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HEART AND BLOOD VESSELS

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Original article

What we have learned from the Regional Pulmonary Embolism Registry (REPER)?

Slobodan D. Obradovic[1,2] , Ivica R. Djuric[1], Boris M. Dzudovic[2,3], Bojana N. Subotic[1], Jelena M. Dzudovic[4], Jovan A. Matijasevic [5,6], Marija D. Benić[5], Sandra M. Pekovic [5], Jadranka Trobok[5], Sonja S. Salinger[7], Irena Mitevska[8], Marijan Bosevski[8], Ljiljana V. Kos[9], Tamara Kovacevic-Preradovic[9], Stefan M. Simovic[10], Ema Jevtić[10], Maja Nikolić[10], Vladimir M. Miloradovic[10], Ana M. Kovacevic-Kuzmanovic[11], Tanja D. Savicic[11], Bjanka Z. Bozovic[12], Nebojsa S. Bulatovic [12,13], Srdjan V. Kafedzic [14], Sasa S. Pancevacki [15], Bojan Mitrovic[14], Milica Radovic[14], Aleksandar N. Neskovic [14,16], Nikola I. Kocev [17], Jelena M. Marinković[17]

[1]Clinic of Cardiology, Military Medical Academy, Belgrade, Serbia, [2]School of Medicine, University of Defense, Belgrade, Serbia, [3]Clinic of Emergency Internal Medicine, Military Medical Academy, Belgrade, Serbia, [4] National Poison control center, Military Medical Academy, Belgrade, Serbia, [5]Institute for Pulmonary Diseases of Vojvodina, Serbia, [6]School of Medicine, University of Novi Sad, Serbia, [7]Clinic of Cardiology, Clinical Center Nis, University of Nis, Serbia, [8]Clinic of Cardiology, School of Medicine University of Skopje, North Macedonia, [9]Clinic of Cardiology, Clinical Center Banja Luka, School of Medicine, University of Banja Luka, Republic of Srpska, Bosnia and Herzegovina, [10]Clinic of Cardiology, Clinical Center Kragujevac, School of Medicine, University of Kragujevac, Serbia, [11]Department for Internal Medicine, General Hospital Pancevo, Serbia, [12]Clinic of Cardiology, Clinical Center Podgorica, Montenegro, [13]School of Medicine Podgorica, University of Podgorica, Montenegro, [14]Department of Cardiology, Clinical Hospital Center Zemun, Serbia, [15] Intensive Care Unit, Clinic of Internal Medicine, Clinical Hospital Center Zemun, Serbia, [16]School of Medicine Belgrade, University of Belgrade, Serbia, [17] Institute for medical statistics School of Medicine, University of Belgrade, Serbia

Abstract

Introduction. The management of acute pulmonary embolism (PE) is still full of controversies, and the number of randomized trials in this field is relatively small. For the individual doctor and the health system who deal with acute pulmonary embolism it is very important to analyze the number of treated patients, hospital and out of hospital mortality and morbidity, how the patients' treated, what are the most important obstacles for the management of the disease.

Methods. Here, we present the Regional PE registry (REPER), in brief its development, purposes and the scientific results published in the journals on the scientific citation list, doctor thesis and studies accepted and presented at the European Society of Cardiology annual congress. This is academic initiated, non-interventional research and the patients are informed and gave their permission to be part of the registry. However, no public patient's personal data was used. The basic criterion for the enrollment is objectively proven (positive CT-pulmonary angiography) acute PE.

Results. The REPER was found as the single center PE registry at 2011 which enrolled patients hospitalized for the acute PE in the clinic of Internal Emergency Medicine of Military Medical Academy. As we realized that one institution could not have enough patients with acute PE to create the valid registry, we started to join other institutions under the principles of transparency and equality, and the first two were Institute for Pulmonary Diseases Vojvodina and Clinical Center Nis, which enrolled high number of patients from 2015. The registry became an international when the Clinical Center of Banja Luka joined as, followed by Clinical Center of Podgorica and Skopje. Till now, 1776 patients with acute PE are enrolled in the data base with more than 300 variables. During the last 5 years, 15 original scientific articles were published with the cumulative impact factor of 39.2, 5 doctor thesis were defended, and 5 scientific researches were presented at the ESC meeting.

Conclusion. For the clinician scientist it is crucial to develop qualitative data-base with as many as possible variables which are important for the understanding pathophysiology, diagnostic process and therapy management of the disease in focus. For that it is vital to cooperate with other doctors and institutions. We think that this registry full-filled their purpose, and thanks for these data our knowledge about PE is much deeper and we become better doctors.

Kew words pulmonary embolism, registry, treatment, risk stratification, bleeding

Address for correspondence: Prof. dr Slobodan Obradovic, MD, PhD, 1Clinic of Cardiology, Military Medical Academy, Belgrade, Serbia.
E-mail: sloba.d.obradovic@gmail.com

Introduction

The Regional Pulmonary Embolism Registry (REPER) has been found as the single center registry of the hospitalized acute pulmonary patients in the Military Medical Academy at 2011. As we could not enroll enough patients for the qualitative scientific work, we decided to call other institutions to join us. The Institute of Pulmonary Diseases Vojvodine has become the first hospital that become the member of the multicenter PE registry. After that, permanently or transiently, several institutions joined to the registry, and from the period of 2015 to 2022 we enrolled 1776 patients with acute PE in our regional registry. Besides the Institute for pulmonary diseases Vojvodine, Clinical Center Nis, Kragujevac, Zemun and Zvezdara (for some period) and general hospital Pancevo became the part of the registry. From 2016 Clinical Center Banja Luka and after that Clinical Center Podgorica and Skopje became the multinational members of the registry. The number of enrolled patients regarding the institutions are presented in Figure 1.

During the period of 2015-2022, we managed to publish 15 articles in-extenso in the journals on the SCI list with the cumulative impact factor of 39.265, we had 6 accepted abstracts on the European Society of Cardiology congress, 5 doctor thesis are defended till know and one monography was published[1-27]. Several studies from our registry are currently under review in the journals ranking M21 and M22.

Here, we aimed to summarize the main published results from the REPER registry.

Risk stratification

We studied the role of pre-existing heart failure in the respect of all-cause, and PE-related hospital mortality in patients with acute PE. Heart failure with reduced ejection fraction was the independent predictor for 7-day hospital death in our cohort of 1201 patient (hazard ratio 2.22, 95% confidence interval 1.25-4,38.41, P=0.021)[1]. Glomerular filtration rate was also independent risk factor for hospital death, HR was 7.109 for GFR<30 ml/min, and 2.554 for GFR<60 ml/min)[2].

Electrocardiographic changes during acute PE were also important for the early risk stratification and the estimation of the efficacy of initial therapy. In the subgroup of 110 patients with intermediate-high and high risk PE we have found that early resolution (<72 h) of S waves in the first precordial lead and aVL lead were associated to better right ventricle function after few days and lower hospital mortality rate[3]. Early resolution od S waves was more often and earlier achieved in patients who were treated with thrombolytic therapy. This result is similar to the significance of ST segment resolution during the treatment of ST elevation myocardial infarction and shdismal owed the presence of re-perfused lungs.

