Časopis Udruženja kardiologa Srbije

SRCE i krvni sudovi

Heart and Blood Vessels

Journal of the Cardiology Society of Serbia

1955 UKS CSS
UDRUŽENJE KARDIOLOGA SRBIJE
CARDIOLOGY SOCIETY OF SERBIA
www.uksrb.org

The echocardiographic features of left ventricular dysfunction in men with chronic obstructive pulmonary disease
Ehokardiografske osobine disfunkcije leve komore kod muškaraca sa hroničnom opstruktivnom bolesti pluća

The effects of cardiovascular rehabilitation in patients with reduced, mildly reduced, and preserved ejection fraction - do they benefit equally?
Efekti kardiovaskularne rehabilitacije kod pacijenata sa smanjenom, blago smanjenom i očuvanom ejekcionom frakcijom – da li je korist ista za sve?

Spontaneous coronary artery dissection as a cause of acute myocardial infarction in young people
Spontana disekcija koronarne arterije, uzročnik akutnog infarkta miokarda kod mladih osoba

Individual approach in the treatment of aortic stenosis with contemporary TAVI valves
Individualni pristup terapiji aortne stenoze pomocu savremenih TAVI proteza

Interventional cardiology in Serbia during COVID-19 pandemic for the period of 2019-2022
Interventna kardiologija u Srbiji za vreme COVID-19 pandemije za period 2019-2022

Volumen 41 Broj 2
2022. godina

Vi ste original.
Vaš život je original.
Vaše srce i mozak zaslužuju original!

Budite verni originalu.

BAYER
ASPIRIN® PROTECT 100 mg
gastrorezistentne tablete

BAYER

Aspirin® protect 100 mg
Nosilac dozvole za stavljanje leka u promet:
BAYER D.O.O. BEOGRAD, Omladinskih brigada 88b, Beograd
Broj poslednje obnove dozvole:
28x100 mg: 515-01-00879-18-002
98x100 mg: 515-01-00885-18-002
Broj odobrenja ALIMS: 515-08-00416-19-001
PP-ASP-RS-0007-1

Pre prve primene leka neophodno je konsultovati lekara.
Pre upotrebe detaljno proučiti uputstvo!
O indikacijama, merama opreza i neželjenim reakcijama na lek, posavetujte se sa lekarom ili farmaceutom.

UDRUŽENJE KARDIOLOGA SRBIJE
CARDIOLOGY SOCIETY OF SERBIA

SRCE I KRVNI SUDOVI
HEART AND BLOOD VESSELS

Časopis izlazi redovno od 2011. godine i predstavlja nastavak časopisa Kardiologija (www.uksrb.rs)

Volumen 41 Broj 2 2022. godina

ADRESA UREDNIŠTVA
EDITORIAL OFFICE
Udruženje kardiologa Srbije
Višegradska 26
11000 Beograd
Email: srceikrvnisudovi.urednistvo@gmail.com
www.uksrb.org

UPUTSTVO AUTORIMA

„Srce i krvni sudovi" je časopis Udruženja kardiologa Srbije koji objavljuje originalne radove, prikaze bolesnika, kardiovaskularne slike ("cardiovascular images"), pregledne i specijalne članke. Uz rukopis obavezno priložiti pismo koje su potpisali svi autori, a koje treba da sadrži:

- izjavu da rad prethodno nije publikovan i da nije istovremeno podnet za objavljivanje u nekom drugom časopisu,
- izjavu da su rukopis pročitali i odobrili svi autori.

Rukopis rada i sve priloge uz rad dostaviti elektronskim putem na adresu: sloba.d.obradovic@gmail.com, naslovljeno na: prof. dr Slobodan Obradović, glavni urednik časopisa „Srce i krvni sudovi". Prispele rukopise uređivački odbor šalje recenzentima radi stručne procene. Ukoliko recenzenti predlože izmene i dopune, tada se recenzirani rukopis dostavlja autorima s molbom da tražene izmene unesu u tekst ili pak u protivnom da argumentovano izraze svoje neslaganje sa datim primedbama recenzenta. Konačnu odluku o prihvatanju rada za štampu donosi glavni i odgovorni urednik zajedno sa uređivačkim odborom.
Za objavljene radove se ne isplaćuje honorar, a autorska prava se prenose na izdavača.
Časopis se štampa na srpskom jeziku, sa kratkim sadržajem prevedenim na engleski jezik. Inostrani autori mogu svoje članke, u celini, poslati na engleskom jeziku.
Molimo saradnike da svoje radove za časopis „Srce i krvni sudovi" pišu jasno, koncizno, racionalno, gramatički ispravno i u skladu sa sledećim uputstvima.

UPUTSTVA ZA PISANJE RADA

Tekst rada kucati u programu za obradu teksta Word, latinicom, fontom Times New Roman i veličinom slova 12 tačaka (12pt). Sve margine podesiti na 25 mm, veličinu strane na format A4, sa levim poravnanjem i uvlačenjem svakog pasusa za 10 mm. Ukoliko se u tekstu koriste specijalni znaci (simboli), koristiti font Symbol. Stranice numerisati redom u okviru donje margine desno, počev od naslovne strane. Podaci o korišćenoj literaturi u tekstu označavaju se arapskim brojevima u običnim zaokruženim zagradama, i to onim redosledom kojim se pojavljuju u tekstu. Rukopis rada dostaviti urađen po sledećem redosledu:

- naslovna strana,
- sažetak na srpskom jeziku,
- sažetak na engleskom jeziku, sa naslovom i institucijom odakle dolazi rad takođe na engleskom jeziku,
- tekst rada,
- tabele,
- opisi slika,
- posebno slike (grafikoni) ili fotografije.

Naslovna strana. Na posebnoj, prvoj stranici treba navesti sledeće:

- naslov rada bez skraćenica
- puna imena i prezimena autora (bez titula)
- kratak naslov rada
- zvaničan naziv i mesto ustanova u kojima autori rade: ukoliko su u radu autori iz različitih institucija, indeksirati autore iz raličitih institucija arapskim brojevima
- na dnu stranice navesti kontakt osobu, odnosno ime i prezime, adresu, broj telefona, faksa i e-mail adresu radi korespodencije

Kratak sadržaj na srpskom i engleskom jeziku. Na sledećoj strani priložiti kratak sažetak rada obima do 250 reči. Za originalne radove kratak sadržaj rada treba da sadrži: uvod, metod, rezultati i zaključak.
Prikazi bolesnika, pregledni i specijalni članci treba da imaju nestrukturisan sažetak obima do 150 reči.
Na kraju sažetka dostaviti i 2-4 ključne reči.
Svaki sažetak, sa naslovom i institucijom, mora biti preveden na engleski jezik.

Tekst rada. Tekst treba da sadrži sledeća poglavlja: uvod, metodi, rezultati, diskusija, zaključak, literatura. Svi podnaslovi se pišu malim slovima i boldovano. U radu koristiti kratke i jasne rečenice. Za nazive lekova koristiti isključivo njihova internacionalna nezaštićena imena. U radu se mogu koristiti određene skraćenice, ali samo kada je to neophodno. Za svaku skraćenicu koja se prvi put javlja u tekstu treba navesti i pun naziv. Sve rezultate navoditi u metričkom sistemu prema Međunarodnom sistemu jedinica (SI).
Originali rad ne treba da prelaze 4000 reči.
Prikaz bolesnika čine: uvod, prikaz bolesnika, diskusija, literatura. Prikaz bolesnika ne treba da prelazi 1500 reči.
Kardiovaskularne slike (cardiovascular images) ne treba da budu struktuirane i ne treba da prelaze 500 reči.
Pregledni i specijalni članci ne moraju da budu struktuirani po prethodnom modelu. Pregledni i specijalni članci ne treba da prelazi 5000 reči.

Literatura. Reference numerisati rednim arapskim brojevima prema redosledu navođenja u tekstu. Broj referenci ne bi trebalo da bude veći od 30, a broj citiranih originalnih radova mora da bude najmanje 80%. Izbegavati korišćenje apstrakta kao reference. Reference članaka koji su prihvaćeni za štampu označiti kao ,,u štampi" (in press) i priložiti dokaz o prihvatanju rada. Reference se citiraju prema Vankuverskim pravilima, koja su zasnovana na formatima koja koriste National Library of Medicine i Index Medicus. Naslove časopisa takođe treba skraćivati prema načinu koji koristi Index Medicus (ne stavljati tačke posle skraćenice).
Ukoliko rad koji se navodi ima više od 6 autora, onda navoditi tako što se posle trećeg autora staviti: et al. Stranice se citiraju tako što se navode početna i krajnja stranica (npr. 134-138).
Primer za navođenje reference iz časopisa: Leal J, Ramon Luengo-Fermnandes R, Gray A, Petersen S, Rayner M. Economic burden of cardiovascular diseases in the enlarged European Union. Eur Heart J 2006;27:1610-1619.
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.

Tabele se označavaju arapskim brojevima po redosledu navođenja u tekstu. Tabele raditi u programu Word, koristiti font Times New Roman, veličinu slova 12 pt, sa jednostrukim proredom i bez uvlačenja. Tabela mora da ima naslov i ukoliko se u tabeli koriste skraćenice, iste treba objasniti u legendi ispod tabele. Svaku tabelu dati na posebnom listu papira.

Slike (grafikoni) se označavaju arapskim brojevima po redosledu navođenja u tekstu. Na posebnom listu dati naslov sa opisom slika (grafikona) i ukoliko se koriste skraćenice, iste treba objasniti u nastavku. Svaki grafikon treba dati na posebnom listu papira. Slike (grafikone) dati u formatu ppt, ai ili eps.
Fotografije se označavaju arapskim brojevima po redosledu navođenja u tekstu. Primaju se isključivo originalne fotografije (crno-bele ili u boji) na sjajnom, glatkom (a ne mat) papiru. Na poleđini svake fotografije treba napisati redni broj. Fotografije moraju da budu u tif, eps ili ai formatu, najmanje rezolucije 300dpi.

Napomena. Rad koji ne ispunjava sve gore navedene tehničke uslove neće biti poslat na recenziju i biće vraćen autorima da ga dopune i isprave.
Glavni urednik i uređivački odbor zadržavaju pravo da radove, za koje smatraju da ne zadovoljavaju osnovne kvalitete i interesovanja publikovanja u časopisu, ne pošalju recenzentima i vrate autorima.

INSTRUCTIONS FOR AUTHORS

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:
Prof. Slobodan Obradovic, MD, PhD
Editor-in-Chief, Heart and Blood Vessels
and mailed to sloba.d.obradovic@gmail.com

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.
We kindly request authors to keep their manuscripts for Heart and Blood Vessels clear, concise, rational, grammatically correct and in accord with the following instructions.

GENERAL INSTRUCTIONS

Manuscript text should be prepared using a Word processing package, in Times New Roman font size 12. All margins set at 25mm of an A4 page, with no alignment and 10mm tab at the beginning of each paragraph. In case special signs are used, please use Symbol font. Keep page numbering in the footer, starting from the Title page. References should be marked by order of appearance in the text in Arabic numerals in round brackets. The manuscript should be submitted in the following order:

- Title Page,
- Abstract,
- Body of the text,
- Tables, Figures' descriptions,
- Figures or photographs.

Title page. A separate, first page should encompass the following:

- the title
- the name(s) of authors,
- the institution(s) and location of all authors (Please, index in Arabic numerals the different Institutions by order of appearance),
- short title,
- at the bottom of the page cite the corresponding author with his contact address, phone, fax number and email address.

Abstract. Next page should contain a 250 words abstract. Original papers should encompass: Introduction, Methods, Results and Conclusion. Structured form of abstracts is not mandatory for case reports, review and special articles, but should not exceed 150 words.

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.
Review and Special Articles don't have to be structured and shouldn't exceed 5000 words.

References. References should be marked in order of appearance in Arabic numerals. The number of quoted references shouldn't exceed 50 out of which 80% should be original articles. It is advised to avoid abstracts as references. When quoting papers that are accepted for publishing, however, not yet published, mark them as in press and enclose a printed proof of the manuscripts' acceptance. References are quoted according to Vancouver style based on the formats used by National Library of Medicine and Index Medicus. Journals' titles should be shortened in accord with Index Medicus (no full stops after the abbreviation). If the paper quoted has over 6 authors, after the third one, et al. should be used Pages are quoted as first and last (i.e. 134-136).
Article citation example: Leal J, Ramon Luengo-Fermnandes R, Gray A, Petersen S, Rayner M. Economic burden of cardiovascular diseases in the enlarged European Union. Eur Heart J 2006;27:1610-1619.
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.

Tables are marked in order of appearance in Arabic numerals. Tables should be prepared using a Word processing package, Times New Roman font size 12, single spaced with no indent. Each Table should have a title. If abbreviations are used in the Table, they should be defined in the explanatory footnote below. Each table should be presented on a separate page.
Figures are marked in order of appearance in Arabic numerals. Please, provide on seprate page Figure legends. Each Figure should be prepared on a separate page using following format: ppt, ai or eps.
Photographs are marked in order of appearance in Arabic numerals. Only original photographs are accepted (black and white or color) on glossy paper. The back of each photograph should have the number and an arrow marking the top. The photograps should be prepared in following format: tip, eps, or ai, with minimal resolution of 300dpi.

Note. A paper not fully compliant with all aforementioned rules and regulations, will not be forwarded to reviewers, but returned to authors for correction. The Editor-in-Chief and the Editorial Board can reject any manuscript they deem not in the scope of the journal or not acceptable in terms of baseline quality of publishing material, even prior seeking reviewers' opinion.

CIP - Katalogizacija u publikaciji
Narodna biblioteka Srbije, Beograd

Srce i krvni sudovi: Časopis Udruženja kardiologa Srbije
Heart and blood vessels: Journal of Cardiology society of Serbia
Editor in-chief Slobodan Obradović, Godina 11,
Volumen 41, Broj 2
Beograd, Višegradska 26: Udruženje kardiologa Srbije
2022-Beograd: Newassist doo
Tromesečno-Broj 1 izašao 2011. god.

ISSN 182-4835=Srce i krvni sudovi
COBISS.SR-ID 174253580

UDRUŽENJE KARDIOLOGA SRBIJE
CARDIOLOGY SOCIETY OF SERBIA

SRCE I KRVNI SUDOVI
HEART AND BLOOD VESSELS

Volumen 41 Broj 2 2022. godina

Sadržaj / *Content*

Srce i krvni sudovi 2022; 41(2): 33-38

Review article

The echocardiographic features of left ventricular dysfunction in men with chronic obstructive pulmonary disease

Aleksandra Milovančev[1,2], Marija Vukoja[1,3], Violeta Kolarov[1,3], Aleksandra Ilić[1,2], Anastazija Stojšić Milosavljević[1,2], Snežana Tadić[1,2], Maja Stefanović[1,2], Tatjana Miljković[1,2], Milovan Petrović[1,2]

[1]Faculty of Medicine, University of Novi Sad, Novi Sad, Serbia, [2]The Institute of cardiovascular diseases of Vojvodina, Sremska Kamenica, Serbia, [3]The Institute of pulmonary diseases of Vojvodina, Sremska Kamenica, Serbia

Abstract

Introduction: Left ventricular dysfunction (LVD) in chronic obstructive pulmonary disease (COPD) increases the risk of mortality. The coexistence of LVD and COPD has substantial number of diagnostic difficulties. It is still not clear how prevalent is it and what causes LVD in COPD patients without cardiovascular diseases. The aim of our study was to assess the prevalence of LVD and its association with the severity of the COPD.

Methods: The prospective cohort study included 120 patients with previously diagnosed stable COPD. In all patients spirometry and transthoracic echocardiography were performed. Patients were divided into four stages of COPD, according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria.

Results: The prevalence of LVDD across the cohort was 65.8%. The first degree of DD was found in 42.5% of COPD patients, second degree in 20.8% and third degree DD in 2.5% of patinets. LVDD was present in all COPD stages, but was not associated with the severity of the COPD disease (p = 0.8). The parameters of systolic function are decreasing with COPD stage, with significant differences between groups (SVI (p=0.01), EF p<0.001). Decreased EF≤49% was found in the 16.6% of cochort, in the first COPD stage 13.3% vs. 10% in GOLD II vs. 20% in GOLD III and 23.3% of patients in GOLD IV.

Conclusion: Undiagnosed LVD in COPD patients without previously diagnosed CVD was highly prevalent. These results highlight the need for regular echocardiography screening to reduce morbidity and mortality in these patients.

Kew words chronic obstructive pulmonary disease, left ventricular dysfunctions, echocardiography

Introduction

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of mortality globaly[1]. COPD and cardiovascular (CV) disorders are very common combination, as they share the same risk factors. Small airway obstruction plays the most important patophysiological role in COPD and represents an important risk factor for cardiac impairment[2]. Patients with mild airflow limitation have more chance to die from CV event than respiratory failure[3]. The forced expiratory volume in the first second (FEV1) is a well established predictor of cardiovascular morbidity and mortality[4]. Hypoxia and systemic inflammation go along with COPD and may lead to ventricular dysfunction[5]. The coexistence of COPD and heart failure (HF) has a number of diagnostic and therapeutic pitfalls and increases the mortality risk[6,7].

