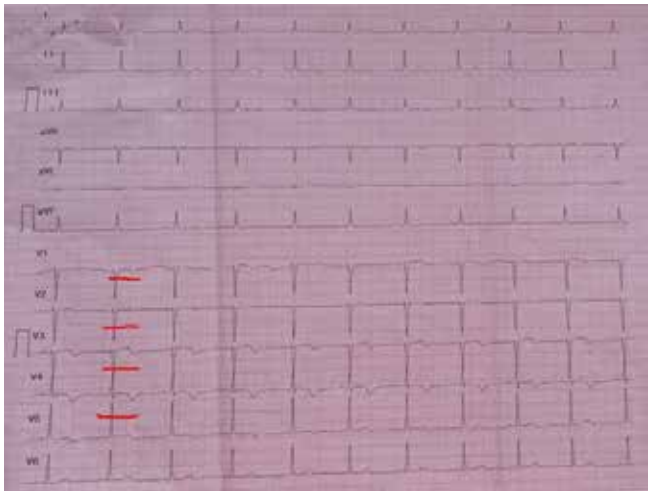

Fig. 3 ECG changes in anterior leads

In this current article we will present two cases of SCAD which took a completely different path in reguards of the treatment approach that was chosen.

Case presentations

Our first case is a 48-years old female, smoker that presents herself to our emergency department with chest pain with irradiation to the back and left arm, sweating and nausea. The ECG showed transient ST-T changes in the anterior leads – peaked T waves and ST-depression in V4-V6. The patient was transferred to our cardiology department for an urgent invasive assessment of the coronary circulation. At admission, patient had no ECG changes, but high levels of troponin were noted. From the echocardiography there was no valvular pathology, no findings of aortic dissection and a preserver ejection fraction. The patient was rushed to the cath lab and from the coronary angiography we observed a proximal prolonged stenosis in LAD, with up to 90% narrowing of the lumen in the mid segment but with TIMI 3 flow in

Fig. 4 LAD during the operation

LAD during the study (Figure 1 and 2). Lcx and RCA were with-out stenosis. Since the patient had no chest pain and was hemodynamically stable, we decided a to go with conservative treatment strategy.

However, after 12 hours, the patient reported another episode of chest pain. The ECG showed ST-elevations with biphasic T-waves in lead V2-V4 (Figure 3). Due to the complexity of the PCI procedure and the risk of iatrogenic damage, with an ongoing acute coronary syndrome with ST-elevation, we decided to change the strategy and proceed with surgical revascularization. LIMA-LAD coronary artery bypass grafting (CABG) was performed without any complications and the patient was discharged five days after the operation (Figure 4).

Fig. 5 LAD has healed one month after the operation

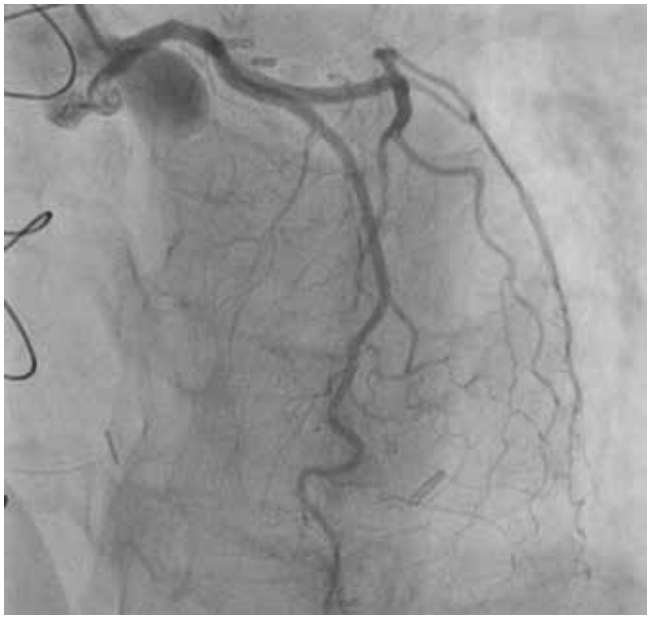

Fig. 7 Normal flow in LAD 1 year after operation

One month after discharge we re-hospitalized the patient in order to assess the coronary status after the surgical revascularization. We found a patent coronary artery bypass graft and normal flow in the LAD (Figure 5 and 6).

One year later, the patient was referred to our department again due to chest pain. We performed a coronary angiography and we found normal blood flow in the LAD but the LIMA-LAD bypass was occluded, since it has served its purpose (Figure 7 and 8).

Our second case is a 46-year-old man, with risk factors for ischemic heart disease – sex, age, arterial hypertension and smoking, who was transported to our hospital with an acute myocardial infarction of the inferior wall of the left ventricle. The complaints have been for about 5 hours prior, and experienced two syncope. The ECG that was presented from the paramedics team was with marked ST-elevations in leads II, III, aVF. In our

Fig. 6 Patent LIMA-LAD graft one month after the operation

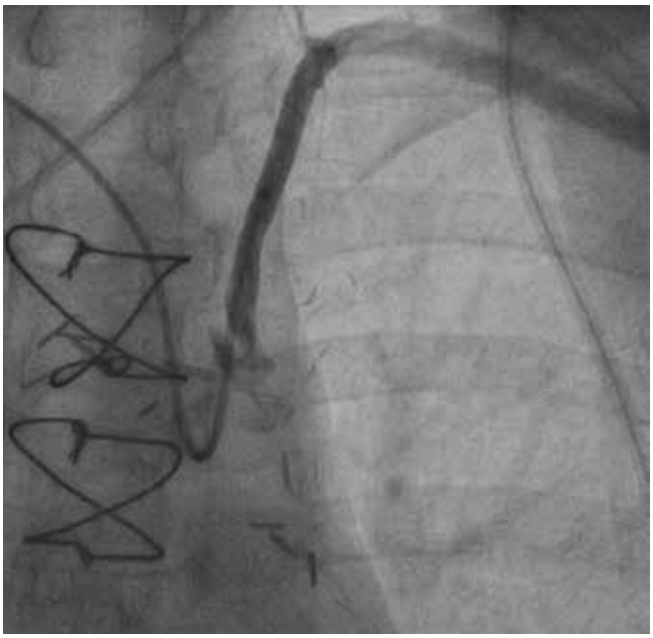

Fig. 8 LIMA-LAD graft is occluded one year after operation, since it has already served its purpose

ECG, however, there was only a slight ST-elevation up to 0.5mm in lead III. We performed an immediate coronary angiography, from which we noted that the left coronary arteries had no stenosis, but the RCA was at first with an unclear finding – reduced diameter of the vessel in the proximal and middle third, preserved distal blood flow and a probable filling defect in the middle segment (Figure 9). In order to clarify, we decided to use a guiding catheter for a more precise image. The selective cannulation revealed a double-lumen dissection starting ostial and propagating to the midsegment (Figure 10). We consider this to be a spontaneous dissection and since the patient started to experience