Finely, we studied the role of gender to the prediction of acute PE. Hence, we have found that syncope has negative predictive value for hospital mortality only in women, and not in men[4]. One of the important finding

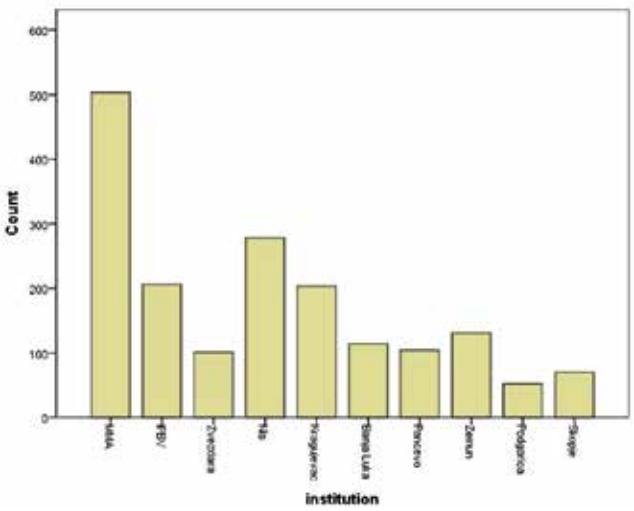

Figure 1. The number of patients from the various institutions which participate in the REPER

from our registry is that tachycardia at admission have had predictive value for early death only in women, and not in men[5]. Sinus tachycardia was also more important dismal sign for younger PE patients that for older[6] (ESC congress 2017).

We also investigated the prognostic role of symptomatic lower limb deep vein thrombosis, and our results pointed out that the presence of these symptoms at admission in patients with intermediate-high PE was associated with better prognosis and that was safe to use thrombolytic therapy in these patients[7].

Biomarkers

Considering biomarkers, we compare the predictive values regarding early death, for four biomarkers, cardiac troponin (cTn), brain natriuretic peptides (BNPs), C reactive protein and D-dimer in spontaneous versus provoked PE, and in the subgroups of provoked PE (major transient, major persistent, minor transient and minor persistent factors). We have found that elevated BNP is the most useful biomarker for predicting early death in acute PE whatever the cause of PE[8-10]. We also directly compared BNP-s x URL and cTn-s x URL (upper rate limit) in the cohort of 758 patients who had measured both markers at admission, and our data is going to conclusion that quantitative elevation of BNPs are much more accurate for prediction early PE death than cTn-s[11] (ESC Congress 2022).

We also studied the value of admission glycaemia for the prediction of hospital death in diabetic versus non-diabetic acute PE patients. We have found than only in diabetic patients, admission glycaemia had significant association with hospital death[12].

The special attention we dedicated to the prognostic role of various coagulation and anticoagulation protein activities during the first 24 hours from admission to PE severity and early death. We have found that lower antithrombin activity was associated to more severe PE presentation and early death[13,14].

Inflammation might play important role for the outcome of spontaneous PE, since CRP levels were signifi-

cant predictor of hospital mortality in this cohort of patients[15,16].

Bleeding in acute pulmonary embolism patients

The problem of bleeding was a central problem and the focus of our investigation for many years. Indeed, the foundation of REPER has begun as an attempt to make a score for the prediction of bleeding in acute PE, and to use it as a tool for the choice of treatment modality. We started with the small study presented at the ESC 2016 Congress, with comparison of 3 scores (simplified PESI, CHA2DS2-VASc and HAS-BLED scores) for the prediction of net adverse event (both death and major bleeding), and the HAS-BLED score had the best performance for this goal[17].

After a very long and hard scientific journey we succeeded to publish our investigation – Pulmonary Embolism Bleeding Score Index (PEBSI score) in the Thrombosis Research this year. We created 5-element's score for the prediction of low risk for bleeding on thrombolytic therapy[18]. Patients who had low risk for major bleeding according to the score have had 2.8% chance of major bleeding during the first seven days from the admission to hospital compare to patients with higher score who had 18.6% chance for major bleeding.

Therapy in acute pulmonary embolism

At the 2015 ESC Congress we presented the study about the efficacy and safety of rivaroxaban in patients with acute PE who were previously treated with thrombolytic therapy[19]. These kind of patients were excluded from the direct oral anticoagulant (DOAC) trials in venous thromboembolism. We have showed that in this high-risk group of patients rivaroxaban was efficacious and safe as the combination of heparins and vitamin K antagonists was.

Military Medical Academy is the pioneer for the catheter directed therapy (CDT) in acute PE. The first balloon angioplasty in subacute PE was performed at 2003 (20), and the first catheter directed thrombolysis with ultrasound facilitated system was used in October 2013. Since then Institute of Pulmonary Diseases Vojvodine and Clinical Center Kragujevac also developed teams which performed catheter directed therapy. 101 patients with acute PE treated with CDT were included in our REPER registry till now.

We published part of these results comparing no-reperfusion to classic systemic thrombolytic therapy with ultrasound assisted catheter thrombolysis in patients with intermediate-high risk PE patients[21,22]. We have achieved the lowest mortality rate in CDT therapy group with the similar rate of major bleeding with systemic thrombolysis.

We also have showed that slow-low dose tPA, (1-5 mg/h, maximum dose 20-50 mg) given either by intravenous or local infusion through the catheter, reduced hospital mortality compare to classic high-dose, faster tPA protocols in the intermediate-high risk patients[23].

Different DOACs have different risk for bleeding, especially gastrointestinal bleeding. We tested the hypothesis that all three DOACs used in Serbia (dabigatran, rivaroxaban and apixaban) have different hemostasis profile one month after stable anticoagulation in patients with acute PE. Patients on apixaban have the highest activity of prothrombin under the drug, and that could explain the lowest rate of bleeding on apixaban together with the most balanced anticoagulation pharmacokinetics[24,25]. This also might partly explain the less efficacy of the lower apixaban dose for the prevention of thromboembolic events. Dzudovic J et al, also developed the original method for the measurement of apixaban blood concentrations[26].

Timing for death in acute PE in respect of PE mortality risk is important for the strategy of planning PE management. According to our results 50% of fatal cases were occurred during the first hospitalization day in high risk PE, and 10% of fatal cases (from the whole group of patients who died during hospitalization) per day for the first 5 days occurred in intermediate-high risk PE. Interestingly about 50% of patients who died from PE died after the fifth hospitalization day in the intermediate-high risk subgroup[27].

Finely, the work on this registry resulted to our participation in the current ESC guidelines for the catheter directed therapy in acute pulmonary embolism[28].

Conclusion

For the clinician scientist, it is crucial to develop qualitative data-base with as many as possible variables which are important for the understanding pathophysiology, diagnostic process and therapy management of the disease in focus. For that it is vital to cooperate with other doctors and institutions. We think that this registry fullfilled their purpose, and thanks for these data our knowledge about PE is much deeper and we become better doctors.

References

1. Obradovic S, Dzudovic B, Subotic B, et al. Predictive value of heart failure with reduced versus preserved ejection fraction for outcome in pulmonary embolism. ESC Heart Failure 2020; 7(6): 4061-4070.
2. Salinger-Martinovic S, Dimitrijevic Z, Stanojevic D, et al. Renal dysfunction as intrahospital prognostic indicator in acute pulmonary embolism. Int J Cardiol 2020;302:143-149.
3. Novicic N, Dzudovic B, Subotic B, et al. Electrocardiography changes and their significance during treatment of patients with intermediate-high and high-risk pulmonary embolism. Eur Heart J Acute Cardiovasc Care 2019; 9(4):271-278.
4. Dzudovic B, Subotic B, Novicic N, et al. Sex-related difference in the prognostic value of syncope for 30-day mortality among hospitalized pulmonary embolism patients. Clin Respir J 2020; 14(7):645-651.
5. Matijašević J, Mirić M, Trobok Vučićević J, et al. Sex-specific differences and risk factors for 30-day mortality in acute pulmonary embolism – Results from the Serbian Multicenter Pulmonary Embolism Registry. VSP in press 2021.
6. Obradovic S, Dzudovic B, Subotic B, et al. Heart rate is better than arterial systolic pressure at admission for the risk stratification in younger patients with pulmonary embolism. Eur Heart J Suppl 2017, ESC Congress 2017.
7. Obradovic SD, Dzudovic BM, Subotic BN, et al. Prognostic significance of symptomatic deep vein thrombosis in patients with acute