The association between left ventricular dysfunction (LVD) and COPD has not been well studied. Conflicting results suggest a prevalence of LVD between 9-52% in COPD patients[8]. The presence of even subclinical diastolic LV dysfunction raises the risk of all cause mortality in COPD[9]. Importantly, when assessing the LV function large amount of studies did not exclude patients with cardiovascular comorbidities such as ischemic heart disease or hypertension that influence the left ventricular function regardless of COPD. The aim of our study was to asses the prevalence of left ventricular dysfunction in stable COPD patients without formerly diagnosed cardiovascular disorders that may influence ventricular function. We also aimed to investigate weather left ventricular dysfunction is associated with COPD severity.

Methods

We performed a prospective cohort study that was conducted at the Institut of pulmonary diseases diseases of Vojvodina, Sremska Kamenica, Serbia. We included 120 male patients who were previously diagnosed with

Corresponding author: Aleksandra Milovančev, Institute of cardiovascular diseases of Vojvodina, Sremska Kamenica, Serbia, +381642746046
Email: aleksandra.milovancev@mf.uns.ac.rs

COPD, according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria. Patients were divided into four stages of COPD considering the FEV1 and arterial blood gas values. We excluded patients with any serious illness previously diagnosed or treated: pulmonary diseases (interstitial, tromboembolic, bronchial carcinoma), pulmonary artery hypertension, CV disorders (coronary artery disease, significant valvular stenosis or regurgitation, prior cardiac surgery, history of heart failure, arterial hypertension, atrial flutter and fibrillation, signs of left ventricular hypertrophy or left brunch bundle block in electrocardiogram).

All patients underwent clinical history assessment, anthropometric measurements (body weight, body height), blood pressure measurement, pulmonary function testing, electrocardiography, and transthoracic echocardiography. The study was approved by the Institutional Ethics committees, according to the Declaration of Helsinki, and informed consent was obtained from all participants. Assasment of the pulmonary function testing included spirometry, total body plethysmography and arterial blood gas analysis. Spirometry was performed according to 2005 ATS/ERS criteria[10]. A postbronchodilator values for forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), and the FEV1/FVC ratio were used according to GOLD recomendations.

Standard two-dimensional echocardiography were performed using echocardiographic instrument GE Vivid, using a probe of 2.5 MHz included a long parasternal, short parasternal apical and subcostal echocardiographic view. Results were analyzed by an echo-cardiologist blinded to all clinical data. We used a two-dimensional (2D), M-mode, Continuous Doppler (CW), Pulsed Doppler (PW), color and tissue Doppler according to the American Society of Echocardiography guidelines[11]. Patients were placed in the position of left lateral decubitus and detailed evaluation of the cardiac chambers were done. The following measurements were made in 2D echocardiography from a parasternal long-axis view: interventricular septum in diastole thickness (IVS), left ventricular end-diastolic diameter (LVEDD), left ventricule end-sistolic diametar (LVESD), posterior wall in diastole thickness (PWT), right ventricular diameter (RVD) and left atrium (LA) diametar in end sistoly.

From apical four, two, and three-chamber views we calculated left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), and left atrial maximal volume (LAVS) using the biplane summation of disks method. The left ventricular ejection fraction (EF) was calculated using the modified Simpson's method. Cardiac dimensions were indexed for BSA. Pulsed wave Doppler parameters were obtained from the apical 4-chamber view at the tip of the mitral leaflets. The peak early diastolic (E) and late diastolic (A) mitral flow velocities and E/A ratio was calculated. Pulsed tissue Doppler of the septal and lateral mitral annulus were acquired from the apical four-chamber view. Peak early diastolic mitral annular velocities (e') were measured both at the septal and lateral annulus. The ratio for E/e' was calculated, both for the septal and the lateral wall, and with e' averaged from the septal and lateral wall. A comprehensive approach was used to diagnose and grade the left ventricular diastolic dysfunction (LVDD) according to the recommendations of the ASE 2016[12]. The pulmonary artery systolic pressure (PASP) was assessed using Bernoulli equation from the jet of the tricuspid regurgitation (TR), while right atrial pressure was obtained from imaging of the inferior vena cava in the subcostal view.

Statistical analysis

Data were collected through a standardized questionnaire and verified by the author, coded and entered into a specialy designed database.

We calculated frequencies, percentages, mean, standard deviation. For variables with normal distribution comparison between the COPD group was performed using analysis of variance, followed by, if necessary, Tukey's multiple comparison test. For variables with normal distribution comparison was performed using the Kruskal Valis test, followed by multiple comparison medium rang test. Rate of correlation was calculated by Spearman's correlation. The statistical software Statistica (Statistica 13.5, The Ultimate Academic Bundle, StatSoft Europe GmbH, Hamburg, Germany; university license for the University of Novi Sad) was used for all analyses.

Results

The study included 120 men, mean age 59.78 ± 7.46 years old. Patients were classified according to GOLD classification to GOLD I, II, III and IV stage. The details of characteristics among different stages are shown in Table 1. Age did not differ statistically between the groups. The BSA decreased in severe COPD, with a significant difference between stage I and IV (p=0.02).

The details of echocardiographic parametars in all groups are presented in Table 2. There is a trend of diasto-

Table 1. Anthropometric and clinical characteristics between groups

Variables	COPD I (*n* = 30)	COPD II (*n* = 30)	COPD III (*n* = 30)	COPD IV (*n* = 30)	*p*-Value
Age . years Mean ± SD	56.90 ± 8.9	57.90 ± 7.4	62.53 ± 6.9	61.76 ± 4.6	0.09
BSA	1.98 ± 0.28	1.94 ± 0.20	1.85 ± 0.17	1.82 ± 0.16	**0.002**
BMI	25.70 ± 4.3	26.33 ± 6.6	23.56 ± 4.2	23.4 ± 4.9	0.09
SBP	123.17±7.25	120.50±10.53	121.17±9.97	121.33±9.00	0.53
DBP	76.33±5.56	76.33±8.80	75.67±6.66	75.83±6.44	0.93
FEV1	93.87± 10.1	62.8 ± 7.7	33.32 ± 7.3	28.13 ± 5.9	**<0.001**

BSA - body surface area, BMI - body mass index, SBP - systolic blood pressure, DBP - diastolic blood pressure, FEV1 - forced expiratory volumen in 1 second

Table 2. Echocardiographic characteristics of patients across the COPD groups

Variables	COPD I (*n* = 30)	COPD II (*n* = 30)	COPDIII (*n* = 30)	COPD IV (*n* = 30)	*p*-Value
LAVSI (ml)	32.87 ± 5.51	33.93 ± 4.98	33.47 ± 5.06	34.69 ± 5.38	0.66
E (m/sec)	0.79 ± 0.21	0.65 ± 0.19	0.58 ±0.15	0.60 ± 0.16	0.00
A (m/sec)	0.80 ±0.18	0.81 ± 0.19	0.83 ± 0.26	0.90 ± 0.25	0.72
E/A	1.07 ± 0.27	0.75 ± 0.13	0.69 ± 0.11	0.71 ± 0.09	0.00
E'(m/sec) average	0.10 ± 0.03	0.08 ± 0.03	0.09 ±0.03	0.09 ± 0.02	0.14
A'(m/sec) average	0.12 ±0.06	0.12 ± 0.04	0.13 ± 0.13	0.12 ± 0.05	**0.94**
E'/A' average	0.99 ± 0.55	0.71 ± 0.19	0.88 ± 0.33	0.78 ± 0.27	**0.02**
E/E' ratio	7.09±2.71	7.56±2.66	7.95±3.51	8.19±3.28	**0.05**
LVESd (mm)	31 ± 6.19	31.07 ± 4.68	32.33 ± 4.96	35.83 ± 8.47	**0.02**
LVEDd (mm)	43.60 ± 6.16	47.57 ± 4.74	47.10 ± 4.25	49.47 ± 7.86	**0.01**
IVSd (mm)	10.77 ± 1.36	10.12 ± 1.08	10.27 ± 1.06	10.5 ± 1.31	0.15
PWd (mm)	10.98 ± 1.29	10.48 ± 1.53	10.32 ± 0.97	10.43 ± 1.25	0.09
EDVI (ml/m2)	56.50 ± 15.62	52.35 ± 12.99	55.34 ± 11.31	58.53 ± 15.60	0.39
ESVI (ml/m2)	23.91 ± 8.93	23.74 ± 6.83	24.13 ± 5.65	31.57 ± 13.38	**0.03**
SVI(ml/m2)	32.58 ± 7.98	28.62 ± 7.00	31.21 ± 7.51	26.96 ± 6.88	**0.01**
EF %	60.03 ± 5.42	55.40 ± 5.35	56.50 ± 5.82	50.03 ± 9.25	**<0.001**
RV (mm)	27.30 ± 3.01	26.57±3.43	29.06±3.72	30.07±4.21	**<0.001**
RVSP	23.31 ± 7.08	26.24 ± 6.72	29.64 ± 10.31	39.20 ± 15.93	**<0.01**
TAPSE	2.03 ±0.32	2.07±0.31	1.79±0.36	1.7±0.34	**<0.001**

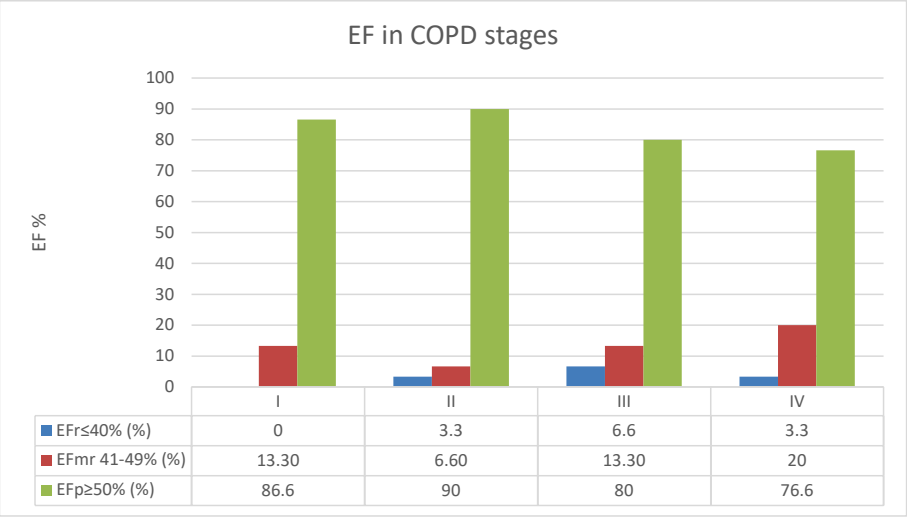
COPD - chronic obstructive pulmonary disease, LAVSI - left atrial volume systolic index, LVEDd - left ventricular end-diastolic diameter, LVESd - left ventricule end-sistolic diametar, IVSd - interventricular septum in diastole thickness, PWd - posterior wall in diastole thickness, EDVi - left ventricular end-diastolic volume index, ESVI - left ventricular end-systolic volume index, SVI - stroke volume index, EF - ejection fraction, RV - right ventricle

lic dysfunction imparment with COPD stage. There were stasticaly significant differences between group in the E vawe (p <0.001), E/A ratio p<0.001, E'/A' ratio p=0.02 and E/E' ratio p=0.05.

There are statistically significant differences between groups in left ventricular systolic (LVESd p=0.02) and diastolic diameters (LVEDd p=0.01) with trend of chamber dilatation increasing with COPD stage. The parameters of systolic function are decreasing with COPD stage, with significant differences between groups (SVI (p=0.01), EF p<0.001). Decreased EF≤49% was found in the 16.6% of cochort, in the first COPD stage 13.3% vs. 10% in GOLD II vs. 20% in GOLD III and 23.3% of patients in GOLD IV.

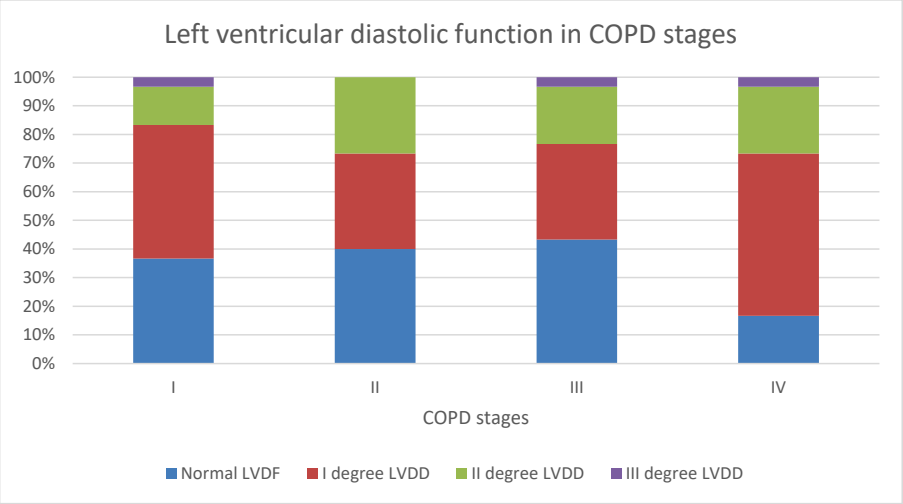
Grading of LVDD across COPD stages is presented in figure 2. The prevalence of LVDD across the cohort was 65.8%. The first degree of DD was found in 42.5% of COPD patients, second degree in 20.8% and third degree DD in 2.5% of patinets. LVDD was present in all COPD stages, but was not associated with the severity of the COPD disease (p = 0.8).

Figure 1. Ejection fraction across the spectum of COPD stages



EF - ejection fraction, COPD - chronic obstructive pulmonary disease

Figure 2. Left ventricular diastolic function across COPD stages



COPD - chronic obstructive pulmonary disease, LVDF - left ventricular diastolic function, LVDD - left ventricular diastolic disfunction

Discussion

Our study showed a high prevalence of unknown ventricular dysfunction in patients with COPD in patient without history of cardiovascular diseases.

LVD in COPD has been described in earlier studies but the prevalence varies widely[9,13-18]. This wide variation is in part due to the dissimilar studied populations' characteristics, and in part due to the different echocardiographic methods used for the assessment of LV diastolic dysfunction[19]. Our study showed that early COPD stages are more prone to have left ventricular diastolic dysfunction, while severe COPD is associated with both left ventricular systolic and diastolic dysfunction. We found no correlation between the severity of COPD and LVDD. Similiar to our results the study from Freixa et al. showed that echocardiographic abnormalities in COPD patients were unrelated to COPD severity[16]. In the same way, there was no relation of pulmonary function parameters to pulmonary artery pressure and diastolic function parameters in study from Ozer et al[15].

The pathophysiology and relationship between LVD and COPD is complex and involves a lot of factors including hypoxia, neurohumoral activation, endothelial dysfunction, inflammation/oxidative stress, ventricular interdependence, hyperinflation/emphysema and coronary artery disease (CAD)[20].

Alveolar hypoxia and consequent hypoxemia causes endothelial dysfunction, arterial stiffness, blood pressure raise[21,22] and triggers LV relaxation impairment. Experimental research in healthy subjects submitted to long periods of altitude induced hypoxia has shown a marked decrease in LV preload, owing to a reduction in their plasma volume[23].

Left and right ventricle are anatomically and physiologicaly bonded, they share pericardium and ventricular septum. Changes in right ventricular (RV) functions may influence left ventricular functions. Ventricular interdependence is a significant phenomenon in patients with COPD[20]. RV structural changes and remodeling with RV subclinical dysfunction is seen even in mild COPD. Pulmonary vascular changes and intermittent increases in pulmonary artery pressure (PAPs) that occur during exercise and/or sleep in early stages of COPD cause RV wall stress, thickening and hypertrophy[24]. RV concentric hypertrophy decreases RV enddiastolic volume and alters right ventricular and left ventricular diastolic function. Dilating RV hypertrophy is usually seen in severe stages of COPD, that has also been seen in our study.

High prevalence of LVDD is described in pulmonary emphysema which is usually seen in severe COPD. Watz et al. found that abnormal LV filling is a consequence of chest hyperinflation in patients with COPD and showed that LVDD is not related to LV myocardial malfunction but rather to a reduced preload[25]. Lung volume reduction surgery showed improvement in the LVD function in patients with emphysema, supporting that the changes in the LVD function are not due to myocardial malfunction[26]. In study from Barr et al severe airflow obstruction were linearly related to impaired left ventricular filling, reduced stroke volume, and lower cardiac output without changes in the ejection fraction. Impared diastolic function is surrogate for decreased left ventricular preload. Reduced preload affect stroke volume and ejection fraction. There are multiple mechanisms affecting left ventricular systolic function in COPD patients[17].

Sistolic left ventricular dysfunction was only present in severe stages of COPD in our study. The LVSD prevalence differs significantly in patients with stable COPD. From 0%–16% in COPD patients without previously diagnosed cardiovascular diseases[7] and from 8-26.7% in all COPD population[9,16,27-28]. LVSD is associated with the severity of COPD i.e., more severe COPD is more likely to have LV systolic dysfunction[27,29], which is consistent with our results. Some investigators postulated that CAD which is not proved with conventional methods may be the cause for LVSD in COPD[30].