Fig. 9 LAD has healed one month after the operation

Fig. 10 Patent LIMA-LAD graft one month after the operation

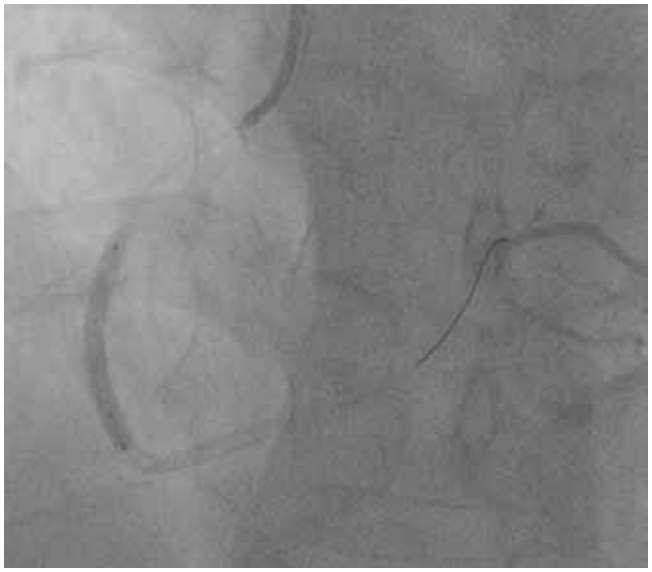

Fig. 11 First of four stents

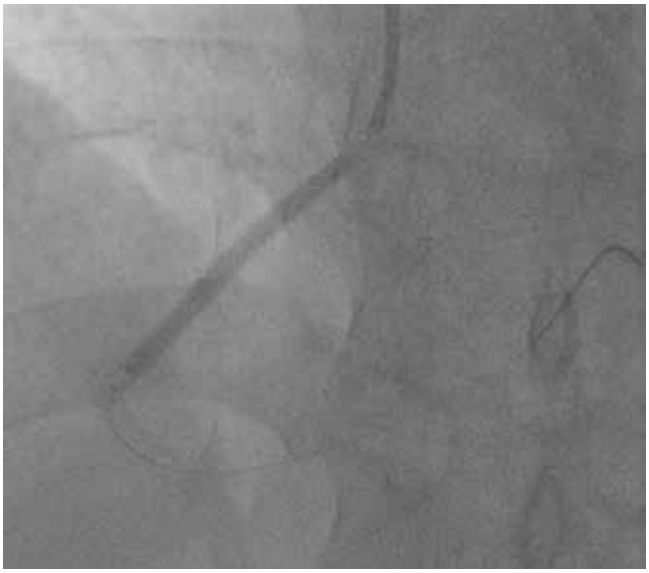

Fig. 12 Second stent

chest pain, we decided to proceed to an interventional treatment. We performed PCI, starting with a stent 3.5/36 from distal to proximal, with the idea to prevent "squeezing" the hematoma and to avoid it's propagation towards the distal segment. Next we implanted a second stent – 3.5/40 from mid to proximal segment. Unfortunately, there indeed occurred a minor propagation of the thrombus in the false lumen, so we had to cover it up as well using a 3.5/16 stent. We finished with a 4.0/16 DES in ostial segment and a post-dilatation with a noncompliant balloon 3.5/18. The final result was good and the patient was discharged on the third day after the procedure (Figure 11, 12 and 13). Follow-up was done by phone after six months and the patient denied having any sort of complains ever since.

Discussion

Spontaneous coronary artery dissection (SCAD) is an infrequent cause of ACS in general but accounts for a significant proportion of ACS cases in young/middle-aged women[5]. The mechanism underlying SCAD is different to that of Type 1 myocardial infarction and therefore – has a different way of management and different outcomes. Compared to the approach in ACS due to atherosclerotic plaque rupture, in SCAD the focus should be less on restoration of normal coronary architecture but rather on the minimal measures necessary to restore TIMI 3 flow. The treatment methods are conservative, interventional (PCI) and surgical (CABG).

Conservative medical management, as opposed to PCI, is generally recommended for patients with SCAD. Until evidence from ongoing trials becomes available, these patients should receive the same pharmacological therapy as other ACS patients.

PCI is recommended for SCAD with associated symptoms and signs of ongoing myocardial ischemia, a large area of myocardium in jeopardy, recurring ventricular arrhythmias and reduced antegrade flow. However,

Fig. 13 Final result

the rate of complications during PCI is high (up to 40%) with the most common being hematoma extension and iatrogenic dissection[6].

The third treatment option is CABG and is recommended when dissection affects the LM or two proximal vessels, or if PCI is not feasible, unsuccessful, or very complex.

If the performing physician is uncertain weather it indeed is a case of SCAD, intracoronary imaging (OCT or IVUS) may come in handy, however it is not generally advised to use those methods routinely, since they could potentially worsen the dissection.[7]

Conclusions

SCAD is a condition that can occur in everyday practice in patients with ACS and can be expected as the cause of ACS in young patients without significant risk factors. There is no universal principal regarding the treatment method, so rushing to perform an intervention (PCI or CABG) is not recommended, unless there is ongoing ischemia. In some of the cases, the dissection regenerates spontaneously, but in the acute phase, intervention or surgery is sometimes required.

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Sažetak

Pristupi rešavanju spontane disekcije koronarne arterije – prikaz slučajeva

Denis Nikolov[1], Oktaj Maksudov[2], Ivan Vasilev[1], Petar Uzov[2], Pavlin Pavlov[1], Iana Simova[1, 3], T. Vekov[3]

[1]MHAT Heart and Brain – Pleven, [2]MHAT Heart and Brain – Burgas, [3]Bulgarian Cardiac Institute

Spontana disekcija koronarne arterije (SCAD) je disekcija u zidu epikardijalne koronarne arterije koja nije uzrokovana traumom, koronarnom intervencijom ili rupturom aterosklerotskog plaka. Dijagnoza se postavlja pomoću koronarne angiografije, kompjuterizovane tomografije koronarografije (CTCA), intravaskularnog ultrazvuka (IVUS) i optičke koherentne tomografije (OCT). Pokazalo se da je SCAD redak uzrok akutnog koronarnog sindroma i iznenadne srčane smrti. Uobičajna klinička slika je slika akutnog infarkta miokarda. Mlade žene predstavljaju oko 70% pacijenata, a 30% takvih slučajeva se odnosi na peripartalni period, zbog hormonalnih promena. Prednja silazna grana (LAD) je najčešće mesto disekcije koje predstavlja 60% slučajeva. Desna koronarn arterija (RCA) je drugo najčešće mesto (češće kod muškaraca), a zatim sledi glavno stable leve koronarna arterija.

Opcije lečenja za ovo stanje su konzervativne, interventne (PCI) ili hirurške (CABG). Konzervativni pristup je pogodan za niskorizične stabilne pacijente, ali u prisustvu ishemije koja je u toku, kardiogenog šoka ili produžene ventrikularne tahikardije/fibrilacije – potrebno je izvršiti intervenciju.

Ovde predstavljamo dva slučaja SCAD-a koji su lečeni potpuno drugačijim načinom. Prvi slučaj je žena od 48 godina koja je primljena na kardiološko odeljenje zbog bolova u grudima i dinamičkih promena EKG-a. Koronarografija je otkrila SCAD u LAD, ali zbog stabilnog stanja pacijenta odlučili smo se za konzervativno lečenje. Međutim, nakon 12 sati, pacijentkinja je prijavila još jednu epizodu bola u grudima sa EKG-om koji pokazuje ST-elevaciju u prekordijalnim odvodima. Zbog velike složenosti intervencije odlučili smo da uputimo pacijenta na operaciju. Urađen je CABG (LIMA-LAD) i pacijent je otpušten pet dana nakon operacije. Naš drugi slučaj je bio 46-godišnji muškarac koji je imao EKG promene zbog inferiornog infarkta miokarda. Angiografija je otkrila SCAD u RCA. Zbog stalnog bola u grudima odlučili smo da idemo na interventno lečenje – PCI je uspešno urađena sa implantacijom četiri stenta sa lekovima.