symptomatic pulmonary embolism regarding the European Society of Cardiology mortality risk model. Int Angiol 2022; 41(4):338-345.
8. Jovanovic **Lj**, Subota V, Stavric M, et al. Biomarkers for the prediction of early pulmonary embolism related mortality in spontaneous and provoked thrombotic disease. Clin Chim Acta 2019; 492:78-83.
9. Jovanović Lj, Subota V, Stavrić M, et al. Different predictive value for short-term all-cause mortality with commonly used biomarkers regarding the cause of pulmonary embolism. Vojnosanit Pregl 2021; 78(5): 542–548.
10. Jovanović Lj. Značaj određivanja humoralnih biomarkera iz venske krvi u predviđanju ishoda kod različitih podgrupa bolesnika sa plućnom embolijom. Doktorska teza, MF Kragujevac 2021.
11. Dzudovic B , Matijasevic J, Salinger S, Obradovic S. Increased B-type natriuretic peptide is a better predictor of hospital mortality then increased troponin in patients with acute pulmonary embolism. Eur Heart J Suppl, ESC Congress 2022.
12. Jovanovic Lj, Rajkovic M, Subota V, et al. Predictive value of admission glycemia in diabetics with pulmonary embolism compared to non-diabetic patients· Acta Diabetologica 2022; 59(5): 653-659.
13. Dzudovic B, Dzudovic J, Subotic B, Obradovic S. Antithrombin activity is a significant predictor of early mortality in pulmonary embolism patients. Vojnosanitetski pregled 2021; Online First December, 2021.
14. Dzudovic B. Prediktivna vrednost aktivnosti faktora hemostazne kaskade izmerene u ranoj fazi akutne plućne tromboembolije u proceni ranog mortaliteta. Doktorska teza, Vojnomedicinska akademija 2022.
15. Milić R, Džudović B, Subotić B, et al. The significance of C-reactive protein for the prediction of net-adverse clinical outcome in patients with acute pulmonary embolism. Vojnosanit Pregl 2019; 76(4):431–436.
16. Milić R. Značaj određivanja C reaktivnog proteina u serumu bolesnika sa akutnom plućnom embolijom. Doktorska teza, MF Kragujevac, 2018.
17. Subotic B, Obradovic S, Dzudovic B, et al. Comparison of simplified PESI, CHA2DS2-VASc and HAS-BLED scores for the prediction of net-adverse clinical outcome in patients with pulmonary embolism. Eur Heart J 2016; (suppl): ESC Congress 2016.
18. Obradovic S, Subotic B, Dzudovic B, et al. Pulmonary embolism bleeding score index (PEBSI): A new tool for the detection of patients with low risk for major bleeding on thrombolytic therapy. Thromb Res 2022;214:138-43.
19. Obradovic S, Dzudovic B, Vukotic S, et al. Comparison of rivaroxaban and vitamin K antagonists' anticoagulant therapy after thrombolysis in patients with intermediate and high risk pulmonary embolism. Eur Heart J 2015;(Suppl): ESC Congress 2015.
20. Obradović S, Rusović S, Gligić B. Plućna tromboembolija kroz prikaze slučajeva. Monografija, Beograd 2011.
21. Sekulic I, Dzudovic B, Matijasevic J, et al. Ultrasound assisted thrombolysis in intermediate-risk patients with pulmonary thromboembolism. Acta Cardiol 2019: 75(7):623-630.
22. Sekulić I. Uporedna analiza efikasnosti I bezbednosti četiri terapijska protokola u lečenju bolesnika sa intermedijarno visokim rizikom od plućne tromboembolije. Doktorska teza, MF Kragujevac 2019.
23. Obradovic S, Dzudovic B, Sekulic I, et al. Efficacy and safety of lower dose slow infusion of t-PA for intermediate-risk pulmonary embolism patients with risk for bleeding. Eur Heart J Suppl 2019; (Suppl.): ESC Congress 2019.
24. Dzudovic J, Dzudovic B, Subota V, et al. Differences between activities of coagulation factors after one month of therapy with different direct oral anticoagulant in pulmonary embolism patients. J Clin Pharm Ther 2019;44(2):236-242.
25. Dzudovic J. Razlike u aktivnosti faktora koagulacione kaskade I koncentracije fibrinogena I d-dimera kod pacijenata sa plućnom embolijom na terapiji oralnim antikoagulansima. Doktorska teza, Vojnomedicinska akademija 2022.
26. Dzudovic J, Crevar Sakac M, Antunovic M, et al. Development and validation of LC-MS/MS method for determination of plasma apixaban. Acta Chromatographica 2022;34:332–337.
27. Obradovic S, Dzudovic B, Matijasevic J, et al. The timing of death in acute pulmonary embolism patients regarding the mortality risk stratification at admission to hospital. Eur Heart J 2022; (Suppl.):ESC Congress 2022.
28. Pruszczyk P, Klok FA, Kucher N, et al. Percutaneous treatment options for acute pulmonary embolism: a clinical consensus statement by the ESC Working Group on pulmonary circulation and right ventricular function and the European Association of Percutaneous Cardiovascular Interventions. Eurointervention 2022;18(8):e623-e38.

Sažetak

Šta smo naučili iz regionalnog registra za plućnu emboliju (REPER)?

Slobodan D. Obradovic[1,2], Ivica R. Djuric[1], Boris M. Dzudovic[2,3], Bojana N. Subotic[1], Jelena M. Dzudovic[4], Jovan A. Matijasevic [5,6], Marija D. Benić[5], Sandra M. Pekovic [5], Jadranka Trobok[5], Sonja S. Salinger[7], Irena Mitevska[8], Marijan Bosevski[8], Ljiljana V. Kos [9], Tamara Kovacevic-Preradovic[9], Stefan M. Simovic[10], Ema Jevtić[10], Maja Nikolić[10], Vladimir M. Miloradovic[10], Ana M. Kovacevic-Kuzmanovic[11], Tanja D. Savicic[11], Bjanka Z. Bozovic[12], Nebojsa S. Bulatovic [12,13], Srdjan V. Kafedzic [14], Sasa S. Pancevacki [15], Bojan Mitrovic[14], Milica Radovic[14], Aleksandar N. Neskovic [14,16], Nikola I. Kocev [17], Jelena M. Marinković[17]

[1]Klinika za kardiologiju, Vojno Medicinska Akademija, Beograd, Srbija, [2]Medicinski fakultet, Univerzitet odbrane, Beograd, Srbija, [3]Klinika za urgentnu internu medicinu, Vojno Medicinska Akademija, Beograd, Srbija, [4]Nacionalni centar za trovanje, Vojno Medicinska Akademija, Beograd, Srbija, [5]Institue za plućne bolesti Vojvodine, Srbija, [6]Medicinski fakultet, Univerzitet Novi Sad, Srbija, [7]Klinika za kardiologiju, Klinički centar Niš, Univerzitet u Nišu, Srbija, [8]Klinika za kardiologiju, Medicinski fakultet Univerzitet Skopje, Severna Makedonija, [9]Klinika za kardiologiju, Klinički centar Banja Luka, Medicinski fakultet, Univerzitet u Banja Luci, Republika Srpska, Bosna i Hercegovina, [10]Klinika za kardiologiju, Klinički centar Kragujevac, Medicinski fakultet, Univerzitet u Kragujevce, Srbija, [11]Odeljenje interne medicine, Opšta bolnica Pančevo, Srbija, [12]Klinika za kardiologiju, Klinički centar Podgorica, Crna Gora, [13]Medicinski fakultet Podgorica, Univerzitet u Podgorici, Crna Gora, [14]Kardiološko odeljenje, Kliničko-bolnički centar Zemun, Srbija, [15]Jedinica intenzivne nege, Klinika interne medicine, Kliničko-bolnički centar Zemun, Srbija, [16]Medicinski fakultet, Univerzitet u Beogradu, Srbija, [17]Institut za medicinsku statistiku Medicinskog fakulteta, Univerzitet u Beogradu, Srbija

Uvod. *Lečenje I dijagnostika akutne plućne embolije (PE) je još uvek puno kontroverzi, I broj randomizovanih studija je relativno mali. Za pojedinačnog lekara I zdravstveni system koji zbrinjava pacijente sa PE veoma je važno da se analizira broj bolesnika, bolnički I van bolnički mortalitet I morbiditet, kako su pacijenti lečeni I koje su najvažnije prepreke u tretmanu ovih bolesnika.*

Metodi. *Ovim radom predstavljamo Regionalni PE registar (REPER), u kratko njegov razvoj, ciljeve, i naučne rezultate, publikovane u časopisima sa SCI liste, doktorske teze i radove koji su prezentovani na Evropskim kongresima*

kardiologa. Ovo je akademski registar, ne-intervencijski, i pacijenti su informisani i dali pristanak za učešće u njemu. Ne koriste se javno personalizovani podaci bolesnika. Osnovni kriterijum za ulazak u studiju je objektivno dokazana akutna PE i hospitalizacija bolesnika.