COPD is a progressive disease, and with slow chronic airflow limitation both left ventricle (LV) and right ventricle (RV) and their systolic and diastolic function[31] are afected. Signs and symptoms of LV failure can be difficult to differentiate from those of COPD. This is partly due to similar clinical manifestations but mainly due to lack appropriate diagnostic tests to diagnose HF and/or COPD[32].

HF in COPD is an independent predictor of hospitalizations and death. Subclinical diastolic dysfunction can be an early predictor of left ventricular dysfunction and heart failure[9]. Both LVDD and LVSD have increased mortality. So even mild stages can be predictor of poor prognosis[9,28]. The results of our study demonstarted that significant portion of COPD patients with no prior history of cardiovascular diseases have LVDD, even among mild COPD stages, suggesting that LVDD is vastly underdiagnosed in COPD which can have a detrimental effect on long term outcomes of these patients. Still, it is not clear which COPD patients are at risk for LVDD. In the same line, about 16.6% of COPD patients had EF<50%, and no previous history of CVD, however high symptom burden could likely obscured the diagnosis.

Our study has several limitations. First, we included a relatively small number of patients which may preclude some statistical analysis. Second, we compared echocardiographic features with spirometric classification of COPD, as the study was designed before the updated simptom/risk GOLD classification of COPD. Finally, patients treated in University hospitals may not represent the general population.

Conclusion

High prevalence of unrecognized ventricular dysfunction in COPD patients with no history of CVD highlights the need for echocardiography in these patients. We may postulate that in mild COPD stages intermitent hypoxia and sistemic inflamation play a major role in LVDD. Ventricular dysfunction may begin to develop from the begining in the progress of pulmonary disease and might stay sub-clinical for a long time.

Literature

1. Pauwels RA, Rabe KF. Burden and clinical features of chronic obstructive pulmonary disease (COPD). Lancet 2004; 364:613–20. DOI:10.1016/S0140-6736(04)16855-4
2. Sin DD. Man P. Why Are Patients With Chronic Obstructive Pulmonary Disease at Increased Risk of Cardiovascular Diseases? Circulation. 2003;107:1514–9. DOI: 10.1161/01.CIR.0000056767.69054.B3
3. Calverley PM, Anderson JA, Celli B, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med. 2007;356:775–89.DOI: 10.1056/NEJMoa 063070
4. Hole DJ, Watt GC, Davey-Smith G, Hart CL, Gillis CR, Hawthorne VM. Impaired lung function and mortality risk in men and women: findings from the Renfrew and Paisley prospective population study. BMJ. 1996 Sep 21; 313(7059):711-5; discussion 715–6.
5. Akane K, Masayuki H. Pathogenesis of COPD (Persistence of Airway Inflammation): Why Does Airway Inflammation Persist After Cessation of Smoking? Chronic Obstructive Pulmonary Disease. 2017. p. 57–72. DOI: 10.1007/978-981-10-0839-9_4
6. Rutten FH, Cramer MJ, Grobbee DE, et al. Unrecognized heart failure in elderly patients with stable chronic obstructive pulmonary disease. Eur Heart J 2005; 26: 1887–94. DOI: 10.1093/eurheartj/ehi291
7. Rutten FH, Cramer MJ, Lammers JW, Grobbee DE, Hoes AW. Heart failure and chronic obstructive pulmonary disease: an ignored combination? Eur J Heart Fail. 2006;8(7):706–11. DOI: 10.1016/j.ejheart.2006.01.010
8. Hawkins NM, Petrie MC, Jhund PS, et al. Heart failure and chronic obstructive pulmonary disease: diagnostic pitfalls and epidemiology. Eur J Heart Fail. 2009;11:130–9. DOI: 10.1093/eurjhf/hfn01
9. Flu WJ, Gestel Y, Kuijk JP, Hoeks SE, Sin DD, et al. Co-existence of COPD and left ventricular dysfunction in vascular surgery patients. Respiratory Medicine 2010;104:690–6. DOI:10.1016/j.rmed.2009.11.013
10. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J. 2005;26(2): 319-38. DOI:10.1183/09031936.05.00034805
11. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015;28:1–39.e14. DOI:10.1016/j.echo.2014.10.003
12. Nagueh SF, Smiseth OA, Appleton CP et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2016;29:277-314. DOI:10.1016/j.echo.2016.01.011
13. Yilmaz R, Gencer M, Ceylan E, Demirbag R. Impact of chronic obstructive pulmonary disease with pulmonary hypertension on both left ventricular systolic and diastolic performance. J Am SocEchocardiogr. 2005;18:873–81. DOI:10.1016/j.echo.2005.01.016
14. Boussuges A, Pinet C, Molenat F, Burnet H, Ambrosi P, Badier M, et al. Left atrial and ventricular filling in chronic obstructive pulmonary disease. An echocardiographic and Doppler study. Am J Respir Crit Care Med. 2000;162:670–5. DOI:10.1164/ajrccm.162.2.9908056
15. Ozer N, Tokgozulu L, Coplu L, Kes S. Echocardiographic evaluation of left and right ventricular diastolic function in patients with chronic obstructive pulmonary disease. J Am Soc Echocardiogr. 2001;14:557–61. DOI: 10.1067/mje.2001.111474
16. Freixa X, Portillo K, Paré C, Garcia-Aymerich J, Gomez FP, Benet M, et al. Echocardiographic abnormalities in patients with COPD at their first hospital admission. Eur Respir J. 2013;41:784–91. DOI: 10.1183/09031936.00222511
17. Barr RG, Bluemke DA, Ahmed FS, Carr JJ, Enright PL, Hoffman EA, et al. Percent emphysema, airflow obstruction, and impaired left ventricular filling. N Engl J Med. 2010;362:217–27. DOI:10.1056/NEJMoa0808836
18. Suchon´ E, Tracz W, Podolec P, Pieculewicz M, Płazak W, Prokop A, et al. Evaluation of left ventricular function in patients with chronic obstructive pulmonary disease. Pol Arch Med Wewn. 2007;117:26–30. DOI: 10.1016/j.ejcdt.2013.08.004
19. Heba Farouk H, Albasmi M, Chilali EK, et all. Left ventricular diastolic dysfunction in patients with chronic obstructive pulmonary disease: Impact of methods of assessment. Echocardiography 2017;34: 359–64. DOI: 10.1111/echo.13469
20. Portillo K, Abad-Capa J, Ruiz-Manzano J. Chronic obstructive pulmonary disease and left ventricle. Arch Bronconeumol. 2015 May;51(5):227-34. DOI:10.1016/j.arbres.2014.03.012
21. Peinado VI, Barbera JA, Ramirez J, Gomez FP, Roca J, Jover L, et al. Endothelial dysfunction in pulmonary arteries of patients with mild COPD. Am J Physiol. 1998;274.6.Pt 1:L908–13.
22. Mills NL, Miller JJ, Anand A, Robinson SD, Frazer GA, Anderson D, et al. Increased arterial stiffness in patients with chronic obstructive pulmonary disease: a mechanism for increased cardiovascular risk. Thorax. 2008;63:306–11.DOI:10.1136/thx.2007.083493.
23. Boussuges A, Molenat F, Burnet H, Cauchy E, Gardette B, Sainty J M, Jammes Y, Richalet JP. Operation Everest III (COMEX'97): modifications of cardiac function secondary to altitude induced hypoxia. An echocardiographic and Doppler study. Am. J. Respir. Crit. Care Med. 2000;161(1):264-70. DOI: 10.1164/ajrccm.161.1.9902096
24. Vonk-Noordegraaf A, Marcus JT, Holverda S, Roseboom B, Postmus PE. Earlychan ges of cardiac structure and function in COPD patients with mild hypoxemia. Chest. 2005;127:1898–903. DOI:10.1378/chest.127.6.1898.
25. Watz H, Waschki B, Meyer T, et al. Decreasing cardiac chamber sizes and associated heart dysfunction in COPD: role of hyperinflation. Chest. 2010;138:32–8. DOI: 10.1378/chest.09-2810
26. Jorgensen K, Houltz E, Westfelt U, Nilsson F, Schersten H, Ricksten SE. Effects of lung volume reduction surgery on left ventri-

cular diastolic filling and dimensions in patients with severe emphysema. Chest. 2003;124:1863–70. DOI: 10.1378/chest.124.5.1863
27. Gupta NK, Agrawal RK, Srivastav AB, Ved ML. Echocardiographic evaluation of heart in chronic obstructive pulmonary disease patient and its co-relation with the severity of disease. Lung India. 2011;28:105–9. DOI: 10.4103/0970-2113.80321
28. Macchia A, Moncalvo RJJ, Kleinert M, Comignani PD, Gimeno G, Arakaki D, et al. Unrecognized ventricular dysfunction in COPD. Eur Respir J. 2012;39:51–8. DOI:10.1183/09031936.00044411
29. Render ML, Weinstein AS, Blaustein AS. Left ventricular dysfunction in deteriorating patients with chronic obstructive pulmonary disease. Chest. 1995 Jan;107(1):162-8.
30. García MJ. Diagnóstico y guía terapéutica de la insuficiencia cardíaca diastólica. Rev Esp Cardiol. 2003;56:396–406. DOI:10.1016/S0300-8932(03)76884-5
31. Paudel B, Dhungel S, Paudel K, Pandru K, Paudel R. When left ventricular failure complicates chronic obstructive pulmonary disease: hypoxia plays the major role. Kathmandu Univ Med J (KUMJ). 2008 Jan-Mar;6(1):37-40.
32. Houben-Wilke S, Spruit MA, Uszko-Lencer NHMK, Otkinska G, Vanfleteren LEGW, Jones PW, et al. Echocardiographic abnormalities and their impact on health status in patients with COPD referred for pulmonary rehabilitation. Respirology. 2016; 22: 928–34. DOI: 10.1111/resp.12968

Sažetak

Ehokardiografske osobine disfunkcije leve komore kod muškaraca sa hroničnom opstruktivnom bolesti pluća

Aleksandra Milovančev[1,2], Marija Vukoja[1,3], Violeta Kolarov[1,3], Aleksandra Ilić[1,2], Anastazija Stojšić Milosavljević[1,2], Snežana Tadić[1,2], Maja Stefanović[1,2], Tatjana Miljković[1,2], Milovan Petrović[1,2]

[1]Medicinski fakultet, Univerzitet Novi Sad, Novi Sad, Srbija, [2]Institut za kardiovaskularne bolesti Vojvodina, Sremska Kamenica, Srbija, [3]Institut za plućne bolesti Vojvodina, Sremska Kamenica, Srbija

Uvod: *Disfunkcija miokarda leve komore (LVD) kod bolesnika sa hroničnom obstruktivnom bolesti pluća (HOBP) povećava rizik od mortaliteta. Istovremeno postojanje LVD i HOBP nosi veliki broj dijagnostičkih poteškoća. Još uvek nije jasno kolika je učestalost i šta dovodi do LVD u HOBP kod bolesnika bez prethodne kardiovaskularne bolesti. Cilj studije je bio odrediti učestalost disfunkcije miokarda leve komomre i njenu povezanost sa stepenom težine HOBP.*

Metodologija: *Prospektivna kohortna studija je uključila 120 bolesnika sa prethodno dijagnostikovanom stabilnom hroničnom obstruktivnom bolesti pluća. Svim bolesnicima je urađena spirometrija i ehokardiografija. Bolesnici su podeljeni u četiri stadijuma HOBP prema kriterijumima globalne inicijative za HOBP (GOLD).*

Rezultati: *Prevalencija dijastolne LVD u celoj kohorti bila je 65.8%, prvi stepen nađen je kod 42.5% pacijenata sa HOBP, drugi stepen kod 20.8%, a treći stepen kod 2.5% pacijenata, bez statistički značajne povezanosti sa težinom HOBP bolesti (p = 0.8). Sistolna funkcija opada sa stadijumom HOBP, sa značajnim razlikama između grupa (SVI (p=0,01), EF p<0,001). Smanjenje EF≤49% nađeno je u 16.6% kohorte, u prvoj fazi HOBP 13.3% naspram 10% u GOLD II prema 20% u GOLD III i 23.3% pacijenata u GOLD IV.*

Zaključak: *Veliki broj bolesnika bez prethodne srčane bolesti je imao neprepoznatu disfunkciju leve komore. Ovi rezultati naglašavaju važnost ehokardiografije u skreeningu radi pravovremene dijagnostike i lečenja u cilju sprečavanja morbiditeta i mortaliteta ovih bolesnika.*

Ključne reči: hr*onična opstruktivna bolest pluća, disfunkcija leve komore, ehokardiografija*

Srce i krvni sudovi 2022; 41(2): 39-43

Review article

The effects of cardiovascular rehabilitation in patients with reduced, mildly reduced, and preserved ejection fraction - do they benefit equally?

Milovan Stojanović[1,2], Marina Deljanin Ilić Marina[1,2], Stevan Ilić[3]

[1]Institute for Treatment and Rehabilitation Niška Banja, Niš, Serbia. [2]Faculty of Medicine, University of Niš, Serbia, [3]Clinic for Internal Diseases CardioPoint, Niš, Serbia

Abstract

Background. Coronary artery disease (CAD) is the leading cause of heart failure (HF). The beneficial effects of cardiac rehabilitation (CR) in CAD patients are well known but whether they depend on ejection fraction (EF) is rather unknown.

Aim. To examine whether CAD pts with reduced, mildly reduced, and preserved EF benefit equally from comprehensive CR in terms of exercise tolerance.

Methods. 828 CAD pts attended a three-week CR program at the residential center. Before attending CR all patients underwent an echocardiographic exam after which pts were divided into three groups: heart failure with reduced (HFrEF≤40%), mildly reduced (HFmrEF 41-49%), and preserved EF (HFpEF≥50%). At baseline and at the end of CR exercise stress test (EST) was taken.

Results. There were 84 HFrEF pts (10.14%), 246 HFmrEF pts (29.71%), and 498 HFpEF pts (60.15%). At the first EST (EST1) and at the second EST (EST2) HFpEF and HFmrEF patients showed better strain tolerance compared to pts with HFrEF by reaching a higher strain levels and longer duration of EST. However, all three groups showed better strain tolerance at the EST2. Namely, they all reached higher strain level (for all three groups p=0.000) and longer duration of EST (for all three groups p=0.000). Also, in all three groups significantly higher percentage of patients reached submaximal heart rate at the EST2 compared to EST1 (p=0.001 for HFrEF, p=0.006 for HFmrEF, and p=0.000 for HFpEF). Pts with HFrEF had a significantly higher rate of arrhythmia at the EST2 compared to pts with HFmrEF and HFpEF (p=0.009). Improvement of physical strain level and duration of EST on EST2 compared with EST1 was more pronounced in pts with reduced (by 19,2% and 28,7%), than in pts with mildly reduced (by 13,9% and 17,5%) and pts with preserved LVEF (14,1% and 16,8%).

Conclusion. Results indicate that CR significantly improved physical strain tolerance in patients with coronary artery diseases independent of ejection fraction. In pts with HFmrEF and HFpEF CR resulted in higher level of strain tolerance than in pts with HFrEF. However, improvement in exercise capacity was more pronounced in pts with HFrEF.

Kew words coronary artery disease, heart failure, cardiovascular rehabilitation

Introduction

Heart failure (HF) is a clinical syndrome consisting of clinical signs and symptoms caused by structural or functional heart abnormalities that lead to reduced cardiac output or elevated intracardiac pressure[1]. The prevalence of HF is 1-2%, but rises with age and appears to be higher than 10% in patients aged 70 years or older[2]. The most common causes of HF are coronary artery disease (CAD) and arterial hypertension (HTA)1.

HF is divided into three categories based on left ventricular ejection fraction (LVEF): HF with reduced EF (HFrEF) with EF ≤40%, HF with mildly reduced EF (HFmrEF) with EF 41-49%, and HF with preserved EF (HFpEF) with EF ≥50% ([1]). About 1/2 of HF patients have HFrEF, and the other half have HFmrEF or HFpEF[3]. It seems that patients with HFrEF have a worse prognosis compared to patients with HFmrEF or HFpEF[1]. However, in many cases HFpEF and HFmrEF progress to HFrEF[1].

A well-designed cardiovascular rehabilitation (CVR) is of tremendous importance in the treatment of cardiovascular diseases and secondary prevention of cardiovascular events. It improves the quality of life, reduces the risk of secondary cardiovascular events and prolongs life[4]. Moreover, in CAD patients CVR reduces inflammation and oxidative stress[5] and has a great impact on hemodynamics[6]. These positive effects are noted in both genders[7]. The latest European Association of Cardiology (ESC) Guidelines for the diagnosis and treatment of acute and chronic HF give IA recommendation for exercise rehabilitation in all HF patients "who are able in

Corresponding author: Milovan Stojanovic, Institute for treatment and rehabilitation Niska Banja, Serbia, Street: Srpskih junaka 2, 18205 Niska Banja, Serbia
Mail: milovanstojanovic1987@gmail.com, Tel: +381637710470

order to improve exercise capacity, quality of life, and reduce HF hospitalization"[1]. These recommendation is given for all three classes of HF, although there is no date on beneficial effects of CVR on patients with HFmrEF.