SCAD je stanje koje se može javiti u svakodnevnoj praksi kod pacijenata sa akutnog koronarnoig sindroma (AKS) i može se očekivati kao uzrok AKS kod mladih pacijenata bez značajnih faktora rizika. Ne postoji univerzalni princip u vezi sa metodom lečenja, tako da se ne preporučuje žurba sa izvođenjem intervencije (PCI ili CABG), osim ako ne postoji produžena ishemija. U nekim slučajevima disekcija se spontano regeneriše, ali je u akutnoj fazi ponekad potrebna intervencija ili operacija.

Ključne reči: *spontana koronarna disekcija, infarkt miokarda, lečenje*

Srce i krvni sudovi 2023; 42(4): 111-114

Original article

Transradial Carotid Artery Stenting: A Comprehensive Registry Analysis and Comparative Evaluation of Access Routes for Improved Outcomes

Oliver Kalpak, Hristo Pejko

Department for cardiac catheterization laboratories, University Clinic for Cardiology, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, North Macedonia

Abstract

Introduction. Carotid artery stenting via the radial route is being investigated as a potential strategy to mitigate access-related bleeding in carotid artery interventions. Ongoing trials and procedural initiatives seek to enhance the overall efficacy of these interventions. The utilization of transradial access (TRA) for Carotid Artery Stenting (CAS) holds promise in reducing bleeding incidents compared to the traditional transfemoral approach (TFA).

Methods. Clinical trials are currently examining the comparative benefits of carotid revascularization versus exclusive reliance on best medical therapy for asymptomatic patients. Our interventions primarily targeted symptomatic or high-grade carotid stenosis. A comprehensive five-year registry analysis of carotid artery stenting was conducted, encompassing a comparison of outcomes between transfemoral and trans-radial interventions, as well as inter-operator and patient subset analyses.

Results. Over the five-year period from 2018 to 2022, a total of 573 CAS procedures were performed. The majority of patients (77%, or 442) underwent TRA, with a predominant male representation (68%). Four operators exhibited varying proportions of TRA/TFA utilization, and the choice of approach was at the operator's discretion. The interventions predominantly involved the use of embolic protection (EP). The primary outcome measure, encompassing major events such as stroke, death, or bleeding, occurred more frequently in the TFA group, with rates of 6.2% (8/131) compared to 2.5% (11/442) in the TRA group, resulting in an overall incidence of 3.3% major adverse events in the entire registry. Notably, the majority of major adverse events were attributed to bleeding, with rates of 3.8% in the TFA group and 1.6% in the TRA group.

Conclusions. While our findings suggest superior outcomes for TRA CAS compared to TFA CAS, it is important to acknowledge the presence of real and significant confounding factors associated with operator variability and the absence of randomization between groups. Consequently, statistical comparisons are deemed neither fair nor scientifically robust in this context. This observational analysis of registry data serves as a hypothesis-generating exercise, underscoring the necessity for further investigations into the impact of access route on CAS outcomes.

Kew words carotid artery stenting, trans-radial approach

Introduction

Carotid artery stenting via the radial route is being explored as a potential strategy to minimize access-related bleeding in carotid artery interventions.[1] Minimally invasive percutaneous endovascular neurointerventions have rapidly evolved and gained more popularity over the past three decades, overshadowing conventional surgical repair.[2] Ongoing trials and procedural initiatives aim to enhance the overall efficacy of these interventions. The utilization of transradial access (TRA) for Carotid Artery Stenting (CAS) holds promise in reducing bleeding incidents compared to the traditional transfemoral approach (TFA).[3] CAS has become an accepted alternative to carotid endarterectomy for revascularization of the internal carotid artery (ICA) among high-risk patients. The femoral approach in CAS can present challenges due to access site complications, technical difficulties related to peripheral vascular disease (PVD), and anatomical variations of the aortic arch.

Traditionally, transfemoral arterial access is the preferred approach for CAS due to broad operator experience, ease of navigating the carotid vasculature from the aortic arch femorally, and the larger vessel size allowing for a wide range of devices. However, anatomical variations, advanced atherosclerotic disease, severe iliac artery tortuosity, peripheral arterial disease, and morbid obesity can complicate selective catheterization of the carotid arteries via the femoral route. This complexity may lead to a higher risk of access site complications, prolonged multiple catheterization attempts, and potentially in-

Address for correspondence: Oliver Kalpak, MD, PhD, Faculty of Medicine , Ss. Cyril and Methodius University in Skopje, Department for Cardiac, Catheterization Laboratories, University Clinic for Cardiology, address: blvd. Mother Theresa 17, 1000 Skopje, R.N.Macedonia, cell phone: +389 70 270 923
email: kalpakoliver@gmail.com ; oliver.kalpak@medf.ukim.edu.mk

crease the risk of cerebral embolization and stroke.[1,2,3,4] Our interventions primarily targeted symptomatic or high-grade carotid stenosis, with all cases having CA stenosis greater than 80% and comorbid conditions increasing the risk of carotid endarterectomy. A comprehensive five-year registry analysis of carotid artery stenting was conducted, comparing outcomes between transfemoral and transradial interventions, as well as inter-operator and patient subset analyses.

Methods

Patients undergoing CAS are generally at higher risk for vascular access-related complications and bleeding. This is due to the use of larger-bore catheters compared to coronary procedures, and carotid atherosclerosis is often associated with lower-limb arteriopathy. Carotid artery stenting is typically performed through femoral vascular access using 6–9 Fr guiding catheters. [5]Transradial CAS (TRCAS), though performed routinely in very few centers worldwide, is reserved for selective cases. Thorough imaging of the aortic arch and supra-aortic vessels with computed tomography or magnetic resonance is considered helpful in meticulous planning for this approach. TRCAS is indicated for cases like a Type 2 bovine arch with left internal carotid artery (LICA) stenosis, while right ICA (RICA) stenosis with Type 2 or 3 aortic arch is considered favorable for transradial access. Lack of other viable peripheral vascular access becomes an obligatory indication for TRCAS. [6]Short hemostasis time could potentially allow operators to perform these procedures without discontinuation of oral anticoagulation. Radial access has been shown to reduce acute kidney injury (AKI) compared to femoral access due to a reduction in bleedings, vascular complications, and renal cholesterol embolization. Early mobilization of patients treated with CAS transradially may also reduce post-procedural hypotension, a determinant of contrast-induced AKI. Clinical trials are currently examining the comparative benefits of carotid revascularization versus exclusive reliance on the best medical therapy for asymptomatic patients.[1,3]

Artery Approach

Transfemoral CAS was performed according to standard clinical practice with the same 6 F guiding sheath choice as radial procedures. For the femoral approach, after local anesthesia, the femoral artery was punctured with a 19-gauge needle through which a J-wire was advanced into the femoral artery. In all cases, a 5 Fr short sheath was introduced initially, and then the procedure was performed using a 6 Fr 90 cm long sheath. The sheath was removed immediately after the procedure, and a closure device (Angio-Seal™; St. Jude Medical, St. Paul, MN, USA) was used. A mechanical compression bandage was used for four hours, and the patients were mobilized afterward.[2,6]