Rezultati. *REPER je nastao kao registar bolesnika sa akutnom plućnom embolijom jednog centra – Klinike za urgentnu internu medicinu, Vojnomedicinske akademije 2011 godine. Kako smo shvatili da kao jedna bolnica ne možemo da napravimo validan registar, odlučili smo se da pozovemo druge bolnice da nam se priključe po principu jednakosti i otvorenosti. Prvo nam se priključio Institut za plućne bolesti Vojvodine I Klinički Centar u Nišu – klinika za kardiologiju koji su počeli da uključuju svoje bolesnike u registar od 2015-te godine. Registar je postao internacionalni kada nam se pridružila Klinika za kardiologiju Banja Luke prvo, a zatim i Klinika za kardiologiju iz Podgorice i iz Skoplja. Do danas je 1776 bolesnika uključeno u registar, u bazu sa više od 300 varijabli. Tokom proteklih 5 godina, 15 originalnih radova je proisteklo iz registra sa kumulativnim impact faktorom 39,2, odbranjeno je 5 doktorskih teza i 5 radova je prikazano na ESC-u. Zahvaljući ovom radu smo postali i deo najnovijih ESC preporuka o kateterskom lečenju akutne PE.*

Zaključak. *Za kliničara-naučnika, je jako važno da razvija baze podataka od interesa, sa što više kvalitatetnih varijabli što je neophodno za shvatanje patofiziologije bolesti, dijagnostičkog procesa I terapijskih opcija. Zbog toga je od vitalnog značaja da se sarađuje sa drugim doktorima i institucijama. Mi mislimo da je ovaj registar ispunio svoje ciljeve, i zahvaljujući sopstvenim podacima naše znanje o tretmanu akutne PE je postalo dublje i postali smo bolji doktori.*

Klučne reči: *plućna embolija, registri, lečenje, stratifikacija rizika, krvarenje*

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Case report

Calcified left main stenosis – is there a room for us interventionalists?

Ivan Ilić[1,2], Stefan Timcic[1], Matija Furtula[1], Srdjan Boskovic[1,2] Petar Otasevic[1,2]

[1]Institute for cardiovascular diseases Dedinje, Belgrade, Serbia, [2]Medical Faculty, University of Belgrade, Belgrade, Serbia

Abstract We present a case of 79 years old gentleman admitted to our institution suffering from low effort angina with dilated left ventricle, moderate mitral regurgitation and severely decreased left ventricular ejection fraction (LVEF) of 15%. he had cholangiocarcinoma that has been scheduled for surgery. Coronary angiography revealed occluded right coronary artery in the middle segment and critical lesion of distal left main (LM) and significant stenosis of proximal left anterior descending (LAD) artery with extensive calcifications. Patient was denied surgery and underwent complex PCI of distal LM with mechanical circulatory support (MCS) using intravascular lithotripsy. Use of advanced calcium treatment techniques should be supplemented with intravascular imaging especially in LM lesions in order to assess the vessel, lesion preparation and result after stent implantation. MCS might provide useful hemodynamics support in complex PCI where prolonged balloon inflations and calcium treatments are used.

Kew words low ejection fraction, complex calcific lesion, mechanical circulatory support, intravascular lithotripsy

Case presentation

We here present a case of 79 years old gentleman admitted to our institution suffering from low effort angina in Canadian Cardiovascular Society (CCS) class III and New York Heart Association (NYHA) class II. He was previously treated for hypertension and diabetes on oral medications. He received aspirin, beta blocker, angiotensin converting enzyme (ACE) inhibitor, trimetazidine, furosemide and spironolactone. His estimated glomerular filtration rate was eGFR 100ml/min/m^2. Transthoracic echocardiography revealed dilated left ventricle 63/45mm, enlarged left atrium of 51mm, moderate mitral regurgitation and severely decreased left ventricular ejection fraction (LVEF) of 15%. His right heart systolic function was preserved with TAPSE of 19 but there was moderate tricuspid regurgitation with increased estimated right ventricular systolic pressure (RVSP) of 65mmHg. At the admission he reported being examined for cholangiocarcinoma (Klatskin type I) that has been scheduled for surgery.

His coronary angiography revealed occluded right coronary artery in the middle segment and critical lesion of distal left main (LM) and significant stenosis of the proximal left anterior descending (LAD) artery with extensive calcifications in both coronaries (Figure 1).

Patient underwent thorough evaluation by the institutional Heart team with SYNTAX score of 33 and SYNTAX II score estimating four years mortality of 63% with PCI and 30.6% with coronary bypass grafting (CABG), while surgical risk scores were Euroscore II 14.38% and STS score 2.5% mortality and 15.4% morbidity with surgery. Although surgical risk scores demonstrated lower mortality with surgery patient was denied surgery due to very low LVEF and presence of cancer.

Patient underwent PCI via right radial approach with transfemoral implantation of mechanical circulatory support (MCS) device iVAC 2L (PulseCath BVm Arnhem, The Netherlands). We used extra back up guiding catheter in 7 F size, wired both branches LAD and Cx and performed optical coherence tomography (OCT) using DragonFly Optis catheter (Abbott Vascular, Santa Clara, CA, US) in order to evaluate vessel size, plaque distribution and extent of calcifications. Recording from LAD demonstrated calcified nodule at distal LM protruding into LAD severely reducing lumen area, while pullback from Cx revealed mild calcifications with preserved ostial lumen and absence of plaque at the ostium of Cx (Figure 2). Initial plan was to use "provisional" strategy and to implant stent from LM to LAD. Predilatation was done using 2.5x12mm non-compliant balloon then Shockwave balloon 3.0x12mm (Shockwave Medical Inc., Santa Clara, CA, US) was used with four pulses in proximal LAD and LM. The control angiography revealed dissection extending towards Cx and we've changed initial strategy of "provisional" to two stent strategy with "culotte" stenting. First, we've implanted 2.75x18mm and 3.26mm DES in proximal to middle LAD then after Shockwave treatment of ostial Cx with two pulses we've

Address for correspondence: Assist. Ivan Ilic, MD, PhD, Institute for cardiovascular diseases Dedinje, Heroja Milana Tepica 1, Belgrade, Serbia.
E-mail: ivan1ilic@yahoo.com