The aim of the study was to examine whether patients with coronary artery disease and reduced, mildly reduced, and preserved EF benefit equally from comprehensive cardiovascular rehabilitation in terms of exercise tolerance.

Methods

The study involved eight hundred twenty-eight CAD patients, 202 (24.4%) women and 626 (75.6%) men. All patients participated in a three-week CVR program at the Institute for Treatment and Rehabilitation "Niska Banja" after surviving myocardial infarction (MI), percutaneous coronary intervention or coronary artery bypass grafting (CABG). Before the beginning of CVR an echocardiographic exam was performed and all patients were divided into three groups: patients with HFrEF (84 patients, 10.14%), HFmrEF (246 patients, 29.71%), and PFpEF (498 patients, 60.15%). All patients belonged to New York Heart Association (NYHA) I-II class.

During a three-week CVR all patients underwent a dosed and individualized physical training which included bicycle riding, walking and cardiovascular exercise programs. At baseline and at the end of CVR exercise stress test (EST) was done. ESTs were performed on the treadmill (3017 Full Vision Drive, Newton, Kansas, USA) according to the Bruce protocol. Tests were limited by symptoms and signs like chest pain, lack of air, dizziness, etc., complex heart rhythm disorders, pathological changes on the electrocardiogram (ECG), or submaximal heart rate (calculated as 85% from 220-age equation). Pathological changes on ECG were defined as the occurrence of horizontal and/or down-sloping ST depression ≥ 01 mm. Complex heart rhythm disorders were defined as long-term episodes of bigeminy of ventricular premature complex (VPC), couplets of VPC, and ventricular tachycardia. All data were collected, compared, and analyzed based on EF values.

Statistical analysis was performed using SPSS for Windows (Version 20; SPSS, Chicago, IL, USA). Frequencies and percentages were used for the description of the patient's characteristics. Numerical data were expressed as mean ± standard deviation (SD). The Kolmogorov-Smirnov test was used to test the normality of data. Statistical significance for nominal data was tested with the $\chi 2$ test and, where appropriate, the Fisher exact test. The Student's t- test was used to assess the statistical significance of parametric continuous data, and Mann–Whitney U-test and Wilcoxon Signed Ranks Test were for nonparametric continuous variables. The Pearson's correlation was used to determine the correlation between variables. Statistical significance was set to a level of $p < 0.05$.

Results

Women were more present in the group with HFpEF compared to the other two groups (27.51% vs. 19.51 HFmrEF, and 20.24% HFrEF), with statistically significant difference noted between HFmrEF and HFpEF (p=0.37). The age structure was similar in all three groups. Smokers were more present in group with HFmrEF (58.54%) compared to the group with HFpEF (48.19%) and HFpEF (52.38%), with statistically significant difference noted between HFmrEF and HFpEF (p=0.033). Other risk factors for cardiovascular diseases (hyperlipidemia, diabetes mellitus, arterial hypertension, heredity) did not differ between the groups (Table 1).

At the beginning of CVR, the first exercise stress tests (EST1) were performed. Patients with HFpEF showed better strain tolerance compared to HFrEF and HFmrEF as they achieved higher strain level. Also, EST1 lasted the longest in patients with HFpEF. On the other hand, patients with HFrEF showed the worse strain tolerance. For both parameter statistically significant differences

Table 1. Baseline characteristic of patients

EF ≤40%		Groups			Total	χ2	p
		41%-49%	≥50%				
Gender n (%)	Women	17 (20.24%)	**48 (19.51%)**	**137 (27.51%)**	202 (24.4%)	6.587	**.037**
	Men	67 (79.76%)	**198 (80.49%)**	**361 (72.49%)**	626 (75.6%)		
Hyperlipidaemia n (%)	No	9 (10.71%)	29 (11.79%)	46 (9.24%)	84 (10.14%)	1.209	.546
	Yes	75 (89.29%)	217 (88.21%)	452 (90.76%)	744 (89.86%)		
Hypertension n (%)	No	13 (15.48%)	32 (13.01%)	69 (13.86%)	114 (13.77%)	.329	.848
	Yes	71 (84.52%)	214 (86.99%)	429 (86.14%)	714 (86.23%)		
Diabetes mellitus n (%)	No	63 (75%)	184 (74.8%)	371 (74.5%)	618 (74.64%)	.014	.993
	Yes	21 (25%)	62 (25.2%)	127 (25.5%)	210 (25.36%)		
Heredity n (%)	No	57 (67.86%)	148 (60.41%)	294 (59.04%)	499 (60.34%)	2.338	.311
	Yes	27 (32.14%)	97 (39.59%)	204 (40.96%)	328 (39.66%)		
Smoking n (%)	No	40 (47.62%)	**102 (41.46%)**	**257 (51.61%)**	399 (48.19%)	6.797	**.033**
	Yes	44 (52.38%)	**144 (58.54%)**	**241 (48.39%)**	429 (51.81%)		
Age (m±sd)		61.93±10.01	59.78±9.75	60.79±9.6	60.61±9.69	3.856	.145

Table 2. The first exercise stress test (EST1)

EF ≤40%		Groups			Total	χ2	p
		41%-49%	≥50%				
Level		1.98±0.86	2.3±0.91	2.34±0.99	2.29±0.96	10.066	**.007**
Duration (min)		4.32±2.43	5.42±2.48	5.52±2.69	5.37±2.63	15.086	**.001**
DP before		9704.29±2030.22	10113.58±5310.56	9926.81±6664.13	9959.73±5955.86	2.620	.270
DP after		19109.35±4272.01	22233.87±13138.37	21681.51±4005.08	21584.67±7960.08	24.689	**.000**
SHR achieved n (%)	No	47 (55.95%)	103 (41.87%)	209 (41.97%)	359 (43.36%)	6.039	**.049**
	Yes	37 (44.05%)	143 (58.13%)	289 (58.03%)	469 (56.64%)		
Arrhythmia n (%)	No	51 (89.47%)	143 (89.38%)	308 (91.12%)	502 (90.45%)	.455	.797
	Yes	6 (10.53%)	17 (10.63%)	30 (8.88%)	53 (9.55%)		
Ischemic changes n (%)	No	80 (95.24%)	219 (89.39%)	434 (87.15%)	733 (88.63%)	4.865	.088
	Yes	4 (4.76%)	26 (10.61%)	64 (12.85%)	94 (11.37%)		

DP – double product; SHR – submaximal heart rate.

were noted between HFmrEF and HFpEF on one hand, and HFrEF on the other (p=0.007 for level, and p=0.001 for duration). Also, a significantly greater percentage of patients with HFmrEF and HFpEF achieved submaximal heart rate at the end of EST1 compared to HFrEF (p=0.049, Table 2).

After three weeks of CVR the second EST (EST2) was performed. Results were similar to EST1. Namely, patients with mildly reduced and preserved LVEF showed better strain tolerance compared to patients with reduced LVEF by reaching a higher strain levels and longer duration of EST. On the other hand, arrhythmias were more present in HFrEF compared to HFpEF and HFmrEF (Table 3).

However, all three groups showed better strain tolerance at the EST2. Namely, they all reached higher strain level (for all three groups p=0.000) and longer duration of EST (for all three groups p=0.000). Also, in all three groups significantly higher percentage of patients reached submaximal heart rate at the EST2 compared to EST1 (p=0.001 for HFrEF, p=0.006 for HFmrEF, and p=0.000 for HFpEF), but only patinets with HFrEF had higher values of double product at the end of EST2 compared to the end of EST1 (0.031). On the other hand, patients with HFrEF had a significantly higher rate of arrhythmia at the EST2 compared to patients with mildly reduced and preserved LVEF (p=0.009) (Table 4). Improvement of physical strain level and duration of EST2 compared with EST1 was more pronounced in patients with reduced (by 19,2% and 28,7%), than in patients with mildly reduced (by 13,9% and 17,5%) and patients with preserved LVEF (14,1% and 16,8%).

Discussion

A well-designed CVR includes exercise training, dietary advices, psychosocial support, patient education, control of modifiable cardiovascular and non-cardiovascular risk factors and adequate medication therapy[8]. It is known that personalized and well-organized CVR may lead to the better lipid profile, anxiety and depression reduction, better blood pressure control, reduction in hospitalization and mortality rate[9]. These positive effects of CVR are shown in patients with arterial hypertension, valvular heart diseases, coronary artery disease, and heart failure. This is why all recent and relevant Guidelines advice CVR in secondary prevention of cardiovascular diseases giving it a IA recommendation[1,10-13].

Interestingly, the first Guideline which emphasized the importance of CVR in secondary cardiovascular

Table 3. The second exercise stress test (EST2)

EF ≤40%		Groups			Total	χ2	P
		41%-49%	≥50%				
Level		2.36±0.82	2.62±0.99	2.67±0.96	2.62±0.96	8.427	**.015**
Duration (min)		5.56±2.28	6.35±2.78	6.45±2.74	6.33±2.72	8.055	**.018**
DP before		9409.94±2122.07	9717.66±1804.27	9641.4±2091.13	9640.57±2012.82	1.713	.425
DP after		20112.86±3554.76	21835.98±3807.56	21929.65±3690.82	21717.51±3747.32	16.521	**.000**
SHR achieved n (%)	No	31 (36.9%)	83 (33.74%)	153 (30.72%)	267 (32.25%)	1.615	0.446
	Yes	53 (63.1%)	163 (66.26%)	345 (69.28%)	561 (67.75%)		
Arrhythmia n (%)	No	47 (81.03%)	140 (86.42%)	310 (92.54%)	497 (89.55%)	9.385	**.009**
	Yes	11 (18.97%)	22 (13.58%)	25 (7.46%)	58 (10.45%)		
Ischemic changes n (%)	No	77 (91.67%)	213 (86.59%)	427 (85.74%)	717 (86.59%)	2.173	.337
	Yes	7 (8.33%)	33 (13.41%)	71 (14.26%)	111 (13.41%)		

DP – double product; SHR – submaximal heart rate.

Table 4. Comparison between the first and the second exercise stress test in men

EF		≤40%			41%-49%			≥50%		
		M±SD	Z/ χ2	P	M±SD	Z/ χ2	p	M±SD	Z/ χ2	p
EST1 Level		1.98±0.86	-4.326[c]	**.000**	2.3±0.91	-6.404[c]	**.000**	2.34±0.99	-9.366[c]	**.000**
EST2 Level		2.36±0.82			2.62±0.99			2.67±0.96		
EST1 duration		4.32±2.43	-5.818[c]	**.000**	5.42±2.48	-8.959[c]	**.000**	5.52±2.69	-11.584[c]	**.000**
EST2 duration		5.56±2.28			6.35±2.78			6.45±2.74		
EST1 DP before		9704.29±2030.22	-1.066[d]	.286	10113.58±5310.56	-.701[d]	.483	9926.81±6664.13	-.266[c]	.790
EST2 DP before		9409.94±2122.07			9717.66±1804.27			9641.4±2091.13		
EST1 DP after		19109.35±4272.01	-2.163[c]	**.031**	22233.87±13138.37	-1.715[c]	.086	21681.51±4005.08	-1.184[c]	.236
EST2 DP after		20112.86±3554.76			21835.98±3807.56			21929.65±3690.82		
SHR	EST1	37 (44.05%)	6.126	**0.013**	143 (58.13%)	3.458	0.063	289 (58.03%)	13.609	0.000
	EST2	53 (63.1%)			163 (66.26%)			345 (69.28%)		
Arrhythmia n (%)	EST1	6 (10.53%)	1.625	0.202	17 (10.63%)	0.660	0.416	30 (8.88%)	0.448	0.503
	EST2	11 (18.97%)			22 (13.58%)			25 (7.46%)		
ST depression n (%)	EST1	4 (4.76%)	0.876	0.349	26 (10.61%)	0.912	0.340	64 (12.85%)	0.420	0.517
	EST2	7 (8.33%)			33 (13.41%)			71 (14.26%)		

prevention was the one about the diagnosis and treatment of chronic heart failure back in 2008[14]. Cardiac rehabilitation is of tremendous importance in HF patients as it may improve the quality of life, functional capacity and cardiac function. These beneficial effects are recognized in center-based, home-based and hybrid (short term center-based and then home-based) cardiac rehabilitation[15]. It seems that high-intensity interval training in HF leads to better exercise capacity. A meta-analysis which included 24 studies with CAD, HFrEF or HFpEF patients showed a significantly greater improvement in VO2 peak after high-intensity exercise compared to moderate-intensity continuous training (by 1.40 mL/min/kg; 95% confidence interval (CI) 0.69–2.11; P ≤0.001)[16]. However, in the SMARTEX-HF study which included 261 NYHA II-III HFrEF patients, high-intensity training wasn't superior to moderate-intensity continuous training[17]. Nevertheless, both types of exercise training did lead to better strain tolerance in HF patients.

Although beneficial effect of CVR are well-known, patients with HF seldom attend cardiac rehabilitation programs. Even in HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) trial, which was the largest trial of CVR in patients with HFrEF, the long-term adherence was below 30% ([18]). There are many factors that led to these disappointing results. One of the most important was physician inertia ([9]). There is no doubt that stronger physician endorsement can significantly increase the participation of HF patients in CVR programs.

Both, HFrEF and HFpEF, are characterized by reduced physical tolerance and chronic fatigue. HFpEF patients suffer from exercise intolerance due to vascular, skeletal muscle, and cardiac abnormalities[19]. A personalized moderate to high-intensity training in these patients can increase VO_2 peak, quality of life and exercise stress tolerance[19]. Many studies have shown the beneficial effects of well-designed CVR on physical strain tolerance in patients with HFpEF and HFrEF. These positive effects CVR was shown regardless of age, sex, comorbidities, and frailty[20]. However, there is no study which investigated the effects of CVR on patients with HFmrEF.

In our study, CAD patients with HFpEF had the best strain tolerance on the first and on the second EST. The worst exercise strain tolerance was noted in CAD patients with HFrEF. These findings were somewhat expected. However, in our study all three classes of HF showed a significant improvement of exercise stress tolerance after finishing a three-week rehabilitation program. Moreover, the greatest improvement was noted in CAD patients with HFrEF. These results, once again, emphasize the importance of CVR in patients with HF.

Conclusion

Results indicate that cardiovascular rehabilitation significantly improves physical strain tolerance in patients with coronary artery diseases independent of ejection fraction. In patients with HFmrEF and patients with HFpEF cardiovascular rehabilitation resulted in higher level of strain tolerance than in patients with HFrEF. However, improvement in exercise capacity was more pronounced in patients with HFrEF.

References

1. McDonagh TA, Metra M, Adamo M, et al.; ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2021; 42(36): 3599-3726.
2. van Riet EE, Hoes AW, Wagenaar KP, Limburg A, Landman MA, Rutten FH. Epidemiology of heart failure: the prevalence of heart failure and ventricular dysfunction in older adults over time. A systematic review. Eur J Heart Fail 2016;18:242252.
3. Bleumink GS, Knetsch AM, Sturkenboom MC, et al. Quantifying the heart failure epidemic: prevalence, incidence rate, lifetime risk and prognosis of heart failure The Rotterdam Study. Eur Heart J 2004;25:16141619.
4. Leon AS, Franklin BA, Costa F, et al. Cardiac rehabilitation and secondary prevention of coronary heart disease: an American Heart Association scientific statement from the Council on Clinical Cardiology (Subcommittee on Exercise, Cardiac Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity, and

Metabolism (Subcommittee on Physical Activity), in collaboration with the American association of Cardiovascular and Pulmonary Rehabilitation. Circulation 2005;111(3):369-376.
5. Ilić MD, Kocić G, Lazarević G, et al. Exercise training and inflammatory markers in coronary artery disease patients. Acta Facultatis Medicae Naissensis 2022; 39(2): 294-309.
6. Stojanović M, Deljanin-Ilić M, Ilić S, Petrović D, Ilić B. The effects of cardiac rehabilitation on haemodynamic parameters measured by impedance cardiography in patients with coronary artery disease. Vojnosanitetski pregled 2022;79(5):419-426.
7. Deljanin-Ilić M, Stojanović M, Ilić S. The effect of cardiovascular rehabilitation on physical strain tolerance–does gender really matter?. Vojnosanitetski pregled 2021; 78(8): 844-850.
8. Ambrosetti M, Abreu A, Corrà U, et al. Secondary prevention through comprehensive cardiovascular rehabilitation: From knowledge to implementation. 2020 update. A position paper from the Secondary Prevention and Rehabilitation Section of the European Association of Preventive Cardiology. Eur J Prev Cardiol 2020:2047487320913379.
9. Bozkurt B, Fonarow GC, Goldberg LR, et al.; ACC's Heart Failure and Transplant Section and Leadership Council. Cardiac rehabilitation for patients with heart failure: JACC Expert Panel. J Am Coll Cardiol 2021;77(11):1454-1469.
10. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts). Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J 2016;37:2315–2381.
11. Ibanez B, James S, Agewall S, et al.; ESCS cientific Document Group. 2017 ESC Guidelines for the management of acute myocardial infarction inpatients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2018;39:119–177.
12. Neumann FJ, Sousa-Uva M, Ahlsson A, et al.; ESC Scientific Document Group. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J 2019;40:87–165.
13. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J 2020;41:407–477.
14. Dickstein K, Cohen-Solal A, Filippatos G, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur J Heart Fail 2008;10:933–989.
15. Imran HM, Baig M, Erqou S, et al. Home-based cardiac rehabilitation alone and hybrid with center-based cardiac rehabilitation in heart failure: A systematic review and meta-analysis. J Am Heart Assoc 2019; 8(16): e012779.
16. Pattyn N, Beulque R, Cornelissen V. Aerobic interval vs. continuous training in patients with coronary artery disease or heart failure: an updated systematic review and meta-analysis with a focus on secondary outcomes. Sports Med 2018;48:1189–1205.
17. Ellingsen Ø, Halle M, Conraads V, et al.; SMARTEX Heart Failure Study (Study of Myocardial Recovery After Exercise Training in Heart Failure) Group. High-intensity interval training in patients with heart failure with reduced ejection fraction. Circulation 2017;135:839–849.
18. O'Connor CM, Whellan DJ, Lee KL, et al.; HF-ACTION Investigators. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. JAMA 2009;301(14):1439-1350.
19. Tucker WJ, Angadi SS, Haykowsky MJ, Nelson MD, Sarma S, Tomczak CR. Pathophysiology of exercise intolerance and its treatment with exercise-based cardiac rehabilitation in heart failure with preserved ejection fraction. J Cardiopulm Rehabil Prev 2020;40(1):9-16.
20. Kamiya K, Sato Y, Takahashi T, et al. Multidisciplinary cardiac rehabilitation and long-term prognosis in patients with heart failure. Circ Heart Fail 2020;13(10):e006798.