For the radial approach, the wrist is hyperextended, and local anesthesia (1 mL lidocaine 2%) is administered. The optimal access site is 1-2 cm proximal to the styloid processus of the radius bone along the axis with the most powerful pulsation of the radial artery (RA). A 20-G plastic cannula-over-needle (Glidesheath insertion kit, Terumo, Tokyo, Japan) is inserted at a 30” to 60” angle along the vessel axis using the single-wall puncture or, if not possible, counter puncture technique. When good arterial back-bleed is obtained, the 0.021” hydrophilic guidewire is advanced, and the hydrophilic 5-Fr sheath (Radifocus, Terumo, Tokyo, Japan) is introduced over the guidewire.[2,5,6]

Medication

Intra-arterial vasodilator (5 mg verapamil) is injected to reduce RA spasm (RAS). Sedation is only administered to anxious patients because circulating catecholamines can precipitate RAS. Immediately after sheath insertion, intravenous unfractionated heparin (50–70 m/kg, up to 5000 units) weight-based dosage for obese patients is administered. RA angiography is performed through the cannula or sheath before catheter insertion. This crucial step defines the RA anatomy from midforearm to brachial/axilar anastomosis and provides a roadmap for secured access. A diluted solution of 3 mL of contrast mixed with 7 mL of blood is injected briskly and recorded. In cases with RAS, tortuosity, and/or radial loops and high takeoff RA, a careful advancement is attempted under fluoroscopy guidance. In most cases, these anatomic variations may be negotiated for diagnostic carotid arteriography. However, patients with unfavorable RA anatomy (severe tortuosity, significant 360” RA loops, and high-takeoff, small-caliber RA) should not be considered for the use of large-bore devices. All patients were pre-treated with Clopidogrel and Aspirin. Those who were naive to antiplatelet therapy were loaded with 300 mg of Clopidogrel o.d. and/or 250 mg of Aspirin i.v. 12–24 h before the procedure. Oral anticoagulation with Apixaban or Rivaroxaban was not suspended before the procedure when indicated for any patient in any group. After the completion of the procedure, hemostasis was obtained using a TR Band (Terumo Corporation, Japan). After discharge, the majority received DAPT for 1 month, and a minority of patients in need of anticoagulation received triple antithrombotic therapy.[6]

Carotid Angiography

First, an aortography was performed in LAO 30 projection with a small contrast volume (15 ml at 10 ml/s) to visualize the aortic arch. Then, the non-symptomatic or non-severely stenotic carotid artery was cannulated. Secondly, the diseased common carotid artery (CCA) was deeply engaged with the Simmons 1 catheter.[5,6] There are two simple methods of utilizing the natural reversed curve of the Simmons catheters within the aortic arch. The first involves passing the catheter over a standard 0.035” wire previously positioned into the descending thoracic aorta. The shape is reformed by withdrawing the guidewire into the primary curve and furthermore to prolapse the catheter into the ascending aorta with a quarter up to half rotation. The second is a loop in the ascending aorta using a hydrophilic Glidewire or another extra support wire in patients with a

very tortuous and dilated aortic arch. In any case, the catheter should be withdrawn and directed to engage the left carotid and then into the right common carotid.[2]

Carotid Intervention

The target common carotid artery (CCA) was initially cannulated via the radial artery using a 5F Simmons 1 or 2 diagnostic catheter, which was then advanced to the external CA (ECA) over an extra support 0.014" coronary guidewire. After removing the coronary guidewire, a 0.035" guidewire was advanced into the ECA, and the Simmons 1 was exchanged for a 5F or 6F shuttle sheath and positioned in the distal CCA. The diagnostic catheter is removed, keeping the position of the super stiff wire constant in the distal branch of the ECA (i.e., the superficial temporal branch). When a severe stenosis of the ECA was also present, the tip of the stiff wire was shaped as a pigtail to increase support and positioned in the distal CCA.[1,2,6] The 6 Fr × 90 cm introducer sheath (DestinationTM, Terumo, Japan; Flexor ® Shuttle Select®, Cook Medical, Bloomington, IN, USA, sometimes Flexor Shuttle Guiding Sheath 6 Fr × 110 cm) was positioned in the CCA. The wire and dilator are then removed slowly, leaving the sheath in a secure position in the mid-CCA. CAS was performed under local anesthesia without sedation. Blood pressure, pulse, and oxygen saturation were continuously monitored throughout the procedure, and neurological assessment was performed by experienced nursing staff.[6]
Transfemoral CAS was performed according to standard clinical practice with a guiding sheath, and the same embolic protection and stents in both groups.

Definitions

A successful angioplasty was defined as no more than 30 percent post-intervention stenosis and an improvement of at least 20 percent in the degree of stenosis. Access-site bleeding was considered major if associated with a hemoglobin loss of at least 2 mmol/l, administrations of blood transfusions, vascular repair, and prolonged hospitalization, and minor if bleeding at the vascular access site only resulted in hematoma formation and did not require specific therapy or interruption of antiplatelet or anticoagulation regimen.[6,7] Major Adverse Cardiovascular and Cerebrovascular Events (MACCE) were assessed as the composite of stroke, death, non-fatal acute myocardial infarction, repeated revascularization of the target vessel by percutaneous transluminal angioplasty (PTA), or vascular operation during the hospital stay and at 30 days. Stroke was defined as an acute neurological event with focal symptoms and signs lasting >24 hrs and was considered a complication of carotid revascularization if it occurred within 30 days of the procedure. Independent certified personnel performed baseline and post-procedure neurological assessments on all patients.[4,7]

Results

Over the five-year period in a single center, a total of 573 CAS procedures were performed. The majority of patients (77%, or 442) underwent TRA, with a predominant male representation (68%). Four operators exhibited varying proportions of TRA/TFA utilization, and the choice of approach was at the operator's discretion. The interventions predominantly involved the use of embolic protection (EP). The primary outcome measure, encompassing major events such as stroke, death, or bleeding, occurred more frequently in the TFA group, with rates of 6.2% (8/131) compared to 2.5% (11/442) in the TRA group, resulting in an overall incidence of 3.3% major adverse events in the entire registry. Notably, the majority of major adverse events were attributed to bleeding, with rates of 3.8% in the TFA group and 1.6% in the TRA group.
Two of the operators contributed to the TFA group far more than the other two who performed over 96% of CAS via radial or ulnar artery. This creates bias in the data regarding access and complications. Thus, the 27 percent of attempted radial and switched towards femoral is biased and not reliable for all operators. This is the reason we only count frequencies and simple proportions without any statistical comparison between the radial and femoral group.

Discussion

This study has various limitations. It is a prospective single-center, single-arm observational registry, with the intrinsic shortcomings of potentially limited external validity and intrinsic bias. The sample size was relatively small. Nevertheless, this study represents the real-life report on the use of radial access for carotid artery stenting. While our findings suggest superior outcomes for TRA CAS compared to TFA CAS, it is important to acknowledge the presence of real and significant confounding factors associated with operator variability and the absence of randomization between groups. Consequently, statistical comparisons are deemed neither fair nor scientifically robust in this context. Data suggested comparable procedural outcomes between the transradial and transfemoral approaches when performing carotid stenting; however, high-level evidence regarding postoperative brain images and the risk of stroke are lacking.[1,7] Therefore, it is reasonable for interventionists to weigh up the risks of neurological events and potential benefits, including fewer access site complications, before choosing the radial or femoral arteries as access sites. Future large-scale randomized controlled trials are imperative.[1,3,7]

Conclusion

TRA showed less access bleeding than femoral. This observational analysis of registry data serves as a hypothesis-generating exercise, underscoring the necessity for further investigations into the impact of access route on CAS outcomes.