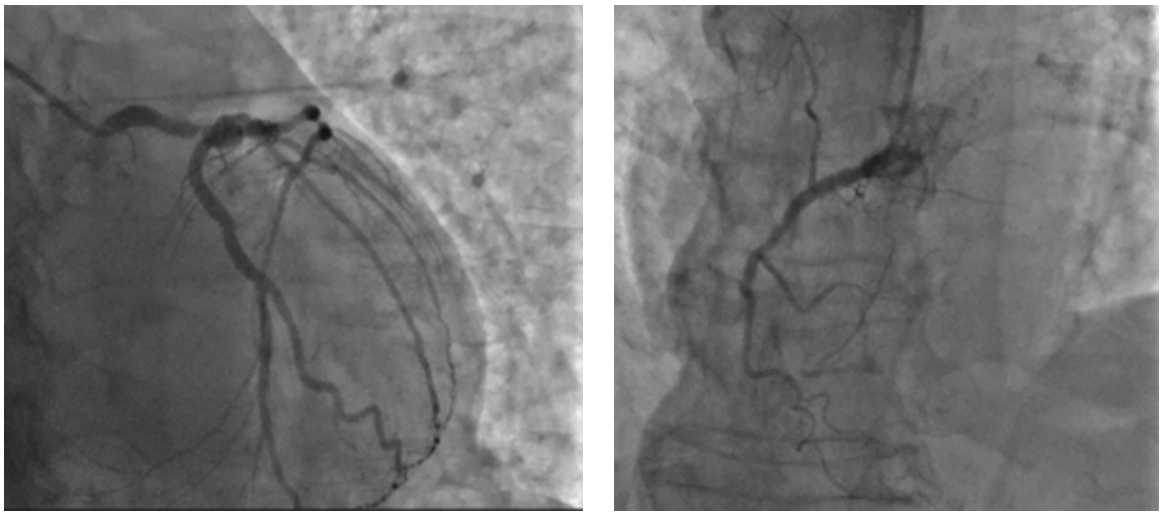

Figure 1. Coronary angiography of left and right coronary artery

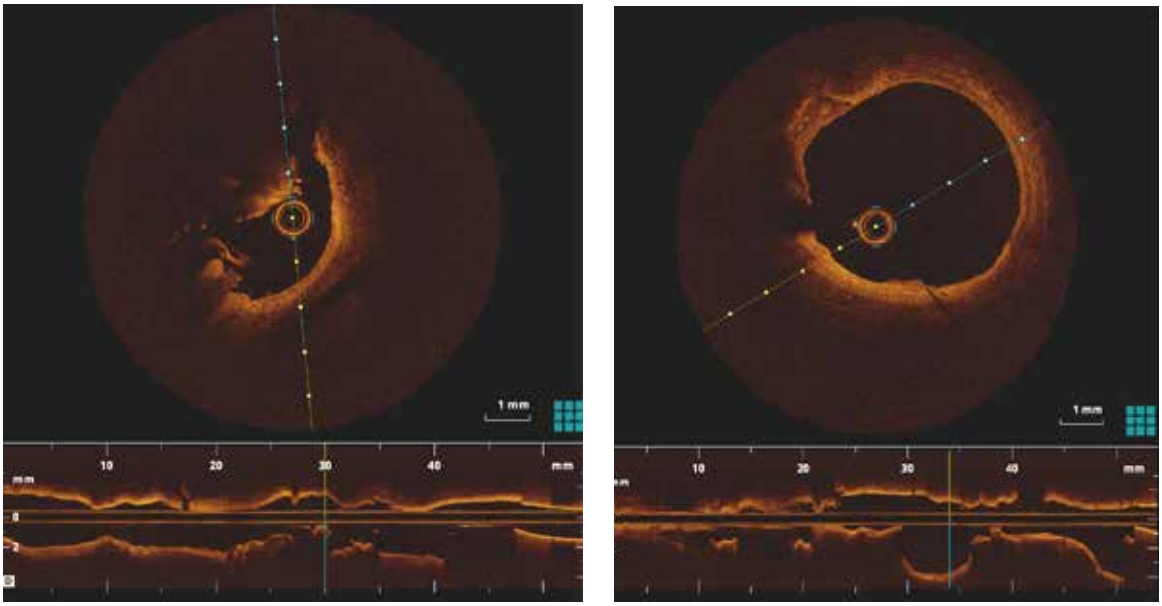

Figure 2. OCT pullback from LAD (left) and Cx artery (right)

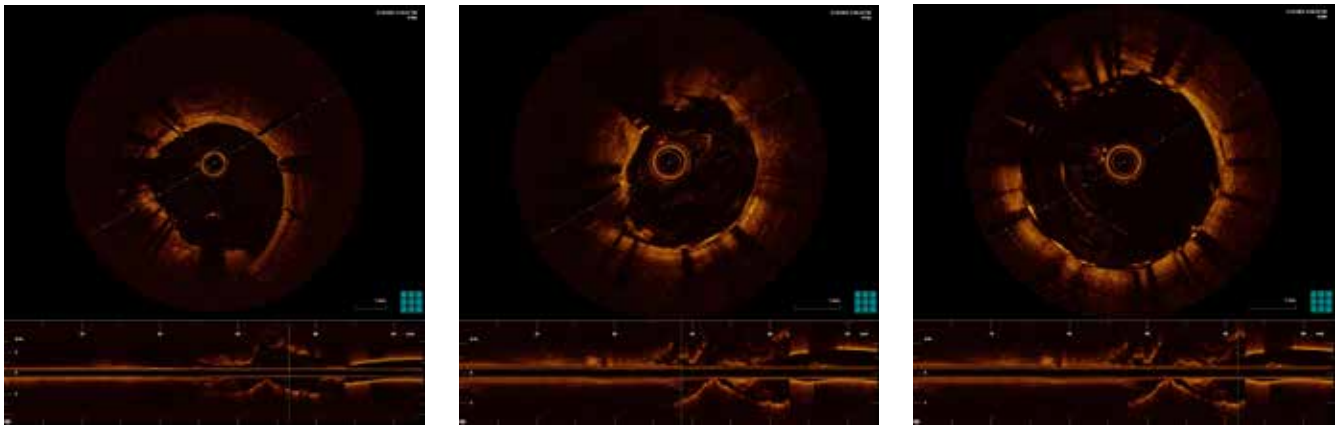

Figure 3. Final OCT run of the left LM, middle LAD, and Cx coronary artery

implanted 3.5x24mm DES from Cx to LM, then after proximal optimization treatment (POT) in LM with 4.5x6mm NC balloon, we've opened the strut towards LAD and implanted 3.5x34mm DES from LM towards LAD. After stent implantation, kissing balloon inflation was done using 3.5x15mm NC balloon in LAD and 3.0x15mm balloon in Cx with inflation up to 8 atm. Finally rePOT was done in LM using 5.0x12mm NC balloon with high pressure inflation (Figures 3 and 4).

Patient had an uneventful stay in hospital and was discharged two days later. He was seen in an office visit after six months free from angina and doing well in NYHA class II.