Sažetak

Efekti kardiovaskularne rehabilitacije kod pacijenata sa smanjenom , blago smanjenom I očuvanom ejekcionom frakcijom – da li je korist ista za sve?

Milovan Stojanović[1,2], Marina Deljanin Ilić Marina[1,2], Stevan Ilić[3]

[1]Institut za lečenje i rehabilitaciju Niška Banja, Srbija, [2]Medicinski fakultet, Univerzitet u Nišu, Srbija, [3]Klinika za interne bolesti CardioPoint, Niš, Srbija

Uvod. *Koronarna arterijska bolest (KAB) je vodeći uzrok srčane insuficijencije (SI). Pozitivni efekti kardiovaskularne rehabilitacije (KVR) kod pacijenata sa KAB su dobro poznati, ali je nepoznato da li zavise od ejekcione frakcije (EF). Cilj ovog rada je biod a se ispita da li bolesnici sa KAB i redukovanom, blago redukovanom i očuvanom EF imaju jednaku korist od KVR u smislu tolerancije napora.*

Metode. *828 pacijenata sa KB je pohađalo tronedeljni program KVR. Pre započinjanja KVR svi pacijenti su podvrgnuti ehokardiografskom pregledu nakon* ***čega*** *su bolesnici podeljeni u tri grupe: srčana insuficijencija sa smanjenom (engl. HFrEF≤40%), blago smanjenom (engl. HFmrEF 41-49%) i očuvanom EF (engl. HFpEF≥50%). Na početku i na kraju KVR urađen je test fizičkim opterećenjem (TFO).*

Rezultati. *Bilo je 84 HFrEF (10,14%), 246 HFmrEF (29,71%) i 498 HFpEF (60,15%). Na prvom TFO (TFO1) i na drugom TFO (TFO2) HFpEF i HFmrEF pacijenti su pokazali bolju toleranciju fizičkog napora u poređenju sa bolesnicima sa HFrEF dostizanjem viših nivoa opterećanja i dužim trajanjem TFO. Međutim, sve tri grupe su pokazale bolju toleranciju napora na TFO2. Naime, svi su dostigli viši nivo opterećenja (za sve tri grupe p=0,000) i duže trajanje TFO2 (za sve tri grupe p=0,000). Takođe, u sve tri grupe značajno veći procenat pacijenata je dostigao submaksimalnu srčanu frekvencu na TFO2 u odnosu na TFO1 (p=0,001 za HFrEF, p=0,006 za HFmrEF i p=0,000 za HFpEF). Bolesnici sa HFrEF su imali* ***češće*** *aritmije na TFO2 u poređenju sa bolesnicima sa HFmrEF i HFpEF (p=0,009).*

Zaključak. *Rezultati pokazuju da je KVR značajno poboljšala toleranciju fizičkog napora kod pacijenata sa oboljenjem koronarnih arterija nezavisno od ejekcione frakcije. Kod pacijenata sa HFmrEF i HFpEF KVR je doprinela višem nivu tolerancije napora u poređenju sa HFrEF bolesnicima. Međutim, sveukupno poboljšanje tolerancije napora bilo je izraženije kod pacijenata sa HFrEF.*

Ključne reči: koronarna bolest, srčana slabost, kardiovaskularna rehabilitacija

Srce i krvni sudovi 2022; 41(2): 44-47

Case report

Spontaneous coronary artery dissection as a cause of acute myocardial infarction in young people

Dragana Dabović[1,2], Milovan Petrović [1,2] , Milenko Čanković [1,2], Svetlana Apostolović [3,4]

[1]University of Novi Sad, Faculty of Medicine, Novi Sad, Serbia; [2]Institute of Cardiovascular Diseases of Vojvodina, Clinic of Cardiology, Sremska Kamenica, Serbia, [3]University of Nis, School of Medicine, Nis, Serbia, [4]Clinical Centre Nis, Clinic of cardiology, Nis, Serbia

Abstract

Introduction. Spontaneous coronary artery dissection (SCAD) represents a dissection that occurred without atherosclerosis, trauma or has not developed iatrogenically. The true prevalence of SDKA is unknown, as they are often unrecognized. It most often occurs in young women, who do not have the classic risk factors for the development of cardiovascular diseases. In only 10% of cases, it occurs in men after physical exertion.

Case report. A 35-year-old man was admitted to the emergency department due to an acute myocardial infarction with ST elevation. Urgent coronarography was performed and the SCAD, type I of the first marginal branch (OM), was registered. During primary percutaneous coronary intervention drug-eluting stent was implanted in the OM branch, guided by optical coherence tomography (OCT). In the further time, the patient is without problems, hemodynamically and rhythmically stable. After a month, re-coronarography was performed, as well as OCT analysis of the first marginal branch, which registered a significant malaposition and insufficient expansion of the previously implanted stent in the distal segment OM. Dilatation with a non-compliant balloon was performed with optimal result. After OCT-guided balloon dilatation, excellent stent apposition and expansion, was registered. Optical medical treatment was indicated. In the follow-up period after three months, the patient is without problems.

Conslusion. Because the SDKA are often unrecognized, careful evaluation of the angiographic findings and the use of intravascular imaging in unclear cases is necessary. In the following period, randomized controlled studies are needed to define patients who require revascularization, as well as those who require dual antiplatelet therapy and the length of its use.

Kew words spontaneous coronary artery dissection; acute myocardial infarction; optical coherence tomography

Introduction

Spontaneous coronary artery dissection (SCA) is a dissection that is not associated with atherosclerosis, trauma or iatrogenic. The true prevalence of SCA is unknown, as they are often unrecognized. They are considered to be the cause of 1-4% of all acute coronary syndromes[1], 15-20% of women in the peripartum period[2], and up to 35% of acute coronary syndromes in women under 60 years of age[3,4]. It occurs most often in young women, who do not have classic risk factors for the development of cardiovascular diseases. In only 10% of cases, it occurs in men after physical exertion. A number of conditions are associated with SCA, such as fibromuscular dysplasia, chronic inflammatory diseases, connective tissue disorders, and hypothyroidism[4]. Recently, several gene loci have been isolated that are associated with a higher risk of SCA[1]. In addition, various factors that contribute to the development of SCA, consumption of various drugs, emotional stress, intense exercise, Valsalva maneuver and vomiting have been defined. Herewith, we shall present the case of a 35-year-old man in whom the cause of an acute ST-elevation myocardial infarction was SCA.

Case presentation

A 35-year-old patient was admitted as an emergency due to an acute myocardial infarction with ST elevation in the lateral region. Intense chest pain occurred about 5 hours before admission and was repeated on several occasions. The evening before the reception, he consumed a large amount of alcohol, energy drinks and tobacco. Denies other diseases. He cites smoking experience as a risk factor. On admission, he was hemodynamically and rhythmically stable, cardiac compensated. Dual antiplatelet therapy (acetylsalicylic acid and ticagrelor) was prescribed. An urgent coronary angiography was performed, which found the first marginal branch narrowed in the medial segment by 50%, and then in the distal segment by 75%, caused by spontaneous dissection of the coronary artery, type 1 (Figure 1). Other coronary blood vessels are without significant narrowing. For the purpose of a more detailed evaluation, an optical coherence tomography

Correspoding author: Dragana Dabović. Cardiology Clinic, Institute for cardiovascular diseases Vojvodine, Put dr Goldmana 4, 21204 Sremska Kamenica, Mobile: 063/8358888, E-mail: dragana.dabovic@ikvbv.ns.ac.rs

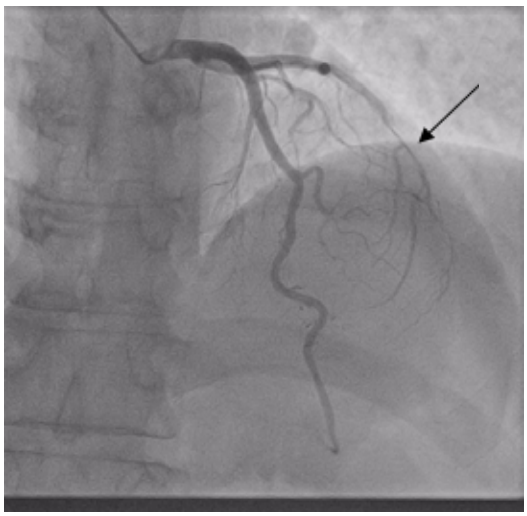


Figure 1. Angiography presenting spontaneous coronary dissection type 1 of circumflex coronary artery (arrow)

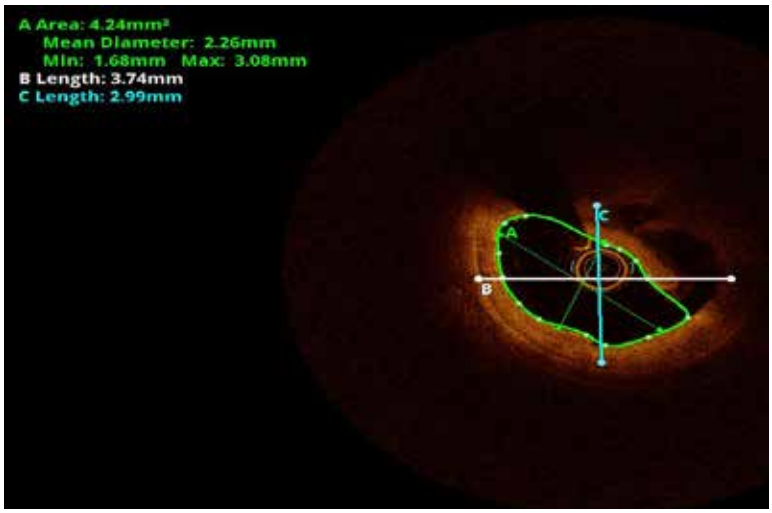


Figure 2. Optical coherence tomography showing dissection flap with 180 degrees angle and 3mm in lenght

(OCT) was performed, which registered a dissection flap with an angle of about 180 degrees and a length of up to 3 mm, MLA 1.62 mm^2, stenosis 75% in the distal segment (Figure 2). An intramural hematoma is registered in a length of about 60 mm. An OCT-guided primary percutaneous coronary intervention was performed with the implantation of a drug-coated stent 28x2.5 mm (Xience PRO, Abbott, USA) with an optimal result of the intervention (Figure 3). An OCT analysis was performed after stent implantation and satisfactory expansion and apposition of the stent was registered, without signs of "edge dissection". An intramural hematoma was registered proximal and distal to the implanted stent. Echocardiographic examination shows a left ventricle of normal dimensions, without clear disturbances of segmental kinetics, preserved systolic function and without signs of diastolic dysfunction. After seven days, the patient was discharged to home treatment, without subjective complaints, hemodynamically and rhythmically stable, cardiac compensated. He was discharged with aspirin, ticagrelor, bisoprolol, ramipril, rosuvastatin and a proton pump inhibitor. After one month, recoronarography and OCT analysis of the first marginal branch was performed, which registered significant malaposition and insufficient expansion of the previously implanted stent in the distal segment. Dilation was performed with a 12x3.5mm non-compliant balloon (Apollo, BrosMed, China). After OCT-guided balloon dilatation, satisfactory expansion and apposition of the stent was registered (Figure 4). The described malaposition of the stent was understood as a consequence of the reabsorption of the intramural hematoma. Further medical treatment is indicated. A doppler of the carotid arteries and a doppler of the renal arteries were performed, which registered a normal finding.
At the follow-up examination after three months, the patient has no subjective complaints.

Discussion

A significant increase in scientific interest in SCA arose after defining the aniographic classification of SDKA in 2014 according to Saw and the consensus document of the European Association of Cardiologists[5,6]. Namely, type 1 represents a dissection that is angiographically

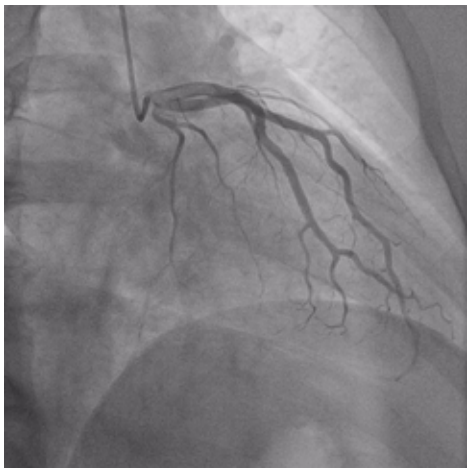
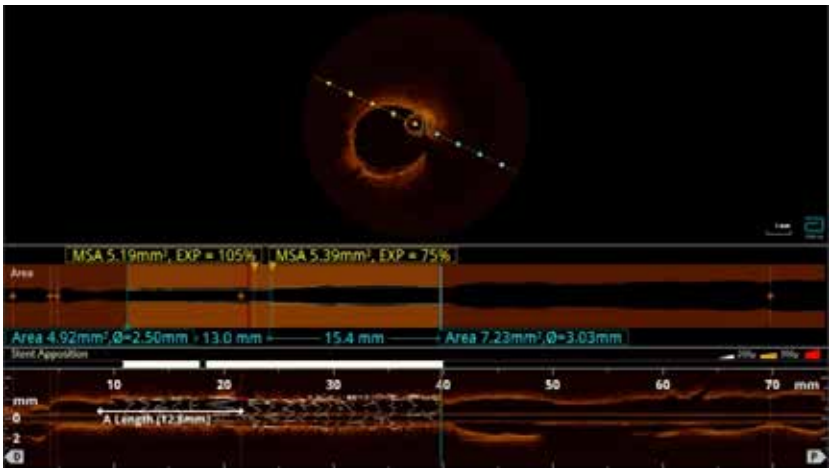


Figure 3. Angiography after stent implantation in OM branch



Slika 4. Optical coherence tomography following stent implantation with good expansion, apposition, without tissue prolapse and significant edge dissections

registered as contrast retention in the blood vessel wall and multiple radiolucent lumens. Type 2 is characterized by a long, diffuse (more than 20mm) stenosis with varying degrees of narrowing of the lumen, while type 3 mimic atherosclerotic stenoses and are defined as focal or tubular stenoses (less than 20mm in length)[7]. The cause of acute myocardial infarction in our patient is SCA type 1. Type 3 is the rarest type of dissection that occurs in about 3.4% of patients, while the most common is type 2 that occurs in about 67.5% of patients[7].

SCA were previously considered rare as they are often unrecognized on angiography. However, with the increasing use of intravascular imaging, they are not uncommon. Optical coherence tomography is a useful tool, since intramural hematoma and dissection membrane can be visualized due to its high resolution. On the other hand, one should be careful because of the possibility of extension of the dissection when applying contrast and manipulating the catheter. . The literature describes cases in which SCA was initially unrecognized, while SCA was clearly registered after intravascular imaging[8].

The clinical presentation of SCA is different, but they are most often manifested by acute coronary syndrome. The most common complaint is typical chest pain (96% of cases). ST segment elevation is registered on the electrocardiographic record in 30 to 49% of patients, while 47 to 70% of patients present with acute myocardial infarction without ST elevation[9,10]. A very small number of patients present with ventricular tachycardia, cardiac arrest or cardiogenic shock.