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Sažetak

Trans-radijalno stentiranje karotidne arterije: Sveobuhvatna analiza i komparativna evaluacija pristupnih mesta za poboljšani ishod

Oliver Kalpak, Hristo Pejkov

Odeljenje za kateterizaciju srca, Univerzitetska klinika za kardiologiju, Medicinski fakultet, Univerzitet Svetih Ćirila i Metodija u Skopju, Severna Makedonija

Uvod. *Stentiranje karotidne arterije radijalnim putem se istražuje kao potencijalna strategija za ublažavanje krvarenja vezanog za pristup u intervencijama na karotidnoj arteriji. Tekuće proceduralne inicijative nastoje da poboljšaju ukupnu efikasnost ovih intervencija. Korišćenje trans-radijalnog pristupa (TRA) za stentiranje karotidne arterije (CAS) obećava smanjenje incidenata krvarenja u poređenju sa tradicionalnim transfemoralnim pristupom (TFA).*

Metodi. *Klinička ispitivanja trenutno ispituju komparativne prednosti karotidne revaskularizacije u odnosu na isključivo oslanjanje na najbolju medicinsku terapiju za asimptomatske pacijente. Naše intervencije su prvenstveno bile usmerene na simptomatsku ili karotidnu stenozu visokog stepena. Sprovedena je sveobuhvatna petogodišnja analiza stentiranja karotidnih arterija, koja je obuhvatala poređenje ishoda između trans-femoralnih i trans-radijalnih intervencija.*

Rezultati. *Tokom petogodišnjeg perioda od 2018. do 2022. godine obavljene su ukupno 573 CAS procedure. Većina pacijenata (77% ili 442) je podvrgnuta TRA, pri čemu je dominantna zastupljenost muškaraca (68%). Četiri operatera su pokazala različite proporcije korišćenja TRA/TFA, a izbor pristupa bio je na diskreciji operatera. Intervencije su pretežno uključivale upotrebu embolijske zaštite (EP). Primarna mera ishoda, koja obuhvata glavne događaje kao što su moždani udar, smrt ili krvarenje, javljala se češće u TFA grupi, sa stopama od 6.2% (8/131) u poređenju sa 2.5% (11/442) u TRA grupi, što je rezultiralo sa ukupnom incidencom od 3.3% velikih neželjenih događaja u celom registru. Značajno je da je većina velikih neželjenih događaja pripisana krvarenju, sa stopama od 3.8% u TFA grupi i 1.6% u TRA grupi.*

Zaključci. *Dok naši nalazi ukazuju na superiorne rezultate za TRA CAS u poređenju sa TFA CAS, važno je istaći prisustvo značajnih dodatnih faktora povezanih sa ekspertizom operatera i odsustvom randomizacije između grupa. Shodno tome, statistička poređenja se u ovom kontekstu ne smatraju naučno robusnim. Ova opservaciona analiza podataka iz registra služi za stvaranje hipoteze, naglašavajući neophodnost daljih istraživanja uticaja pristupne rute na ishode CAS-a.*

Ključne reči: *stentiranje karotidne arterije, trans-radijalni pristup*

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Case review

Diagnostic and Therapeutic Approach to a Patient with High-risk Pulmonary Thromboembolism - a Case Report and Commentary in the Context of ESC Guidelines

Milan Nikolić, Vladimir Mitov, Aleksandar Jolić, Dragana Adamović, Marko Dimitrijević

Department of invasive cardiology; Department of internal medicine Health center Zaječar

Abstract Pulmonary thromboembolism (PTE) is a common and potentially fatal disease for the diagnosis and treatment of which European Society of Cardiology (ESC) guidelines have been published in 2019. They emphasize the importance of risk stratification of early mortality in suspected or confirmed PTE and treatment according to the risk class: use of anticoagulant or systemic fibrinolytic therapy. The aim of this paper is to present a patient with typical electrocardiographic and echocardiographic findings stratified as high - risk PTE who was treated with systemic fibrinolytic therapy. A 70-year-old patient was admitted to the Intensive Care Unit of the Department of internal medicine of the Zajecar Health Center. On admisson he was hypotensive, dyspnoeic, diaphoretic with signs of organ hypoperfusion. Electrocardiographically, the S1Q3T3 sign and right bundle branch block (RBBB) were verified and a high-risk PTE suspected. Bedside echocardiographic exam revealed a large, mobile thrombotic mass that prolapses from the right atrium to the right ventricle. Systemic fibrinolytic therapy with alteplase with concomitant unfractionated heparin infusion was given. The patient hemodynamically stabilized with loss of electrocardiographic changes suggestive of PTE and thrombus resolution in the right heart chambers. The patient was discharged home after 12 days of hospital treatment. Early risk stratification of patients with PTE and development of a local protocol for diagnosis and treatment according to the risk class increases the success rate in recognizing and treating this disease and reduces the risk of death and other adverse clinical events.

Kew words high-risk pulmonary embolism, PTE, systemic fibrinolytic therapy, rTPA, UFH, hemodynamic instability, PESI

Introduction

Pulmonary thromboembolism (PTE) together with deep vein thrombosis (DVT) is the third most common cardiovascular syndrome, after myocardial infarction and stroke[1]. Epidemiological studies have suggested data on the incidence of PTE in the range of 39-115 per 100,000 population per year[2,3]. Clinical diagnosis is challenging despite the existence of developed diagnostic-therapeutic algorithms for PTE. In a retrospective clinical study of hospital-treated patients with a lethal outcome in whom a clinical autopsy was performed over a ten-year observation period in 502 patients (3.8% of the total autopsies), PTE was verified. Of these, in 328 patients it was understood as the main cause of death (fatal PTE) and in the remaining 174 as an associated disease (non-fatal PTE). Interestingly, the clinical diagnosis of PTE was considered antemortal in 48.2% of all cases with significantly more frequent clinical suspicion made in fatal than in nonfatal PTE (61.9 vs 22.4%)[4]. Of particular importance is the massive PTE, which in the latest ESC guidelines for acute pulmonary thromboembolism from 2019 is presented as a class of high-risk PTE in which it is necessary to conduct a rapid diagnostic assessment and reperfusion therapy. In order for PTE to be perceived as high-risk, it is necessary that the patient be hemodynamically unstable: after resuscitated cardiorespiratory arrest ; obstructive shock with systolic pressure below 90 mmHg with adequate volemia and signs of organ hypoperfusion (altered mental status, cold skin, oligo / anuria, increase in serum lactate level); systolic pressure maintained above 90 mmHg on vasopressor support with signs of organ hypoperfusion; persistent hypotension with systolic blood pressure below 90 or a drop of more than 40 mmHg than usual for particular person lasting more than 15 minutes and not caused by hypovolaemia, sepsis or arrhythmia. In such patients, parenteral anticoagulant therapy is given at the onset of clinical suspicion of PTE and an urgent diagnostic workup is performed - transthoracic echocardiography and / or CT pulmonary angiography. If the diagnosis is confirmed, it is considered a high-risk PTE and it is necessary to implement an aggressive therapeutic approach: systemic application of fibrinolytic therapy, mechanical or pharmacomechanical reperfusion with the introduction of a catheter

Figure 1

Figure 2

into the pulmonary artery (catheter directed therapy) or surgical embolectomy. The use of systemic fibrinolytic therapy is the most common method of treatment in patients without contraindications for it's use, mainly rTPA (alteplase)[5].