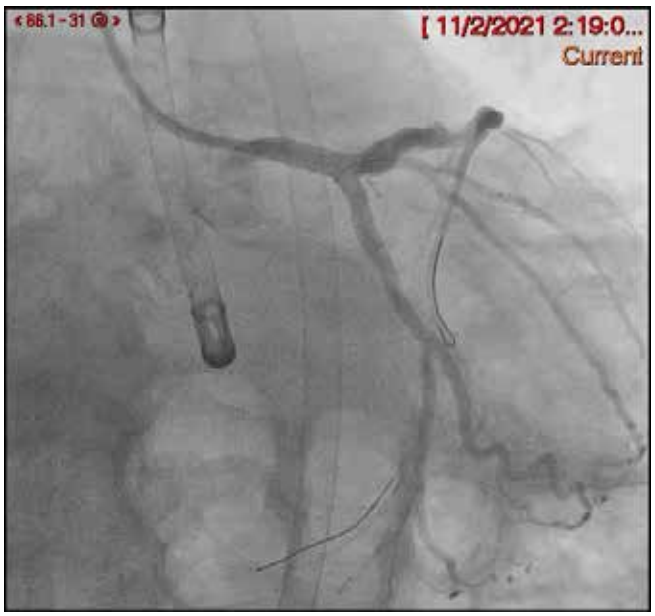

Figure 4. Final angiography of the left coronary artery

Discussion

Left main coronary artery supplies blood to almost two thirds of the heart in a right dominant system, while in left dominant system entire myocardium receives blood from the left coronary artery. Knowing this, atherosclerotic disease of LM jeopardizes a large myocardial territory and could be the cause of substantial mortality and morbidity[1]. Atherosclerosis develops mostly at arterial branching points and that applies to LM disease which is in around 80% of cases at the bifurcation with left anterior descending (LAD) and circumflex (Cx) artery[2].
Appropriate treatment for LM disease remains a matter of debate between interventional cardiologist and cardiac surgeons. Current European Society of Cardiology (ESC) guidelines suggest that in lesions with low anatomical complexity expressed as SYNTAX score below 22 percutaneous coronary intervention (PCI) can be equally effective option as coronary artery bypass grafting (CABG) in patients suitable for both types of revascularizations (3). On the other hand, recently published American Heart Association (AHA) guidelines on coronary revascularization state that CABG should be the first option for LM disease, while PCI can be a choice for selected patients with stable ischemic heart disease where both options are feasible[4]. In the largest meta-analysis comparing PCI and CABG patients with isolated LM disease there was no difference regarding five years mortality between PCI or CABG[5].
Due to prolonged life expectancy and development in medical treatment, severe coronary calcifications are more frequent findings in coronary angiographies. PCI can be very challenging in calcified lesions and is associated with increased rate of procedural complications and higher rate of adverse events due to inadequate lesion preparation, stent under-expansion and increased rates of stent thrombosis and re-stenosis[6]. In order to effectively treat calcified lesions several techniques have been developed like rotational atherectomy, orbital atherectomy and scoring or cutting balloons and their use is steadily rising in everyday practice. Intravascular lithotripsy (IVL) has been recently developed and has shown promising results in vast array of calcified lesions. However, LM calcified lesions, despite obvious challenges and added complexity in interventions, were frequently excluded from the registries[7]. There is a small registry of IVL in LM PCI from Salazar and associates that demonstrated feasibility of IVL use in LM stenosis. The study demonstrated significant reduction in diameter stenosis accompanied with achieving large minimal lumen diameters after PCI. The authors sent the word of caution regarding the prolonged inflation of IVL balloon in LM causing significant ischemia and suggested the abbreviated cycles of IVL treatment in order to reduce large myocardial territory ischemia[8].
In our case we did IVL using standard protocol that required full cycle of IVL pulses. However due to MCS with iVAC2L pump we achieved adequate lesion preparation with stable hemodynamics. Using OCT prior and after IVL treatment allowed vessel assessment before lesion preparation and the effects of calcified lesion treatment afterwards that can allow stent implantation in LM lesion that would not be compromised by stent underexpansion. Use of advanced calcium treatment techniques should be supplemented with intravascular imaging especially in LM lesions in order to assess the vessel, lesion preparation and result after stent implantation. In the future we expect IVL to be compared in a randomized fashion to other calcium treatments like non-compliant, high pressure or cutting balloons or mechanical atherectomy devices like rotational or orbital atherectomy.

References

1. Capodanno D, Di Salvo ME, Seminara D, et al. Epidemiology and clinical impact of different anatomical phenotypes of the left main coronary artery. Heart Vessels 2011;26:138–144.
2. Oviedo C, Maehara A, Mintz GS, et al. Intravascular ultrasound classification of plaque distribution in left main coronary artery bifurcations: where is the plaque really located? Circ Cardiovasc Interv 2010;3:105–112.
3. 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(2):87-165.
4. Lawton J, Tamis-Holland J, et al. 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization. J Am Coll Cardiol 2022;79 (2):e21–e129.
5. Head SJ, Milojevic M, Daemen J, et al. Mortality after coronary artery bypass grafting versus percutaneous coronary intervention with stenting for coronary artery disease: a pooled analysis of individual patient data. Lancet 2018;391(10124):939-948.
6. Fujino A, Mintz GS, Matsumura M, et al. A new optical coherence tomography-based calcium scoring system to predict stent underexpansion. EuroIntervention 2018;13: e2182–2189.
7. Ali ZA, Nef H, Escaned J, et al. Safety and effectiveness of coronary intravascular lithotripsy for treatment of severely calcified coronary stenoses. Circ Cardiovasc Interv 2019;12:46–49.
8. Salazar CH, Gonzalo N, Aksoy A, et al. Feasibility, safety, and efficacy of intravascular lithotripsy in severely calcified left main coronary stenosis. JACC Cardiovasc Interv 2020;13(14):1727-1729.

Sažetak

Kalcifikovana stenoza glavnog stable leve koronarne arterije – da li ima prostora za interventne kardiologe?

Ivan Ilić[1,2], Stefan Timčić[1], Matija Furtula[1], Srđan Boskovic[1,2] Petar Otašević[1,2]

[1]Institut za kardiovaskularne bolesti Dedinje, Beograd, Srbija, [2]Medicinski fakultet, Univerzitet u Beogradu, Beograd, Srbija

Predstavljamo slučaj 79-godišnjeg pacijenta primljenog u našu ustanovu koji boluje od angine pri malom naporu sa dilatacijom leve komore, umerenom mitralnom regurgitacijom i ozbiljno smanjenom ejekcionom frakcijom leve komore (LVEF) od 15%. Imao je holangiokarcinom koji je zakazan za operaciju. Koronarna angiografija je otkrila okludiranu desnu koronarnu arteriju u srednjem segmentu i kritičnu leziju distalnog dela glavnog stable leve koronarne arterije (LM) i značajnu stenozu proksimalne prednje silayne grane (LAD) arterije sa ekstenzivnim kalcifikacijama. Pacijentu je odbijena operacija i podvrgnut je kompleksnoj PCI distalnog LM sa mehaničkom cirkulatornom podrškom (MCS) primenom intravaskularne litotripsije. Upotreba naprednih tehnika lečenja kalcijumom treba da bude dopunjena intravaskularnim snimanjem, posebno kod lezija LM, kako bi se procenio krvni sud, pripremila lezija i dobio adekvatan rezultat nakon implantacije stenta. MCS može da pruži korisnu hemodinamičku podršku u kompleksnoj PCI gde se koriste produženo naduvavanje balona i uređaji za lečenje kalcifikovanih lezija.

Ključne reči: *niska ejekciona frakcija, kompleksna kalcificirana lezija, mehanički cirkulatorni oslonac, intravaskularna litotripsija*

Srce i krvni sudovi 2022; 41(4): 172-176

Case report

Infektivni endokarditis inicijalno prezentovan septičnom embolizacijom centralnog nervnog sistema - prikaz slučaja

Marija Popović[1], Đorđe Stevanović[1,2], Ljiljana Marić Stepanović[1], Mina Poskurica[1], Vladimir Zdravković[1,2]

[1] Klinika za kardiologiju, Univerzitetski Klinički centar Kragujevac, Srbija, [2] Katedra za Internu medicinu, Fakultet medicinskih nauka Univerziteta u Kragujevcu, Srbija

Sažetak

Uvod. Infektivni endokarditis (IE) je potencijalno fatalno oboljenje, čija klinička prezentacija često nije patognomonična, naročito u inicijalnom stadijumu, zbog čega pravovremeno postavljanje dijagnoze može biti otežano.

Prikaz slučaja. U našem prikazu, pacijentkinja je hospitalizovana zbog povišene telesne temperature, gušenja i poremećaja stanja svesti. Zbog podatka o dva prethodno preležana cerebrovaskularna insulta (*CVI)* i izmenjenog stanja svesti na prijemu, uz *MSCT*-om endokranijuma verifikovanu zonu ishemije sa potencijalnom reinfarkcijom, pacijentkinja je inicijalno vođena kao ponovni *CVI* i septično stanje nepoznate etiologije. S obzirom na naizgled jasan uzrok neurološkog stanja i pneumoniju kao potencijalno objašnjenje inflamacije, trijažni postupak i pregled pacijentkinje bio je skraćen. Tek nakon dodatnog kliničkog pogoršanja praćenog porastom kardiospecifičnih markera konsultujući kardiolog dijagnostikuje IE mitralne valvule, osmog dana hospitalizacije u našoj ustanovi. U narednom periodu infektivni endokarditis lečen je medikamentno, a pacijentkinja je, uz perzistiranje neurološke simptomatologije, razvila septičnu embolizaciju burega, mehaničku komplikaciju IE u vidu rupture horde za zadnji mitralni kuspis i akutni kardiorenalni sindrom. Planiran prevod u kardiohiruršku ustanovu odložen je pozitivnim antigenskim testom na *SARS-CoV-2*, a pacijentkinja prevedena u *COVID* bolnicu, gde egzitira nakon dva meseca lečenja.