Considering the small number of patients, treatment recommendations for these patients are primarily based on the opinion of experts and the results of observational studies. Conservative treatment is recommended in stable patients without signs of ongoing ischemia, given the high percentage of failure of percutaneous coronary intervention (PCI). In a retrospective study that included 189 patients with SCA, a procedural complication was noted in 53% of patients treated with PCI (11). The reasons for failure were the passage of the wire through the false lumen, loss of flow under the implanted stent, and remaining residual stenosis. PCI is associated with a significantly higher percentage of patients undergoing urgent surgical revascularization (12%) compared to those treated conservatively (2%). Surgical myocardial revascularization is reserved for patients with CAD involving the main trunk, those with ongoing ischemia, life-threatening arrhythmias, and hemodynamically unstable patients.

In terms of medication, in patients who have been treated with PCI, it is recommended to use dual antiplatelet therapy for up to 12 months, as in the case of acute coronary syndrome of another etiology. In a cohort of 64 patients with CAD, 59 (92%) received dual antiplatelet therapy (Aspirin plus one antiplatelet drug: Clopidogrel, Prasugrel, or Ticagrelor)[12]. Out of 40 patients who underwent recoronarography, healing of the dissection was noted in all but one. In patients who have not been treated with a PCI, the addition of another antiplatelet drug is controversial.

Long-term follow-up of these patients aims to perform screening for early detection of fibromuscular dysplasia, prevent recurrent events, and perform cardiac rehabilitation.

Fibromuscular dysplasia is an idiopathic arteriopathy that is often associated with CAD, with a prevalence of 25% to 86%[13]. Renal, carotid and vertebral arteries are most often affected. In our patient, the renal and carotid arteries doppler showed a normal finding.

A retrospective study in which 189 patients were included is reported in the literature and recurrent SDKA was registered in 27% of patients. During the follow-up period of three months, our patient has no subjective complaints.

In the following period, randomized controlled studies are necessary to define patients who need revascularization, as well as those who need dual antiplatelet therapy and the duration of its administration.

References

1. Kim ESH. Spontaneous coronary-artery dissection. N Engl J Med. 2020;383(24):2358-2370.
2. Gad MM, Mahmoud AN, Saad AM, et al. Incidence, clinical presentation, and causes of 30-day readmission following hospitalization with spontaneous coronary artery dissection. JACC Cardiovasc Interv 2020;13(8):921-932.
3. Saw J, Humphries K, Aymong E, et al. Spontaneous coronary artery dissection: clinical outcomes and risk of recurrence. J Am Coll Cardiol 2017;70(9):1148-1158.
4. Gulati R, Behfar A, Narula J, et al. Acute myocardial infarction in young individuals. Mayo Clin Proc 2020;95(1):136–156.
5. Saw J. Coronary angiogram classification of spontaneous coronary artery dissection. Catheter Cardiovasc Interv 2014;84(7): 1115-1122.
6. Adlam D, Alfonso F, Maas A, Vrints C. European Society of Cardiology, Acute Cardiovascular Care Association, SCAD study group: a position paper on spontaneous coronary artery dissection. Eur Heart J 2018;39(36):3353-3368.
7. Hayes SN, Kim ESH, Saw J, et al. Spontaneous coronary artery dissection: Current state of the science: a scientific statement from the American heart association. Circulation. 2018;137(19):e523-557.
8. Ivanović V, Dabović D, Petrović M, Ivanov I, Bjelobrk M. Spontaneous coronary artery dissection as a cause of acute myocardial infarction with ST elevation. Srp Arh Celok Lek. 2021;149(5-6): 348-352.
9. Daoulah A, Al-Faifi SM, Madan M, et al. Clinical presentation and outcome of patients with spontaneous coronary artery dissection versus atherosclerotic coronary plaque dissection. Crit Pathw Cardiol 2021;20(1):36-43.
10. Tweet MS, Hayes SN, Pitta SR, et al. Clinical features, management and prognosis of spontaneous coronary artery dissection. Circulation 2012;126(5):579-588.
11. Tweet MS, Eleid MF, Best PJ, et al. Spontaneous coronary artery dissection: revascularization versus conservative therapy. Circ Cardiovasc Interv 2014;7(6):777-786.
12. Rogowski S, Maeder MT, Weilenmann D, et al. Spontaneous coronary artery dissection: angiographic follow-up and long-term clinical outcome in a predominantly medically treated population. Catheter Cardiovasc Interv 2017;89(1):59-68.
13. Garcia-Guimarães M, Bastante T, Antuña P, et al. Spontaneous coronary artery dissection: mechanisms, diagnosis and management. Eur Cardiol 2020;15:1–8.

Sažetak

Spontana disekcija koronarne arterije, uzročnik akutnog infarkta miokarda kod mladih osoba

Dragana Dabović[1,2], Milovan Petrović[1,2] , Milenko Čanković[1,2], Svetlana Apostolović[3,4]

[1]Univerzitet u Novom Sadu, Medicinski Fakultet, Novi Sad, Srbija, [2]Institut za kardiovaskularne bolesti Vojvodine, Klinika za kardiologiju, Sremska Kamenica, Srbija, [3]Univerzitet u Nišu, Medicinski fakultet, Niš, Srbija, [4]Klinički centar Niš, Klinika za kardiologiju, Niš, Srbija

***Uvod**. Spontana disekcija koronarne arterije (SDKA) predstavlja disekciju koja nije povezana sa aterosklerozom, traumom niti je nastala jatrogeno. Prava prevalenca SDKA je nepoznata, obzirom da su često neprepoznate. Najčešće se javlja kod mladih žena, koje nemaju klasične faktore rizika za razvoj kardiovaskularnih bolesti. U samo 10% slučajeva se javlja kod muškaraca nakon fizičkog napora.*

***Prikaz slučaja.** Muškarac dobi 35 godina je primljen kao hitan zbog akutnog infarkta miokarda sa ST elevacijom. Urađena je urgentna koronarografija kojom se nađe SDKA, tip I prve marginalne grane(OM). Urađena je primarna perkutana koronarna intervencija sa implanitacijom lekom obloženog stenta u OM granu vođena optičkom koherentnom tomografijom (OCT). U daljem toku bolesnik je bez tegoba, hemodinamski i ritmički stabilan. Nakon mesec dana je urađena rekoronarografija, i OCT analiza kojom prve marginalne grane kojom se registruje signifikantna malapozicija i nedovoljna ekspanzija ranije implantiranog stenta u distalnom segmentu. Urađena je dilatacija nekomplijantnim balonom, sa optimalnim rezultatom. Nakon OCT-om vođene balon dilatacije registruje se zadovoljavajuća ekspanzija i apozicija stenta. Indikovan je dalji medikamentni tretman. U periodu praćenja nakon tri meseca bolesnik je bez tegoba.*

***Zaključak**. Imajući u vidu da su SDKA često neprepoznate, neophodna je pažljiva evaluacija angiografskog nalaza i upotreba intravaskularnog imidžinga u nejasnim slučajevima. U narednom periodu su neophodne randomizovane kontrolisane studije za definisanje pacijenata kod kojih je neophodna revaskularizacija, kao i onih kojima je neophodna dvojna antiagregaciona terapija i kao I dužina primene iste.*

Ključne reči: spontana disekcija koronarne arterije, akutni infarct miokarda, optička koherentna tomografija

Srce i krvni sudovi 2022; 41(2): 48-51

Case report

Individual approach in the treatment of aortic stenosis with contemporary TAVI valves

Nikola Zaric

Schüchtermann Klinik, Bad Rothenfelde, Germany

Abstract The treatment of severe, symptomatic, aortic stenosis has changed in recent years. A medical-technological breakthrough was presented by the development of the TAVI (transcatheter aortic valve implantation) concept. Namely, earlier therapy included conventional, surgical replacement of the aortic valve on the one hand and, on the other hand, conservative, relatively effective balloon valvuloplasty in high-risk patients. Today, it is possible to help once inoperable patients as well as high-risk patients with transcatheter aortic valve implantation. Thanks to the recent development of medicine and technology, there are more TAVI systems available. Taking into account the conventional and medicinal therapeutic approach, the decision on the method of treatment can best be carried out by the HEART team (cardiologist, cardiac surgeon, radiologist, anesthesiologist). By carefully considering the anatomical and clinical characteristics of each individual patient, we can decide which type of aortic prosthesis provides the patient with the maximum therapeutic benefit.

In the following text, the basic characteristics of the TAVI system, which, in accordance with the clinical results, are most often applied, as well as the characteristics of patients in whom TAVI is already indicated, will be listed.

Key words aortic stenosis, TAVI

Balloon-expanding TAVI system Sapien System (Edwards)

This model is made of bovine pericardium. It is a trivelar aortic prosthesis and a prototype of a transcatheter aortic valve, which was used for the first time in humans, in 2002. The pericardium, from which the valve is made, was treated with a special procedure that prevents calcification, and the stent is covered with a sheath made of polyethylene terephthalate (PET). The valve of the newer generation Sapien Ultra contains a modified, thicker cover. The catheter of this valve is easily bendable, so it is easy to pass through the aortic arch. Sapien is currently the only TAVI system that has the possibility of anterograde and retrograde implantation, so it is also the only system for transapical access (TA - TAVI). The system includes conduits with an internal diameter of 14-16 francs and thus enables therapy in patients with blood vessels with a small or sclerotic lumen. Thanks to the high radial power of this balloon-expanding system, it is possible to treat aortic stenosis with very severe calcifications. The advantage is also the low height of the sheath, which lies intra-annular, which enables good accessibility to the coronary arteries. This must be taken into account in patients with coronary heart disease and in possibly younger patients. Also, further medical-technological development implies in the future the application of the so-called VALVE's VALVE strategy, which would be simpler with this type of valve than with supraannular TAVI systems, which will be discussed in the following text. Severe calcifications in the outflow tract of the left ventricle or a narrow outflow tract represent an obstacle in the application of the Sapien system. In that case, subannular perforation or annulus rupture can occur, which in both cases could be fatal for the patient. The PARTNER study is certainly well known in the world of cardio medicine and as such deserves a specially written review/special article.

Self-expanding TAVI system CoreValve (Evolut R/Pro)

Medtronic models of self-expanding TAVI systems (Evolut R/Pro) are made from porcine pericardium. The trivelar valve is attached to a nitinol sheath, the distal end of which extends to the sinotubular junction of the aorta. The newer generation of Evolut Pro differs from the previous one, because it is reinforced with pericardium on the proximal part, which would prevent the risk of paravalvular leakage (leakage). The guide has an internal diameter of 16 French. The ducts are flexible, which allows access to smaller and calcified blood vessels. The main characteristic of these prostheses is the

Features of TAVI in relation to anatomic characteristics of the patient			
	Especially well suited	***Moderate suited***	***Less suited***
Horisontally positioned aorta	ACURATE neo	Sapien	Evolut, Portico
Calcium in LV outflow tract, bicuspid valve, asymetric calcifications	-	Sapien, Evolut	Portico, ALLEGRA, ACURATE neo
Small aortic root	Evolut, ACURATE neo	Portico, ALLEGRA	Sapien
Possible intervention on coronary arteries	Sapien, ACURATE neo	-	Evolut, ALLEGRA
Valve in Valve	Evolut, ALLEGRA	Portico	Sapien 3
Aortic regurgitation without calcium	ACURETE neo	Sapien 3, Evolut	-
Difficult transfemoral access	Evolut	Sapien, Portico, ALLEGRA, ACURATE neo	-

possibility of repositioning, which enables their precise placement. The supraannular position of the valve gives it an advantage in asymmetric, heavily calcified annuli, as well as in bicuspid valves where the calcification extends all the way to the left ventricular outflow tract. A properly placed prosthesis implies free ostiums of the coronary arteries. In clinical practice, the incidence of Trivelar bovine valve, with a long nitinol stent. This self-expanding prosthesis is characterized by small diameter guides (14 French), which enables its retrograde application in more complex anatomies. The intraannular position and structure of the valve enables good access to the coronary arteries, which should be taken into account in younger patients. Disadvantages are the high postoperative incidence of pacemaker implantation (19%), as well as the more frequent occurrence of paravalvular leakage. The multicenter PORTICO 1 study confirmed a high rate of pacemaker implantation after one year of patient follow-up.postoperative AV block is more frequent than in other TAVI models, so pacemaker implantation is unfortunately unavoidable in 10-15% of cases. In addition to the Sapien Edwards prosthesis mentioned above, the Evolut TAVI system offers through the Ewolut - Low - Risk - Trial a really good record of data on the application of this valve.

Acurate Neo (Boston Scientific, Marlborough, MA, USA)

Acurate Neo is a self-expanding prosthesis made from porcine pericardium. This model is characterized by its crown-like appearance. Namely, the valve consists of two “crowns” of nitinol ring. The position of the valve is supraannular, which reduces the transvalvular gradient and makes the system suitable for small annuluses. Furthermore, due to the low radial strength of the stent, the prosthesis is primarily indicated for stenoses that are medium and symmetrical. In case of bicuspid, asymmetric and narrow stenoses, this valve is not recommended. Postoperatively, the incidence of AV block is lower compared to other TAVI systems (supraannular position). SCOPE I is a randomized study comparing the intraannular Sapien 3 prosthesis and the supraannular Acurate Neo system.

Allegra (NVT, Hechingen, Germany)

Allegra is a self-expanding, supraannular prosthesis with a short nitinol stent. The trivelar valve is made from bovine pericardium. Implantation is planned retrograde, but application through the subclavian/axillary artery (TAX TAVI) is possible. So far, it has shown good results in VALVE in VALVE procedures, especially with biological prostheses of smaller diameter. Also, implantation of pacemakers is lower than with the others. The Nautilus - Pilot - Study is a small prospective study that included 27 high-risk patients. In them, the procedure was successfully performed in 96% with a transfemoral approach, with an incidence of pacemaker implantation of 8%.

Portico (Abbott, Chicago, USA)

Trivelar bovine valve, with a long nitinol stent. This self-expanding prosthesis is characterized by small diameter guides (14 French), which enables its retrograde application in more complex anatomies. The intraannular position and structure of the valve enables good access to the coronary arteries, which should be taken into account in younger patients. Disadvantages are the high postoperative incidence of pacemaker implantation (19%), as well as the more frequent occurrence of paravalvular leakage. The multicenter PORTICO 1 study confirmed a high rate of pacemaker implantation after one year of patient follow-up.

Clinical/anatomical characteristics of patients

For the precise performance of the operation and the prevention of periprocedural complications (more on that in one of the following texts), it is very important to properly perform diagnostics using well-established algorithms. Planning includes echocardiography, coronary angiography, CT scanner and, of course, evaluation by the HEART team.

Echocardiography is the basic non-invasive method for diagnosing aortic stenosis. It confirms the very existence of the disease, enables the visualization of the morphology of the valve, then the assessment of the condition of the outflow tract of the left ventricle and the

The role of the HEART tieam in evaluation of pateints with aortic stenosis		
Patients clinical characteristics	***Anatomzcal and technical aspects***	***Co-morbidities***
Frailty	Porcelan aorta	Disease of other valves (no improvement following treatmen of aortic stenosi)
Deformity of the chest or radiation	Neadekvatna velicina aortnog anulusa (< 18 mm, > 29 mm)	Thromb in left ventricle
Cirosis hepatis	Presence of aneurism or thrombus in aorta	Endocarditis
Previous cardiac surgery	Increased risk of the obstruction of coronary ostia	Decreased ejection fraction
Social aspects (activity, family circumstances, need for a special care...)	Existance of asyemtric calcium, bicuspid valve	Hipertrophy of the septum

native valve. The height of the orifice of the coronary arteries and their position (with bicuspid valves there are anatomical variations), as well as the height of the sinus of Valsalva, represent a diagnostic imperative. Coronary angiography is also a therapeutic procedure, because there is no doubt that the TAVI trend is increasingly applied to younger patients. In this regard, the technology in the hybrid halls will certainly enable the appearance of new catheters (guides) which, depending on the TAVI model, will be selectively applied. Assessment of the size of the aortic root and the ascending aorta belongs to the routine examination.

CT has a very important role in periprocedural planning. The scanner with contrast enables selection of access and visualization of the geometry/dimensions of the valve and aortic root. The approach can be transfemoral, transapical, transaxillary (subclavian), transaortic. The approach itself and its selection represent a very complex topic that requires a separate article, so only a few basic features will be listed here. Transfemoral is the most frequently applied and involves the inner diameter of the blood vessel a. Femoralis/ Iliacae of at least 5.5 mm. The transapical approach is an alternative and is used in patients with marked atherosclerosis in the femoral/iliac blood vessels in whom the transfemoral approach is contraindicated, as well as in the case of kinking of the blood vessels of the pelvis. TAVI implantation through the subclavian artery is a very elegant method that can only be used in centers of high expertise. The transaortic approach is a rarity and does not represent a daily standard in hybrid interventions. By measuring the size of the aortic annulus, we obtain data on the size of the diameter of the prosthesis. This radiological method also accurately determines the height between the coronary ostium and the annulus, as well as the calcifications that extend into the outflow tract of the left ventricle (most often on the front cusp of the miral valve).