Case presentation

In this paper a male patient aged 70 years with a rare but specific electrocardiographic and echocardiographic presentation of acute high-risk PTE successfully treated with systemic fibrinolytic therapy at the Internal Department of the Health Center Zajecar during February 2020. The paper discusses the diagnostic-therapeutic approach to a specific patient in accordance with the latest published ESC guidelines for acute pulmonary thromboembolism. Special attention is paid to the discussion on the application of anticoagulant and fibrinolytic therapy in the early phase of treatment of the disease and the attempt to develop a local protocol for the treatment of PTE

A patient born in 1950, due to the sudden onset of general weakness, malaise and nausea, called the Emergency Medical Service (EMS). During the examination, it was concluded that the patient is hypotensive, and a discrete ST segment elevation of 0.5 mm in D3, aVF leads is verified on the performed ECG recording. The EMS physician suspected the acute coronary syndrome and referred him to the Internal Department of Health center Zajecar. The patient denied any chest pain since the onset of symptoms. Blood presurre was 80/50 mmHg at presentation and the patient was anuric. Electrocardiography revealed sinus tachycardia with a frequency of 120/min, with ST segment elevation up to 0.5 mm in D3, aVF leads but clear McGini White's - S1Q3T3 sign with a complete RBBB (Figure 1). Arterial blood gas analysis indicated hypocapnia with moderate metabolic acidosis and elevated lactate levels (pO2 78 mmHg; pCO2 22 mhg HCO3-11.3 mmol/l pH 7.22 lactate 8.4 mol/l). PTE was strongly suspected and a bolus of 10,000 I.U. unfractionated heparin (UFH) was immediately administered with continuous infusion at a dose of 1000 I.U./h. An emergency bedside transthoracic echocardiographic exam was performed in the Intensive Care Unit. Along with dilatation of the right heart chambers, it clearly verified the thrombotic mass that prolapses through the tricuspid valve (Figures 3 and 4). With all this in mind, the patient was stratified as a high-risk PTE and fibrinolytic therapy with alteplase was administered according to a two-hour protocol. In the further course, patient was hemodynamically stabilized, BP is 135/80 mmHg, HR 90/min, diuresis is established with symptomatic improvement. In the further course, the patient was treated with unfractionated heparin with the consequent introduction of vitamin K antagonists. Throughout hospitalization, the patient was hemodynamically stable, with regression of the characteristic electrocardiographic findings (Figure 2). Prior to discharge, the patient underwent a control echocardiographic exam which did not detect previously seen thrombotic mass, still withmoderate right heart chamber dilation (Figure 5). He was discharged from hospital after 12 days of treatment. During the outpatient follow-up of one year, there were no other clinically significant events other than hospitalization due to viral pneumonia.

Discussion

Acute coronary syndrome (ACS) is one of the most common differential diagnoses in patients with PTE, especially in the presence of significant ECG changes, especially ST segment elevation in one or more electrocardiographic leads. In the *Kukla et al*[6] study, of 292 patients with acute PTE, 2.7% were initially admitted and treated as ACS. In 71.2% of patients there were ECG changes suggestive of myocardial ischemia (negative T waves, ST segment depression / elevation). In the *Otto et al*[7] study, it was found that out of 123 patients with chest pain and ST segment elevation, as many as 59% had a non-ischemic aetiology. In a study of 171 patients presented to emergency triage services with chest pain and ST segment elevation, 56 had acute myocardial infarction, 50 unstable angina, and 65 (38%) noncoronary final diagnosis[8]. Thus, the ST segment elevation, even with associated chest pain, does not necessarily mean it is an acute myocardial infarction. *Wang et al*[9] provide

Figure 3

Figure 4

Figure 5

an overview of 12 conditions in which, in addition to myocardial infarction, the ST segment elevation may occur. Patient presented in this paper was reffered to Internal medicine department with suspected ACS. However, the absence of chest pain as well as reciprocal ST segment depression led us to consider alternative diagnoses. Sudden onset of discomfort and hypotension with 3 electrocardiographic findings: S1Q3T3 sign, RBBB and the presence of sinus tachycardia raised suspicion of acute PTE. The meta-analysis showed that the mentioned three findings together with ST segment elevation in aVR lead, negative T waves in V1-V4 and atrial fibrillation form the so-called "RV strain" which is associated with an increased risk of circulatory collapse and death in PTE. Patients with PTE and hemodynamic collapse or death were shown to have a significantly higher Daniel's electrocardiographic score than patients with PTE without these clinical events (5.9 SD +/- 3.9 vs 2.6 SD +/- 1.5)[10]. In our patient, this score was 7. It was previously shown that a score above 8 carries an increased risk of shock, respiratory failure, and death[11].

In our patient, the level of clinical suspicion of PTE was high despite the fact that there were no strong or moderate predisposing risk factors for venous thromboembolism as reported in the works of *Rogers et al*[12] and *Anderson and Spencer*[13]. The patient had only diabetes mellitus as a weak risk factor for PTE (OR <2).

Since high-risk PTE was suspected, a bedside transthoracic echocardiographic examination was performed in the Coronary care unit, in which, in addition to dilatation of the right heart cavities, a thrombus mass was directly visualized prolapsing through the tricuspid valve into the right ventricle. Echocardiographic or CT pulmonary angiography-seen mobile thrombi in the right heart chambers are seen in about 4% of unselected patients with PTE[14] but in one series of 131 patients with massive PTE treated in the Intensive care unit were seen in as many as 18% of patients by early echocardiography[15]. Mobile thrombi in the right heart practically confirm the diagnosis and are a marker of an increased risk of early mortality in PTE, especially in the presence of right ventricular dysfunction[16,17,18]. Considering clinical and echocardiographic findings, CT pulmonary angiography was not performed and the patient was stratified as a high-risk PTE in accordance with the latest ESC guidelines for acute pulmonary thromboembolism[19].

In patients with verified PTE, the level of risk of early mortality can be determined quickly and easily using prognostic risk scores. The most widely used and validated is the Pulmonary Embolism Severity Index (PESI) which combines clinical indicators of PTE severity and patient's comorbidities[20,21]. In our patient, the PESI score was 150, which placed him in the highest, V risk class in which the estimated 30-day mortality is 10-24.5%[22].

Given the confirmed PTE with signs of hemodynamic instability and the highest PESI risk class for early mortality, the patient was clearly stratified as high-risk PTE with minimal time delay to reperfusion therapy - 15 minutes from patient's presentation to the Department of Internal Medicine. In addition to supplemental oxygen therapy, the patient was cautiously volume challenged with crystalloid solutions in order to avoid the risk of reducing the minute volume of the left ventricle[23,24]. The guidelines state that in the presence of PTE with hemodynamic instability, the use of norepinephrine or dobutamine with class IIa recommendation may be considered[5]. Our judgment was that inotropic support was not necessary and was not applied.