Zaključak. S obzirom na srčane i van-srčane manifestacije potencijalno fatalnog oboljenja, potrebno je najpre imati IE u diferencijalno dijagnostičkom algoritmu kompleksnih pacijenata, a od trenutka postavljanja dijagnoze i multidisciplinarni pristup i kontinuirano praćenje, u cilju boljeg i adekvatnijeg lečenja.

Ključne reči infektivni endocarditis, septične embolizacije, cerebrovaskularni insult COVID-19

Uvod

Infektivni endokarditis predstavlja potencijalno fatalno oboljenje, sa incidencom javljanja od 3-10 slučajeva/100 000 i mortalitetom od 6-30%.[1,2,3] Uzročnici ovog oboljenja mogu biti bakterijske i gljivične infekcije, od kojih su, prema dostupnoj literaturi, *Saphylococcus*, *Streptococcus* i *Enterococcus* najčesšći izazivači. U vulnerabilnu grupu spadaju pacijenti sa veštačkom valvulom, prethodno preležanim infektivnim endokarditisom i srčanim manama, dok faktor rizika predstavlja i intravenska primena lekova, venski kateteri, hemodijaliza, dentalne infekcije, imunosupresija i drugo. [2,3,4] Klinički simptomi i znaci uključuju povišenu telesnu temperaturu, malaksalost, dispneju, bol u grudima, kašalj, novonastali šum na srcu i drugo, dok se kod postojanja septičnih embolizacija javljaju i simptomi od strane zahvaćenih organa. [5,6] Ipak, zbog nespecifičnosti simptoma i različitite kliničke prezentacije infektivnog endokarditisa, postavljanje pravovremene dijagnoze u svakodnevnoj kliničkoj praksi može biti izazovno.

Prikaz slučaja

Pacijentkinja starosti 63 godine, sa istorijom prethodno preležanog cerebrovaskularnog insulta (CVI) i zaostalom desnostranom slabošću ekstremiteta, prevedena je iz matične bolnice u našu ustanovu zbog gušenja, povišene telesne temperature i poremećaja stanja svesti. Pacijentkinja je prethodno četiri dana lečena u matičnoj ustanovi, dok su tegobe u vidu slabosti, malaksalosti i povišene telesne temeperature počele tri dana pre toga. Pri pregledu je somnolentna, tahikardična, dispnoična, subfebrilna, hipotenzivna, otežano komunikativna. Prema izveštaju interniste na prijemu, u fizikalnom nalazu srčana radnja je tahikardična, dok su nad plućima obostrano bazalno prisutni pukoti koji maskiraju auskultatorni nalaz na srcu. Elektrokardiografski beleži se sinusna tahikardija i blok desne grane Hisovog snopa, prosečne frekvence oko 90/min, dok je saturacija kiseonikom 94%. U laboratorijskim analizama beleže se povišene vrednosti biohumoralnih markera zapaljenja i sepse, D-dimera i kardiospecifičnih enzima, (Tabela 1)

Corresponding author: Dr. Đorđe Stevanović; Nikole Pašića 18b/4, 34000 Kragujevac, Phone: +381606969077. E-mail: djordje.stevanovic.kg@gmail.com

uz prisutnu hematuriju. Radiografskim pregledom pluća uočavaju se obostrano difuzno mrljaste senke sa početnim zonama konsolidacije u gornjim plućnim poljima. Zbog laboratorijski i klinički suspektne plućne tromboembolije, uradjena je *MSCT* (eng. *Multi slice computed tomography*) pulmoangiografija, na kojoj nisu viđeni jasni znakovi embolizacije. *MSCT*-om endokranijuma (Slika 1A) vizualizuju hronične ishemijske lezije, uz nemogućnost isključivanja i zona reinfarkcije u predelu kapsule interne levo. Po obavljenoj dijagnostici, pacijentkinja se prevodi na dalje lečenje u Jedinicu intenzivne nege gde se empijski u terapiju uvodi Vankomicin, dok se u daljem toku bolesti antibiotska terapija revidirala od strane kliničkog farmakologa. (Tabela 1) U sklopu ispitivanja etiologije septičnog stanja, radjena je lumbalna punkcija kojom je dobijena bistra cerebro-spinalna tečnost i negativan punktat. Iz hemokulture izoluje se *Staphylococcus aureus*, a na osnovu antibiograma se uz Vankomicin u terapiju uvodi Ciprofloksacin. Sedmog dana hospitalizacije dolazi do skoka kardiospecifičnih enzima, te se konsultuje kardiolog, koji na osnovu kliničke prezentacije i ehokardiografski viđene mase na mitralnoj valvuli postavlja sumnju na infektivni endokarditis. Transezofagealnim ehokardiografskim pregledom (TEE) verifikuje se postojanje hiperehogene formacije dimenzija 13x7 mm pri bazi zadnjeg mitralnog kuspisa, na mitralnom anulusu, odakle polaze i dve heterogene končaste formacije, i mogu odgovarati vegetacijama. (Slika 2A i 2B) U medjuvremenu, nalaz druge hemokulture, kao i urinokulture, pristižu negativni i pacijentkinja se prevodi u Koronarnu jedinicu, gde je lečena naredna 33 dana. U daljem toku lečenja na Klinici za kardiologiju, nakon kratkotrajnog poboljšanja opšteg stanja, pacijentkinja sve vreme blago dezorijentisana, na niskim protocima oksiigeno-terapije, dok se u više navrata registruje ponovni porast biohumoralnih markera zapaljenja i sepse, progresija radiografskog nalaza na plućima u vidu bilateralnih pleuralnih izliva, kao i pojava ponovne febrilnosti. (Tabele 1 i 2) Sve vreme praćena je od strane neurologa, dok se na kontrolnim nalazima *MSCT*-a endokranijuma registruje redukcija inicijalano opisanih ishemijskih zona koje poprimaju radiografske karakteristike hroničnih lezija (Slika 1b). U periodima kratkotrajnih kliničko-laboratorijskih poboljšanja, kontaktirana je referentna kardio-hirurška ustanova, koja indikuje dopunsku dijagnostiku. Na *MSCT*-u abdomena (Slika 3) uočavaju se infarktne lezije u donjem polu desnog bubrega, dok je nalaz na "*color doppler*"-u krvnih sudova vrata bio uredan. Nakon 36 dana hospitalizacije, dolazi do naglog pogoršanja opšteg stanja pacijentkinje koja se žali na gušenje, kratak dah i nelagodnost u predelu grudnog koša. Na kontrolnom ehokardiografskom pregledu verifikovana je ruptura horde za zadnji mitralni kuspis sa posledičnom mitralnom regurgitacijom 4+ i ejekcionom frakcijom leve komore oko 50%, dok su opisivane končaste promene u značajnoj regresiji. (Slika 4A

Tabela 1. Prikaz ordinirane antibiotske terapije prema kliničko-laboratorijskim parametrima.