The role of the HEART team in the treatment of this valvular disease is the basis and all diagnostic methods would not be useful if there was not a team of doctors who look at the entire clinical picture of a patient in whom TAVI per se is already indicated. Namely, in addition to scores that make it easier for us to set an operative indication, there are other conditions that provide information about the patient. The table will list certain general, anatomical and clinical characteristics as auxiliary guidelines in operative therapy.

Conclusion

Cardio - medicine today has several TAVI systems available in the treatment of aortic stenosis. The basic characteristics of modern models are listed in the text. The approach to the treatment of aortic stenosis requires the expertise of the entire team of doctors. Considering the well-known growth trend of this procedure and the emergence of an increasing number of centers, careful selection of patients is of primary importance. Absolute commitment to its performance is imperative in order to maintain procedural results and thereby prevent uncontrolled commercialization of this technique. Good knowledge of the patient himself and the possibilities available to us oblige us to know the differences between TAVI "providers". Today's systems differ in the postoperative incidence of pacemaker implantation, paravalvular disease (PVL) as well as the implantation approach depending on the anatomy of the patient and the characteristics of the prosthesis itself, further, eventual intervention on coronary blood vessels, hemodynamics, etc. There are currently no studies covering these complex issues, so valve selection remains subjective and should therefore always be considered by an interdisciplinary TAVI team.

References

1. Abdel-Wahab M, Mehilli J, Frerker C, et al. Comparison of balloon-expandable vs self-expandable valves in patients undergoing transcatheter aortic valve replacement: the CHOICE randomized clinical trial. JAMA 2014;311:1503–1514.
2. Abdelghani M, Mankerious N, Allali A, et al. Bioprosthetic valve performance after transcatheter aortic valve replacement with self-expanding versus balloon-expandable valves in large versus small aortic valve annuli: insights from the CHOICE trial and the CHOICE-extend registry. JACC Cardiovasc Interv 2018; 11:2507–2518.
3. Abramowitz Y, Maeno Y, Chakravarty T, et al. Aortic angulation attenuates procedural success following self-expandable but not balloon-expandable TAVR. JACC Cardiovasc Imaging 2016; 9:964–972.
4. Alnasser S, Cheema AN, Simonato M, et al. Matched comparison of self-expanding transcatheter heart valves for the treatment of failed aortic surgical bioprosthesis: insights from the valve-in-valve international data registry (VIVID). Circ Cardiovasc Interv 2017;10(4):e4392.

5. Bruschi G, de Marco F, Botta L, et al. Direct aortic access for transcatheter self-expanding aortic bioprosthetic valves implantation. Ann Thorac Surg 2012;94:497–503.
6. Cerillo AG, Griese D, Berti S. Successful percutaneous implantation of symetis ACURATE neo transcatheter aortic bioprosthesis for the treatment of pure aortic regurgitation. Catheter Cardiovasc Interv 2016; 88:319–323.
7. Coughlan JJ, Kiernan T, Mylotte D, et al. Annular rupture during transcatheter aortic valve implantation: predictors, management and outcomes. Interv Cardiol 2018; 13:140–144.
8. Dvir D, Webb J, Brecker S, et al. Transcatheter aortic valve replacement for degenerative bioprosthetic surgical valves: results from the global valve-in-valve registry. Circulation 2012;126: 2335–2344.
9. Fujita B, Schmidt T, Bleiziffer S, et al. Impact of new pacemaker implantation following surgical and transcatheter aortic valve replacement on 1-year outcome. Eur J Cardiothorac Surg 2020; 57:151–159.
10. Gorla R, De Marco F, Garatti A, et al. Impact of aortic angle on transcatheter aortic valve implantation outcome with Evolut-R, Portico, and Acurate-NEO. Catheter Cardiovasc Interv 2020. https://doi.org/10.1002/ccd.28957
11. Holzamer A, Kim WK, Ruck A, et al. Valve-in-valve implantation using the ACURATE Neo in degenerated aortic bioprostheses: an international multicenter analysis. JACC Cardiovasc Interv 2019; 12:2309–2316.
12. Jagielak D, Stanska A, Klapkowski A, et al. Transfermoral aortic valve implantation using self-expanding new valve technology (NVT) Allegra bioprosthesis: a pilot prospective study. Cardiol J 2019. https://doi.org/10.5603/CJ.a2019.0019
13. Mack MJ, Leon MB, Thourani VH, et al.Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. N Engl J Med 2019;380:1695–1705.
14. Sondergaard L, Rodes-Cabau J, Linke AH-P, et al.Transcatheter aortic valve replacement with a repositionable self-expanding prosthesis: the PORTICO-I trial 1-year outcomes. J Am Coll Cardiol 2018;72:2859–2867.
15. Tarantini G, Nai Fovino L, Le Prince P, et al. Coronary access and percutaneous coronary intervention up to 3 years after transcatheter aortic valve implantation with a balloon-expandable valve. Circ Cardiovasc Interv 2020;13:e8972

Sažetak

Individualni pristup terapiji aortne stenoze pomocu savremenih TAVI proteza

Nikola Zarić

Schüchtermann Klinik, Bad Rothenfelde, Nemačka

Terapija teške, simtomatske, aortne stenoze se proteklih godina promenila. Medicinsko - tehnološki pomak se predstavio razvojem TAVI (transcatheter aortic valve implantation) koncepta. Naime, ranija terapija je podrazumevala konvencionalnu, hirurško zamenu aortne valvule sa jedne i sa druge strane konzervativnu, relativno efikasnu balon-valvuloplastiku kod pacijenata sa visokim rizikom. Danas postoji mogućnost da nekada inoperabilnim pacijentima kao i pacijentima visokog rizika možemo pomoći transkateterskom implantacijom aortnog zaliska. Zahvaljujući uporedom razvoju medicine i tehnologije , postoji više TAVI sistema na raspolaganju. Uzimajuci u obzir konvecionalni i medikamentozni terapijski pristup, odluka o načinju lečenja najbolje može biti sprovedena od strane HEART tima (kardiolog, kardiohirurg, radiolog, anesteziolog). Pažljivo razmatrajući anatomske i kliničke karakteristike svakog pacijenta ponaosob, možemo odlučiti koji tip aortne proteze omogućava pacijentu maksimalni terapijski benefit.

U daljem tekstu ce biti navedene osnovne karakteristike TAVI sistema koji se, u skladu sa kliničkim rezultatima najčešće primenjuju, kao i osobine pacijenata u kojih je TAVI već indikovan.

Ključne reči: aortna stenoza, TAVI

Srce i krvni sudovi 2022; 41(2): 52-55

Case report

Interventional cardiology in Serbia during COVID-19 pandemic for the period of 2019-2022

Milan A Nedeljković[1,2], Vladimir Mitov[3], Milan Nikolić[3], Aleksandar Jolić[3], Dragana Adamović[3], Marko Dimitrijević[3], Branko Beleslin[1,2]

[1]Cardiology Clinic, University Clinical center Serbia, [2]Medical Faculty, University of Belgrade, [3]Departmnet of invasive cardiology, Health center Zaječar

Abstract

Background: The aim of this study was to analyze the trends in catheterization laboratory procedures during COVID-19 pandemic for the 2019-2022 period.

Methods: Presentation of results in the interventional treatment of coronary artery disease and, to a lesser extent, structural heart diseases procedures in Cath Labs in Serbia in the 2019-2021 period.

Results: In 2019, in the territory of the Republic of Serbia, interventional cardiology practice was carried out in 17 centers (of which 10 tertiary and 7 secondary level health care centers within general hospitals) with a total of 28 cardiac catheterization labs. Meanwhile, general hospital Novi Pazar and Cuprija cath lab also started to work, so that there are currently 19 state owned centers in the territory of the Republic of Serbia where interventional cardiology procedures are carried out.

In 2019, a total of 47,522 procedures were performed in all Cath Labs, of which: 30,884 coronary angiographies, 16,658 PCI procedures, 1,601 emergency (without STEMI) procedures, 5,345 primary PCI procedures with 24,879 stents implanted, as well as 26 TAVR procedures and 68 percutaneous ASD closure procedures. A total of 96 specialist doctors worked in these labs, along with 38 fellows in training. During 2020, there were a total of 31,052 procedures in all Cath Labs, of which: 19,260 coronary angiographies, 11,792 PCI procedures, 1,299 emergency PCI (without STEMI), 4,807 primary PCI procedures, and 17,499 stents implanted, plus 10 TAVR procedures and 54 percutaneous ASD closures. 109 specialist doctors and 28 fellows in training worked in all labs. In 2021, a total of 37,042 procedures were performed in all labs, including: 24,055 coronary angiographies, 12,987 PCI procedures, 2,248 emergency (without STEMI) PCI procedures, and 5,006 primary PCIs, plus 23 TAVR procedures and 59 percutaneous ASD closures. 110 specialist doctors and 28 fellows in training worked in all labs. In the first 9 months of 2022, a total of 155 TAVR procedures were performed, of which 122 were performed at the ICVD "Dedinje", 17 at the ICVD "Vojvodina" and 16 at the University Clinical Center of Serbia.

Conclusion: The work results in the field of interventional cardiology in Serbia are comparable to European countries, in many segments even with the most economically developed among them. A significant drop in the number of procedures performed in 2020 at the expense of elective procedures is noted, as an unequivocal impact of the COVID19 pandemic and an increase after that with a tendency to return to the pre-pandemic level.

Key words PCI, TAVR, COVID-19, STEMI network

Introduction

The era of development of interventional cardiology, which in addition to diagnostics involves therapeutic, percutaneous procedures on the heart and coronary arteries in the world, begins with the successful performance of the first balloon angioplasty by Andreas Gruntzing in Zurich on September 16, 1977[1]. Then percutaneous coronary balloon angioplasty was performed on an isolated lesion of the proximal LAD in a 38-year-old man with symptoms of stable coronary artery disease[1]. It is interesting that this patient was asymptomatic for the next 23 years and that when the symptoms reappeared in 2001, recoronarography was performed, which revealed that the previously treated coronary artery was patent[2]. However, initially the procedure itself was accompanied by frequent complications: 5-10% of patients had early stent thrombosis due to elastic recoil of the blood vessel, and up to 30% had clinically significant restenosis after 6 months of follow-up. With the later appearance of bare metal stents (FDA approved in 1987) and then drug-eluting

Address for correspondence: Prof. Milan A. Nedeljkovic, MD, PhD, Cardiology Clinic, University Clinical center of Serbia, Medical Faculty, University of Belgrade; E-mail: milanned@hotmail.com.

stents (DES), which were first FDA approved in 2003, there was a significant reduction in the rate of stent thrombosis and restenosis, leading to increasing number of procedures performed all over the world[3]. The first coronary balloon angioplasty in Serbia was performed in December 1981 at IKVD "Dedinje", and in the decades that followed, these procedures became widespread and new Cath Labs started to work in all regions of Serbia. The procedure of transcatheter implantation of a biological aortic valve (TAVR) was first performed in the world by Alan Cribier in Rouen on April 16, 2003[4], and since 2014, this procedure has been successfully performed in Serbia, and the first case series were published in Vojnosanitetski pregled in 2014[5]. The aim of this study was to analyze Cath Lab procedure trends in Serbia in the period of 2019-2022, during COVID-19 pandemic.

Methods

We presented the results of the invasive/interventional treatment of coronary artery disease and, to a lesser extent, structural heart diseases in the Cath Labs in Serbia in the period of 2019-2022. The presented data are indexed according to the size of the gravitating population and compared with the number and structure of procedures done in European countries.

Results

In 2019, on the territory of the Republic of Serbia, interventional cardiology practice was carried out in 17 centers (of which 10 tertiary and 7 secondary level within general hospitals) with a total of 28 cardiac catheterization labs. In the following 2020, the practice took place in 17 centers (10 tertiary and 7 secondary level health care), with the difference that in this calendar year, for technical reasons, there was no work in the General hospital of Čačak, and unlike the previous year, the practice was carried out in General hospital of Leskovac. In 2021, the practice was carried out in all 18 available centers in the state owned health care system along with one hospital from the private health sector (Achi Badem - Bellmedic). Meanwhile, the General hospital of Novi Pazar and Cuprija Cath Lab also started working, so there are currently 22 centers in the territory of the Republic of Serbia where interventional cardiology procedures are performed (19 state owned and 3 private).

In 2019, a total of 47,522 procedures were performed in all Cath Labs, of which: 30,884 coronary angiographies, 16,658 PCI procedures, 1,601 emergency (without STEMI) procedures, 5,345 primary PCI procedures with 24,879 implanted stents, as well as 26 TAVR procedures and 68 percutaneous ASD closure procedures. A total of 96 specialist doctors worked in all labs, along with 38 fellows in training.

During 2020, there were a total of 31,052 procedures in all cath labs done, of which: 19,260 coronary angiographies, 11,792 PCI procedures, 1,299 emergency PCI (without STEMI), 4,807 primary PCI procedures, and 17,499 stents were used, plus 10 TAVI procedures and 54 percutaneous ASD closures were performed. 109 specialist doctors and 28 fellows in training worked in all labs.

In 2021, a total of 37,042 procedures were performed in all labs, including: 24,055 coronary angiographies, 12,987 PCI procedures, 2,248 emergency (without STEMI) PCI procedures, and 5,006 primary PCIs, plus 23 TAVI procedures and 59 percutaneous ASD closures were performed. 110 specialist doctors and 28 fellows in training worked in all labs.

In the first 9 months of 2022, a total of 155 TAVR procedures were performed, of which 122 at the IKVD "Dedinje", 17 at the IKVD "Vojvodine" and 16 at the University Clinical Center of Serbia.

Discussion

Data review on Cath Lab network in the Republic of Serbia shows a clear tendency to start new ones while continuing the work of existing centers. A look at the data shows that in 2020 there were 34.7% total procedures less, 29.2% fewer PCI procedures, 10.1% fewer primary PCI procedures, and 29.7% fewer stents implanted. This is a clear consequence of the COVID-19 pandemic outbreak, which led to a reduction in the number, especially of the elective procedures in the cath labs. The fact that the smallest reduction was in terms of primary PCI procedures indicates that, even in pandemic envioreement, the most severe patients with STEMI were optimally treated using mechanical reperfusion therapy in vast majority of cases. In the following 2021, fewer procedures were also recorded than in 2019: 22.1% fewer total procedures, 22.1% fewer coronary angiographies, 22% fewer PCI procedures and only 6.3% fewer primary PCIs. However, in 2021, there is a clear trend toward increase in the number of all procedures based on the year most affected by the COVID-19 pandemic and indicates a reorganization of the health system. The reduction in the procedural volume in the Cath Labs during the 2020 pandemic was a global phenomenon. European Association for Percutaneous Coronary Interventions organized the research through web questionnaire on the 1-15 of April 2020 period among its members, and found that 27% of responders admitted reduced number of coronary angiography/pPCI in STEMI patients, and 10% completely stopped performing interventions in STEMI patients. When it comes to NSTEMI, 38% reduced and 9% stopped work; in chronic coronary syndrome, 89% reduced and 51% of participants completely stopped working in the cath lab. As many as 48% of responders indicated that there was a delay in reperfusion time in STEMI patients, and 28% indicated that there was an increase in the number of patients with mechanical complications of myocardial infarction and cardiogenic shock, 22% indicated that there was an application of fibrinolytic therapy from logistic reasons dictated by the pandemic[6].

In order to assess the current state of interventional cardiology procedures in Serbia, the absolute number of interventions performed annually is best translated into a rate per million population. In 2020, the European Association for Interventional Cardiology published Atlas

Project - Mapping of Interventional Cardiology[7], a survey conducted at the level of 16 associations' member states with the data for 2016. We compared these data with the rates of procedures performed in our country for the (pre-pandemic) 2019 - in the year of 2019, there were 2.45 hospitals with Cath Lab per million population in Serbia. In the aforementioned survey, the average was 3.44 cath Labs/million population; going from 1 in Egypt to 4.9 in Greece. The total number of Cath Labs ranged from 1 in Egypt to 11.8/million in Germany, an average of 5/million inhabitants (in Serbia 4.03/million inhabitants). In Serbia, there are 1.58 hospitals with Cath Labs working 24/7 per million population, which is on average seen in the research (from 0.2 in Egypt to over 4 in Poland and Belgium; average 2/million population). In the countries covered by the survey, there were an average of 16.7/million population of interventional cardiologists; from 4.3 in Romania to 53.3 in Germany (13.8 in Serbia). 5 131/ million diagnostic coronary angiograms were performed; from 2,500 in Egypt to over 7,000 in Turkey and Germany (in Serbia 4,45/million people). On average, 2,5 PCI procedures were performed/million population; from under 1 in Egypt to over 3 in Switzerland, Poland and Germany (Serbia 2,4). Very heterogeneous data were obtained for primary PCI procedures - from 37 in Egypt to over 600/million in Slovenia, Germany, Netherlands and Poland. STEMI network in Republic of Serbia is well developed and functional which is indicated by the fact that in Serbia there were 770 primary PCI procedures per million population[7]. This number represents an excellent result because the age standardized incidence and prevalence of cardiovascular diseases in Serbia is comparable to countries that gravitate to the European Society of Cardiology (in Serbia 1,273 and 6,992 compared to 1,133 and 6,595 per 100,000 population in thes ESC region in 2017 age[8].