It is recommended that the patients receive parenteral anticoagulant therapy at the initial suspicion of PTE, preferably low molecular weight heparin or fondaparinux

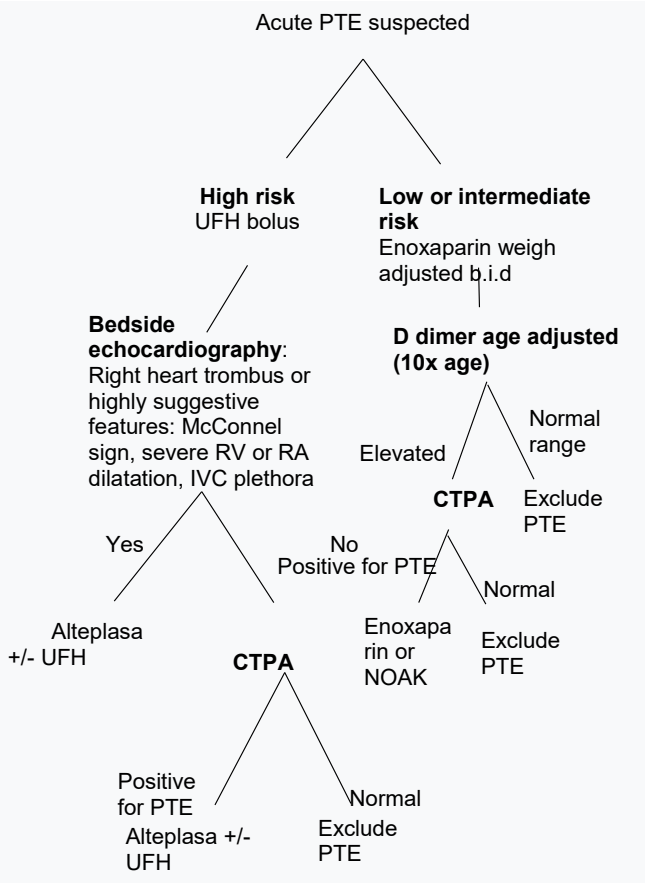

Figure 6

due to a lower risk of clinically significant bleeding and heparin-induced thrombocytopenia than when using unfractionated heparin (UFH) if low or intermediate risk PTE is suspected[5,23,24]. Our patient received a bolus of UFH with the ongoing continuous infusion until echocardiography was obtained, which is in accordance with the ESC guidelines for the treatment of patients with suspected high-risk PTE.[5] The recommended dosage of UFH is 80 I.U./kg immediately with continuous infusion of 18 I.U./kg/h and further dosing according to the activated partial thromboplastin time (aPTT)[27].

According to current ESC guidelines, systemic fibrinolytic therapy is the first choice in the treatment of patients with acute high-risk PTE in the absence of contraindications, while other treatment modalities (catheter directed therapy and surgical embolectomy) are used only in the presence of absolute contraindications or failure of systemic fibrinolysis and are reserved for centers with experience[5]. *Marty et al*[28] conducted a meta-analysis of 15 randomized trials involving 2,057 enrolled patients with PTE, with the first group receiving only parenteral anticoagulant therapy and the second receiving systemic fibrinolytic therapy. They showed that the application of systemic fibrinolytic therapy reduced overall mortality when all studies are included. There was no significant difference in terms of fibrinolytic used (alteplase; tenectaplase; other fibrinolytics, p = 0.86). When 4 studies involving patients with high-risk PTE were excluded from the analysis, the difference in total mortality among the observed groups was not statistically significant. Major bleeding data were available for 12 studies where the use of systemic fibrinolytic therapy carries a significantly higher risk of major bleeding (OR 2.91, p <0.0001). Alteplase administration carries a lower risk of bleeding than tenectaplase administration. However, after exclusion from the analysis of the study *Constantinides et al*[29], which used a more restrictive definition of major bleeding, the analysis of the remaining studies did not find a statistically significant difference between the applied fibrinolytics. In conclusion, it is stated that the use of systemic fibrinolytic therapy reduces PTE-related mortality, cumulative event death and treatment escalation and symptomatic recurrence of pulmonary thromboembolism at a price of an increased risk of fatal, intracranial and major bleeding. Therefore, it is recommended that reperfusion therapy be used only in high-risk PTE and in other categories only in case of hemodynamic deterioration[5].

Since there were no contraindications for the use of systemic fibrinolytic therapy, it was given to our patient, alteplasa 100 mg according to the protocol with simultaneous infusion of UFH, which was then continued after the end of fibrinolytic infusion. There are ambiguities as to whether UFH should be used during systemic fibrinolytic infusion. Alteplase has been approved by the US Food and Drug Administration (FDA) and the European Agency for the Evaluation of Medicinal Products (EMA) for the treatment of acute massive pulmonary embolism with discontinuation of UFH during fibrinolytic infusion and continued use only when aPTT falls below 2 times upper limit of normal[30,31]. The 2019 ESC guidelines for PTE suggest that UFH may be given concomitantly with fibrinolytic infusion in the case of rTPA but must be stopped with streptokinase and urokinase infusion, citing earlier european guidelines from 2014[32]. The 2008 American College of Chest Physicians (ACCP) guidelines state that it is acceptable to either continue or discontinue UFH infusion during the administration of fibrinolytic therapy since the two treatment approaches have never been directly compared[33]. The recommendations of the same society from 2016 do not discuss the simultaneous use of fibrinolytic and anticoagulant therapy[34]. Of the 4 randomized clinical trials in which alteplase was administered in a continuous infusion at a dose of 90-100mg, 3 concomitantly infused UFH at a dose of 1000-1500 I.U./h during fibrinolytic infusion and in one heparin was paused during fibrinolytic infusion[35]. This paper is also an attempt to develop a local treatment protocol for patients with PTE (Figure 6). When PTE is suspected, patients are stratified into those with suspected high-risk and the group with suspected non-high risk PTE. Patients with suspected high-risk PTE are placed in the Coronary Care Unit and receive a bolus of UFH 5000-10000 I.U. depending on body weight with continued infusion of 1000 I.U./h. Blood is sampled for aPTT before heparin is given. Then, bedside transthoracic echocardiography is performed and if it verifies the direct signs of PTE, fibrinolytic therapy with rTPA is given if there are no contraindications. The decision to give UFH during the fibrinolytic infusion is left to the attending physician. In the further course, the dose of UFH is optimized according to the values of aPTT so that it is in the range of 50-70s and oral anticoagulant therapy is introduced. If the echocardiographic

examination is non-conclusive, emergency CTPA is performed. If the test is negative for PTE, alternative clinical diagnoses are considered. If PTE is proven, rTPA is given if there are no contraindications.

In patients with established clinical suspicion of non-high risk PTE, enoxaparin s.c. 1mg / kg body weight on 12h interval is given and D dimer tested. If the age adjusted values are elevated the patient is referred for CTPA. If the D dimer is negative, the diagnosis of PTE is ruled out and an alternative disease is considered.

In rare situations, the existence of absolute contraindications for the use of fibrinolytic therapy decision is made depending on the specific clinical circumstances. Patients who are hemodynamically unstable, in addition to the use of anticoagulant therapy and supportive measures, are generally referred to the Clinic for Emergency Internal Medicine of the Military Medical Academy for the use of catheter directed treatment of PTE.

It is recommended that patients with PTE be treated with some of NOACs (Non-vitamin K antagonist oral anticoagulants) to prevent recurrent episodes of venous thromboembolism[5]. Due to the lack of motivation of the patient to take drugs of this group, oral anticoagulant therapy with vitamin K antagonist (warfarin) was introduced with the achievement of therapeutic values of the International Normalized Ratio (INR).

Conclusion

Stratification of patients with suspected / confirmed PTE into groups according to the risk of early mortality determines the clinician to select an appropriate set of diagnostic and therapeutic procedures. In the high-risk PTE it is necessary to conduct reperfusion therapy after a quick diagnosis, most often using a systemic fibrinolytic.