Although the authors of the ESC Atlas project emphasize a good correlation between the gross national income per capita as a surrogate of the economic power of a country and the achievements in the field of interventional cardiology; in the case of Serbia, the correlation is not so linear. With 5,700 USD per capita in 2016, it is among countries with a medium-high GBI, and among the countries included in the research, it would be in the penultimate place, above Egypt. Nevertheless, most of the parameters are around or above the average values, especially the number of primary PCIs, which speaks of the good organization of intereventional cardiology service and the dispersiveness of the national STEMI network.

There are also segments in which interventional cardiology in our country is below average of the countries of the ESC region. When it comes to the use of intracoronary imaging in Serbia, there were 52.27/million people of PCI procedures guided by OCT or IVUS. In the 16 countries of the ESC region, the average was 166/million PCIs guided by intracoronary imaging. In 2016, there were 48.2/million TAVR procedures in the mentioned countries, with over 100 in highly developed countries (Germany, France, Denmark, Switzerland). In the same year, 1 TAVI procedure was performed in Serbia (0.14/million population)[7]. However, the program of transcatheter implantation of the aortic valve in Serbia started in 2014, much later than in many European countries, and the first results were published in 2016 in Vojnosanitetski Pregled[5]. In the following years, the number increased so that in the first nine months of 2022, 155 of these procedures were performed in Serbia. If the proportional trend of the number of performed TAVR procedures were to continue until the end of the calendar year, the number would reach 29.76/million people per year, which brings our results closer to those of the ESC region. It can be expected that in the years to come, interventional treatment of structural heart diseases in Serbia will be equally represented as in the member countries of the European Society of Cardiology.

Another issue to consider is the number of procedures performed in an individual center with a Cath Lab. A larger volume means experience in the treatment of the clinicaly most serious patients and improves the outcome of the treatment[9]. According to the professional associations in Great Britain data, in the April 2019 - March 2018 period, there were 30% of centers with a Cath Lab that performed less than 400 procedures per year and 15.1% with less than 200 procedures[10]. In Serbia in 2019, 29.3% of centers performed less than 400 and 17.6% less than 200 procedures, which is comparable to one highly developed European country. Due to the impact of the COVID-19 pandemic and the entry of many centers with Cath Labs to work with COVID-19 patients in 2021, as many as 10 out of 19 hospitals with Cath Lab had less than 400 PCI procedures and 6 of them had less than 200.

Conclusion

The results of the work in the field of interventional cardiology in Serbia are comparable to European countries, and in many segments with the most economically developed among them. A significant drop in the number of procedures performed in 2020 at the expense of elective procedures is noted, as an unequivocal impact of the COVID-19 pandemic and an increase after that with a tendency to return to the pre-pandemic levels.

References

1. Barton M, Grüntzig J, Husmann M, Rösch J. Balloon Angioplasty - The Legacy of Andreas Grüntzig, M.D. (1939-1985). Front Cardiovasc Med 2014 Dec 29;1:15
2. Meier B. The first patient to undergo coronary angioplasty - 23-years follow-up. NEJM 2001;344:144-145
3. Canfield J, Totary-Jain H. 40 Years of percutaneous coronary intervention: history and future directions. J Pers Med 2018; 8(4):33.
4. Cribier A. Development of transcatheter aortic valve implantation (TAVI): a 20-year odyssey. Arch Cardiovasc Dis 2012; 105(3):146-152.
5. Nedeljković MA, Beleslin B, Tešić M, et al. Perkutana implantacija samooslobađajuće aortne valvule kod visokorizičnih bolesnika sa teškom aortnom stenozom - prva iskustva u Srbiji. Vojnosanitetski pregled 2016;73(2), 192-197.
6. Roffi M, Capodanno D, Windecker S, et al. EuroIntervention 2020;16:247-250.
7. Barbato E, Noc M, Baumbach A. Mapping interventional cardiology in Europe: the European Association of Percutaneous

Cardiovascular Interventions (EAPCI) Atlas Project, Eur Heart J 2020;41(27),2579–2588.
8. Timmis A, Townsend N, Gale CP, et al. European Society of Cardiology: Cardiovascular Disease Statistics 2019. Eur Heart J 2020;41(1):12–85.
9. Saito Y, Tateishi K, Kanda M, et al. Volume-outcome relationships for percutaneous coronary intervention in acute myocardial infarction. J Am Heart Assoc 2022;11(6):e023805.
10. National audit of percutaneous coronary intervention (NAPCI). 2021 NAPCI Summary Report.

Sažetak

Interventna kardiologija u Srbiji za vreme COVID-19 pandemije za period 2019-2022

Milan A Nedeljković[1,2], Vladimir Mitov[3], Milan Nikolić[3], Aleksandar Jolić[3], Dragana Adamović[3], Marko Dimitrijević[3], Branko Beleslin[1,2]

[1]Klinika za kardiologiju, Univerziteteski klinički centar Srbije, [2]Medicinski fakultet, Univerzitet u Beogradu, [3]Odeljenje invazivne kardiologije, Zdravstveni centar Zaječar

Uvod: *Cilj rada je bio analiza trenda procedura u Sali za kateterizaciju u vremem COVID-19 pandemije za vreme 2019-2022 godina.*
Metode: *Prikaz rezultata u interventnom lečenju koronarne arterijske bolesti i, u manjoj meri, strukturnih bolesti srca razgranate mreže angio sala u Srbiji u periodu 2019-2021. godine.*
Rezultati: *U 2019. godini na teritoriji Republike Srbije interventna kardiološka praksa sprovođena je 17 centara (od toga 10 tercijernog i 7 sekundarnog nivoa zdravstvene zaštitite u sklopu opštih bolnica) sa ukupno 28 sala za kateterizaciju srca. U međuvremenu počela je sa radom i angio sala u OB Novi Pazar i OB Ćuprija tako da aktuelno na tertiriji Republike Srbije postoji 19 centara u vlasništvu države u kojima se sprovode interventno kardiološke procedure.*
U 2019. godini u svim angio sala urađeno je ukupno 47 522 procedure od toga: 30 884 koronarografije, 16 658 PCI procedura, 1 601 hitna (bez STEMI) procedura, 5 345 primarnih PCI procedura uz 24 879 ugraađenih stentova. Urađeno je 26 TAVI procedura i 68 procedura perkutanog zatvaranja ASD-a. U svim salama radilo je ukupno 96 lekara specijalista uz 38 lekara na obuci. Tokom 2020. godine bilo je ukupno 31 052 procedure u svi angio salama a od toga: 19 260 koronarografija, 11 792 PCI procedure, 1 299 hitnih PCI (bez STEMI), 4 807 primarnih PCI procedura i pri tome utrošeno 17 499 stentova. Urađeno je 10 TAVI procedura i 54 perkutanih zatvaranja ASD-a. U svim salama radilo je 109 lekara specijalista i 28 lekara na obuci. U 2021. godini urađeno je u svim salama ukupno 37 042 procedure od toga: 24 055 koronarografija, 12 987 PCI procedura, 2 248 hitnih (bez STEMI) PCI procedura, 5 006 primarnih PCI. Urađeno je 23 TAVI procedura i 59 perkutanih zatvaranja ASD-a. U svim salama radilo je 110 lekara specijalista i 28 lekara na obuci.U prvih 9 meseci 2022. godine urađeno u ukupno 155 TAVI procedura od toga 122 na IKVB "Dedinje", 17 na IKVB "Vojvodine" i 16 u Univerzitetskom kliničkom centru Srbije.
Zaključak: *Rezultati rada u oblasti interventne kardiologije u Srbiji uporedivi su sa zemljama Evrope, u mnogim segmentima sa ekonomski najrazvijenijima među njima. Beleži se značajan pad broja izvedenih procedura u 2020. godini na račun elektivnih procedura, kao nedvosmislen uticaj COVID'19 pandemije i porast nakon toga sa tendencijom povratka na prepandemijski nivo.*

Ključne reči: PCI, TAVI, COVID-19, STEMI mreža

NOVA LK

Sponsori/Sponsors

AMICUS
a Swixx BioPharma company

BAYER

Boehringer Ingelheim

AstraZeneca

ADOC

PHARMASWISS
A Valeant Pharmaceuticals International, Inc. company

АЛКАЛОИД
СКОПЈЕ

Medtronic

Pfizer

Galenika

NOVARTIS

Actavis

SERVIER

AbelaPharm

BERLIN-CHEMIE
MENARINI

KRKA

PROTOPHARMA

intrex

INPHARM

Hemofarm
STADA GRUPA

Takeda

UNION-MEDIC
NOVI SAD

Pfizer

Značajna otkrića koja menjaju živote pacijenata.

Pfizer SRB d.o.o., Trešnjinog cveta 1/VI, 11070 Novi Beograd
tel. 011 363 0000, email: office_serbia@pfizer.com

PP-PFE-EEP-0335
Datum pripreme: januar 2021

Diupot®
eplerenon

SMANJIMO SMRTNI ISHOD

SIGURNOSNI POJAS
za srce Vašeg pacijenta

Samo za stručnu javnost
Lek se može izdavati samo uz lekarski recept.
Detaljnije informacije o leku možete naći u Sažetku karakteristika leka. Datum revizije teksta: Mart 2019.
Nosilac dozvole za stavljanje leka u promet: PharmaSwiss d.o.o., Batajnički drum 5A, Beograd
Broj i datum izdavanja dozvole za stavljanje leka u promet:
Diupot, 25mg film tablete: 515-01-05108-16-001 od 15.03.2019.
Diupot, 50mg film tablete: 515-01-05106-16-001 od 15.03.2019.
ALIMS broj rešenja: 515-08-00365-19-001

PHARMASWISS

EPLERENO-RS-19-8-106-M

Medtronic

Evolut™ PRO

TAVI System

Xerdoxo®

Rivaroksaban

KRKA

Naše inovacije i naša znanja za efikasne proizvode visokog kvaliteta.

Ticagrex®

tikagrelor

90 mg, 60 mg

NA DUGE STAZE

Lek se može izdati samo uz lekarski recept.

Samo za stručnu javnost.

Trombocen®

rivaroxaban

ČISTI SVOJ PUT!

Hemofarm
STADA GRUPA

BERLIN-CHEMIE
MENARINI

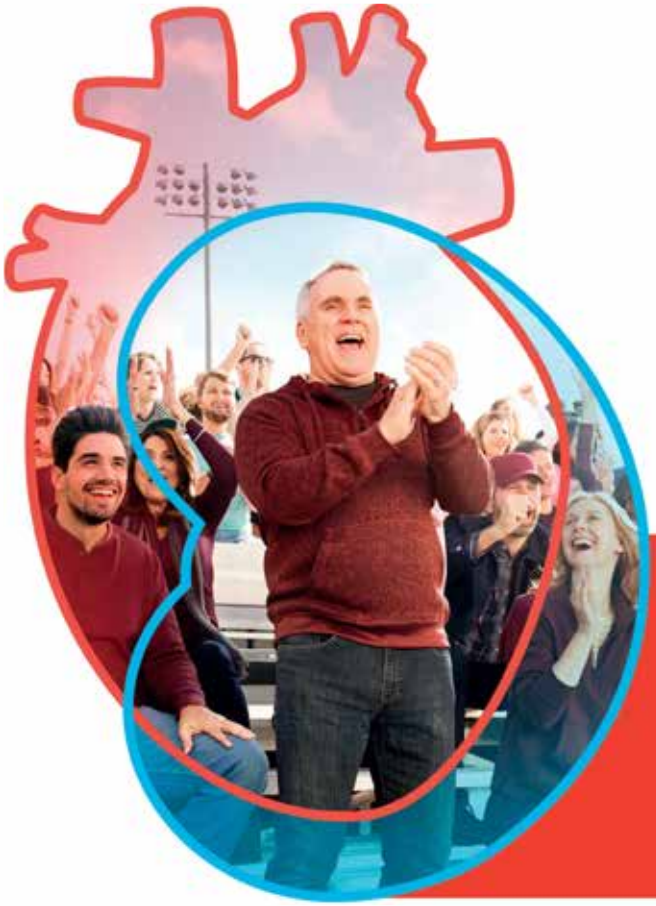
SR_BCM-09-2021_V1_printreminder

Obezbedite Vašem srcu DVOSTRUKU prevenciju

Cardiovitamin® FD3 doprinosi:

- Normalnoj funkciji srca
- Normalnom metabolizmu homocisteina
- Normalnom stvaranju kolagena za funkciju krvnih sudova
- Zaštiti ćelija od oksidativnog stresa
- Smanjenju umora i iscrpljenosti
- Normalnoj apsorpciji i iskorišćenju kalcijuma i fosfora

Dajte Vašem srcu šansu!



forxiga®
(dapagliflozin)

FORXIGA® je PRVI SGLT2i odobren za lečenje simptomatskih pacijenata sa HFrEF u SRBIJI

- **FORXIGA®** redukuje **rizik za KV smrt** i **pogoršanje HF** uz olakšanje simptoma[2,4]
- SGLT2i sa dokazanom **redukcijom KV** i **ukupnog mortaliteta** nezavisno od prisustva T2D[2,3]
- Jednostavno doziranje **10 mg jednom dnevno**, bez titracije[1]

KV - kardiovaskularni T2D - dijabetes tipa 2 HFrEF - srčana insuficijencija sa redukovanom ejakcionom frakcijom SGLT2i - inhibitor natrijum glukoznog kotransportera 2

Reference: 1. Sažetak karakteristika leka Forxiga®, poslednja revizija teksta decembar 2021. **2.** McMurray JJV, et al. *N Engl J Med* 2019;381:1995–2008 **3.** M. Packer et al. NEJM 383;15, October 2020. **4.** Docherty kf et al. eur heart j. 2020; 41, 2379–2392

Broj dozvole: 515-01-01758-19-001 od 30.01.2020.

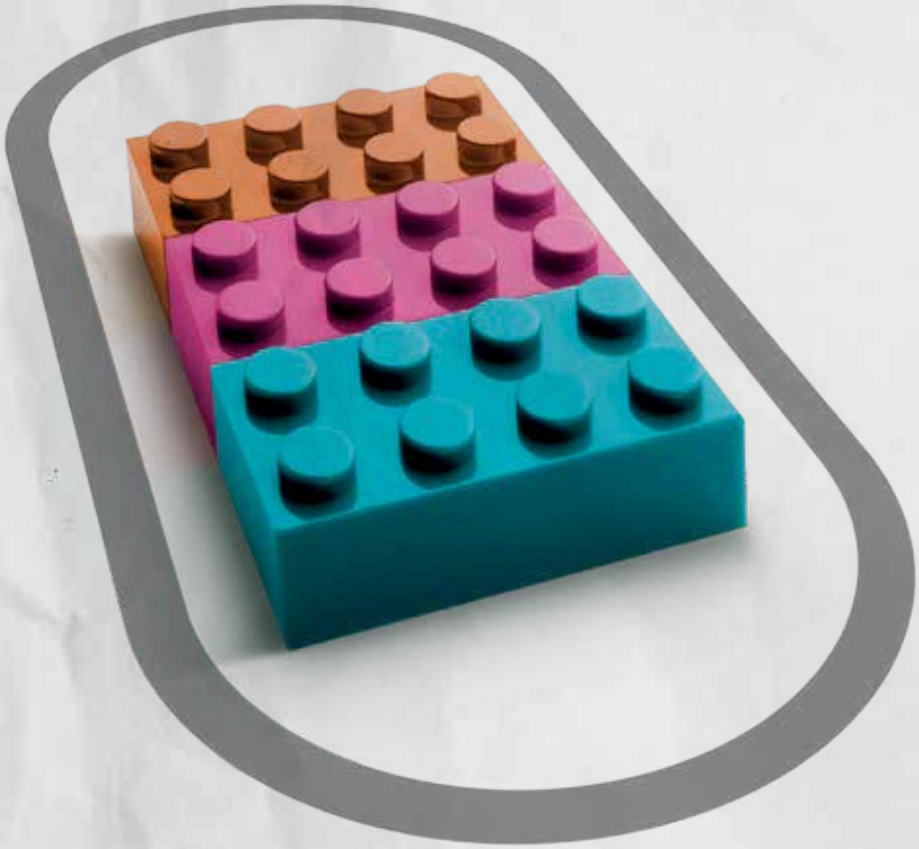
AstraZeneca

Predstavništvo AstraZeneca UK Ltd
Milutina Milankovića 1i, Beograd - Novi Beograd
Tel: 011 3336 900 • Fax: 011 3336 901
SAMO ZA STRUČNU JAVNOST

RS-2060, Oktobar 2021.

trinomia

atorvastatin • acetilsalicilna kiselina • ramipril



AMICUS
a Swixx BioPharma company

Ukoliko Vam je potrebna medicinska informacija o leku kompanije Boehringer Ingelheim molimo Vas pozovite kontakt telefon 011 / 311 59 60 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 2022. | PC-RS-100347

Boehringer Ingelheim

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

SAMO ZA STRUČNU JAVNOST