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Sažetak

Dijagnostičko-terapijski pristup pacijentu sa visokorizičnom tromboembolijom pluća - prikaz slučaja i komentar u kontekstu ESC preporuka

Milan Nikolić, Vladimir Mitov, Aleksandar Jolić, Dragana Adamović, Marko Dimitrijević[1]

Odeljenje invazivne kardiologije Odeljenja interne medicine Zdravstvenog centra Zaječar

Tromboembolija pluća (TEP) je često i potencijalno fatalno oboljenje za čiju dijagnostiku i lečenje su 2019 publikovane ESC smernice. U njima se naglašava značaj stratifikacije rizika od rane smrtnosti kod suspektne ili dokazane TEP i lečenje shodno klasi rizika: primena antikoagulantne ili fibrinolitičke terapije. Cilja rada je prikaz bolesnika sa tipičnim elektrokardiografskim i ehokardiografskim nalazima stratifikovanog u grupu visokorizične TEP koji je lečen sistemskom primenom fibrinolitičke terapije. Bolesnik starosti 70 godina primljen je u Jedinicu intenzivne nege Internog odeljenja ZC Zaječar hipotenzivan, dispnoičan, sa znacima hipoperfuzije organa. Elektrokardiografski se verifikuje S1Q3T3 znak uz blok desne grane Hisovog snopa i postavlja sumnja na visokorizičnu TEP. Urađenim ehokardiografskim pregledom uz krevet bolesnika registruje se velika trombna masa koja prolabira iz desne pretkomore u desnu komoru. Ordinira se sistemska fibrinolitička terapija alteplasa-om po 2h protokolu uz nefrakcionirani heparin. Dolazi do hemodinamske stabilizacije bolesnika, gubitka elektrokardiografskih promena sugestivnih za TEP i rezolucije tromba u desnim srčanim šupljinama. Bolesnik se otpušta kući nakon 12 dana hospitalnog lečenja. Rana stratifikacija bolesnika sa TEP po riziku od rane smrtnosti i izrada lokalnog protokola za dijagnostiku i lečenje bolesnika shodno klasi rizika povećava uspešnost u prepoznavanju i lečenju ovog oboljenja i smanjuje rizik od smrti i drugih neželjenih kliničkih događaja kod bolesnika.

Ključne reči: *visokorizična plućna embolija, TEP, sistemska fibrinolitička terapija, rTPA, UFH, hemodinamska nestabilnost, PESI*

9. ZAJEČARSKI SIMPOZIJUM INTERVENTNE KARDIOLOGIJE

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APTUS

Zlatni sponzor

Galenika

Partneri kongresa

Medtronic

AMICUS a Swixx BioPharma company

HERMES PHARMA

Abbott

Sponzori kongresa

VICOR

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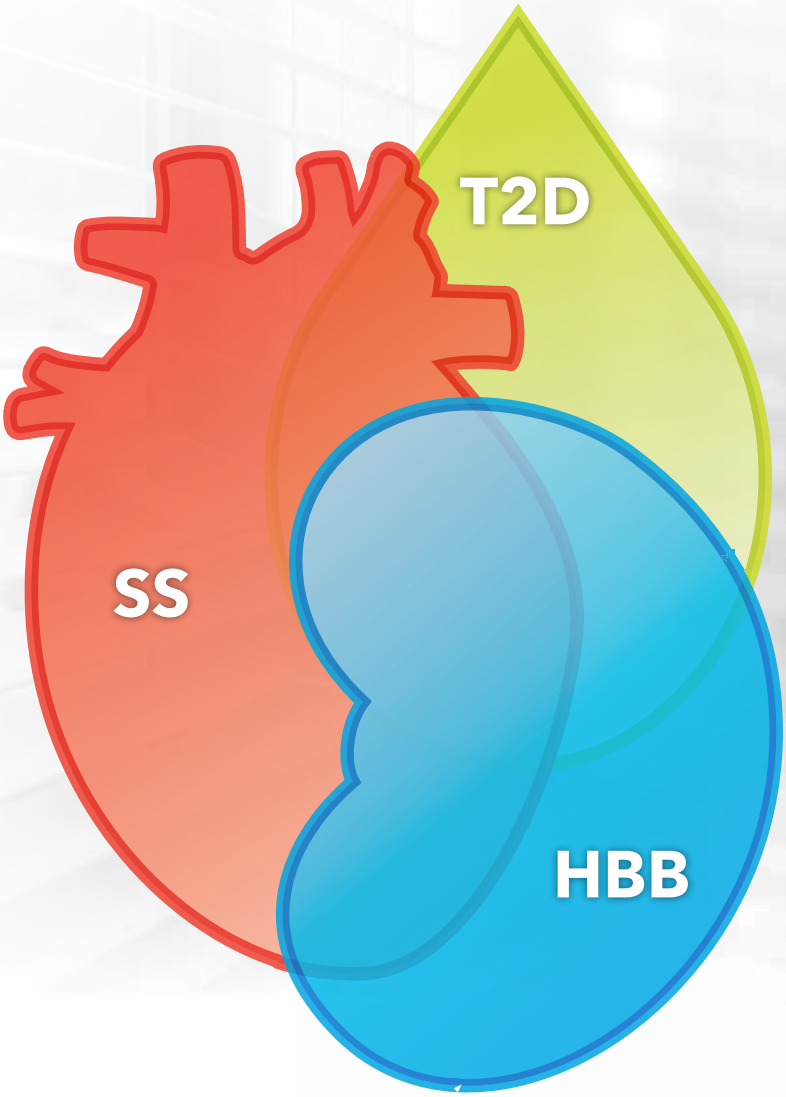
1 LEK / 3 INDIKACIJE

Najpropisivaniji SGLT2i u svetu, u Evropi i Srbiji[1,2]



HBB – hronična bolest bubrega
T2D – tip 2 dijabetes melitusa
SS – srčana slabost
SGLT2i – inhibitor natrijum glukoznog kotransportera 2

Referenca:
1. IQVIA STAR M4-22, YTD M4-22; DOT Volume. Mart 2023.
2. IQVIA podaci Srbija, DOT volume, Jul 2023.
3. Sažetak karakteristika leka Forxiga®, mart 2023.

Broj ALIMS rešenja 515-08-20420-21-006 od 19.04.2022.

Broj dozvole: Forxiga, film tableta, 5 mg, 30 kom. 515-01-01757-19-001
Forxiga, film tableta, 10 mg, 30 kom. 515-01-01758-19-001
Forxiga, film tableta, 10 mg, 28 kom. 515-01-00783-21-001

Datum prve dozvole: 18.08.2014.

AstraZeneca
Predstavništvo AstraZeneca UK Ltd
Milutina Milankovića 1i, Beograd - Novi Beograd
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SAMO ZA STRUČNU JAVNOST • RS-4305, Avgust 2023.

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NOVA SNAGA ZA SRCE

Ukoliko Vam je potrebna medicinska informacija o leku kompanije Boehringer Ingelheim molimo Vas pozovite kontakt telefon 011 / 3115960 ili pošaljite e-mail na adresu medinfo@boehringer-ingelheim.com.
Kompletan sažetak karakteristika leka dostupan na zahtev.
Datum rešenja: 13.05.2020.

Nosilac dozvole: Boehringer Ingelheim Serbia d.o.o. Beograd,
Milentija Popovića 5a, Beograd

Datum pripreme materijala: Mart 2023. | PC-RS-100443

Boehringer Ingelheim

Boehringer Ingelheim Serbia d.o.o. Beograd
Milentija Popovića 5a, 11070 Beograd
info.bel@boehringer-ingelheim.com

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