Dan	1	7	12	28	41	47	51
Aktuelna antibiotska terapija	Vancomycin 1g/12h	Vancomycin 1g/12h Ciprofloxacin 0,5g/12h	Vancomycin 1g/12h Gentamycin 0,08g/24h Meropenem 1g/8h	Vancomycin 1g/12h	Vancomycin 1g/12h Cefepim 2g/12h	Cefepim 2g/12h Hemomycin 0,5g/24h	Hemomycin 0,5g/24h Levofloksacin 0,5g/12h
Laboratorijske analize	Le 9,7*10^9/L; Hgb 94 g/L; Tr 44*10^9/L; CRP 191 mg/L; PCT 2,1 ng/mL; D-dimer 20,75 ug/mL; hsTnI 0,05999 ng/mL; pBNP 10094 pg/mL; Urea 17,4 mmol/L; Kreatinin 101 umol/L.	Le 15,1 *10^9/L; Hgb 93 g/L; Tr 250*10^9/L; CRP 96,8 mg/L; PCT 0,723 ng/mL; TnI 3,32 ng/mL; proBNP 3754 pg/mL.	Le 12,2*10^9/L; Hgb 94 g/L; Tr 264*10^9/L; CRP 292,81 mg/L; PCT 0,362 ng/mL.	Le 5,68*10^9/L; Hgb 101 g/L; Tr 160*10^9/L; CRP 26,7 mg/L; PCT 0,159 ng/mL.	Le 11,9*10^9/L; Hgb 88 g/L; Tr 202*10^9/L; CRP 77,8 mg/L; Urea 13,4 mmol/L; Kreatinin 161 umol/L; proBNP 28560 pg/mL.	Le 6,6*10^9/L; Hgb 104 g/L; Tr 167*10^9/L; CRP 41,4 mg/L.	Le 4,79*10^9/L; Hgb 96 g/L; Tr 124*10^9/L; CRP 92,4 mg/L; PCT 0,07 ng/mL.
Telesna temperatura	37,2 °C	37,4 °C	38,5 °C	36,5 °C	36,8 °C	36,6 °C	36,7 °C
Radiografski snimak pluća	Manje zone početne konsolidacije obostrano u gornjim plućnim poljima.	Obostrani pleuralni izlivi. Obostrano naglašen intersticijum sa mrljastim zonama konsolidacije u gornjim i srednjim plućnim poljima.	U projekciji srednjeg plućnog polja desno zona konsolidacije plućnog parenhima. Razliven pleuralni izliv desno.	Nalaz bez značajnijih izmena.	Obostrano naglašen intersticijum. Manja zona konsolidacije u srednjem plućnom polju desno. Obostrano pleuralni izliv.	Nalaz bez značajnijih izmena.	Difuzno naglašen intersticijum bez zona konsolidacije.

Skraćenice: CRP – C reaktivni protein, Hgb – hemoglobin, hsTnI - visoko senzitivni troponin I (eng. *high sensitive troponin I*), Le – leukociti, pBNP- pro-forma moždanog nitruretskog peptida (eng. *pro-form of Brain natriuretic peptide*), PCT – prokalcitonin, Tr – trombociti, °C - stepeni Celzijusove skale.

Tabela 2. Hronologija događaja tokom hospitalizacije

Urgentni centar (Jedinica intenzivne nege)	
Dan 1	Prijem na hospitalno lečenje zbog respiratorne slabosti, *SIRS*-a i *CVI*.
Dan 3	HK I pozitivna na *Staphylococcus aureus*
Dan 7	Skok kardiospecifičnih markera, na RTG pluća obostrano pleuralni izlivi
Dan 8	Ehokardiografski supsektne vegetacije na mitralnoj valvuli, HK II negativna
Dan 9	Transezofagealnim ehokardiografskim pregledom potvrdjena dijagnoza IE mitralne valvule
Klinika za kardiologiju	
Dan 12	Porast biohumoralnih markera zapaljenja, stacionaran radiografski nalaz na plućima
Dan 22	Progresija nalaza na *RTG* pluća i *MSCT* grudnog koša
Dan 28	Kontaktirana referentna kardiohirurška ustanova, indikovana dopunska dijagnostika
Dan 36	Kliničko pogoršanje, dispneja, tahikardija i nelagodnost u predelu grudnog koša. Ehokardiografski verifikovana ruptura horde za zadnji mitralni kuspis i teška mitralna regurgitacija (MR4+.) Značajna regresija končastih promena, LVEF 50%. Zakazan TEE u kardio-hirurškoj ustanovi
Dan 41	*MSCT* abdomena – infarktna lezija u donjem polu desnog bubrega, porast biohumoralnih markera zapaljenja
Dan 42	RTG pluća u progresiji, Ag test na *SARS-CoV-2* pozitivan
Korona Centar	
Dan 57	Kliničko pogoršanje, konvulzivni napad, devijacija pogleda u desno
Dan 58	Kardiorespiratorno pogoršanje, pacijentkinja intubirana, smrtni ishod

Abrevijacije: CVI - cerebrovaskularni inslut, IE - infektivni endokarditis, HK - hemokultura, LVEF% - istisna moć leve komore (eng. *Left ventricle ejection fraction*), MR - mitralna regurgitacija, MSCT - multislajsna kompjuterizovana tomografija, RTG - radiografski snimak pluća, SIRS - sindrom sistemskog inflamatornog odgovora (eng. *systemic immune resposne syndrome),* SARS-CoV-2 - eng. S*evere acute respiratory syndrome coronavirus 2*, TEE - transezofagealna ehokardiografija.

i 4B) U laboratorijskim analizama se verifikuje nagli porast biohumoralnih markera zapaljenja i markera srčane (proBNP 27388 *pg/mL*) i bubrežne slabosti (urea 12,1 *mmol/L*, kreatinin *161 umol/L*), te se ponovo kontaktira kardio-hirurška ustanova, koja indikuje TEE u njihovoj ustanovi. U sklopu rutinske pripreme pacijentkinje za prevod u drugu ustanovu, pristiže pozitivan test na SARS-CoV-2 infekciju, te se 42. dana hospitalizacije pacijentkinja prevodi u Korona Centar na dalje lečenje. U narednih 16 dana lečena je u Korona Centru, sve vreme na niskim protocima oksigeno-terapije do 2 L/min, dezorijentisana, somnolentna, afebrilna. Nakon 57 dana, pacijentkinja doživljava konvulzivni napad koji spontano prolazi, nakon čega devira pogledom u desno. Na kontrolnom *MSCT*-u endokranijuma (Slika 2C) nisu verifikovane zone reinfarkcije. Nakon 12h dolazi do hemodinamskog pogoršanja, pacijentkinja agonalno diše, nemerljivih vrednosti krvnog pritiska i bez palpabilnih pulseva, širokih, nereaktivnih zenica, i u teškoj laktatnoj acidozi. Pacijentkinja je intubirana i reanimirana, ali dolazi do smrtnog ishoda nakon 58 dana hospitalnog lečenja.

Diskusija

U našem prikazu, pacijentkinja je hospitalizovana zbog povišene telesne temperature, gušenja i poremećaja stanja svesti. Zbog podatka o dva prethodno preležana CVI i izmenjenog stanja svesti na prijemu, uz MSCT-om endokranijuma verifikovanu zonu ishemije sa potencijalnom reinfarkcijom, pacijentkinja je inicijalno vođena kao ponovni CVI i septično stanje nepoznate etiologije. S obzirom na naizgled jasan uzrok neurološkog stanja i pneumoniju kao potencijalno objašnjenje inflamacije, trijažni postupak i pregled pacijentkinje bio je skraćen. Tek nakon osam dana hospitalizacije u našoj ustanovi, odnosno dvanaest dana od inicijalne hospitalizacije u matičnoj bolnici, zbog porasta kardiospecifičnih markera je konsultovan kardiolog. Nakon detaljnog fizikalnog pregleda uočen je sistolni šum nad srčanim vrhom, bez podataka u medicinskoj dokumentaciji da je sličan šum ranije opisivan. Uz kliničku prezentaciju, Staphylococcus aureus izolovan iz hemokulture i transezofagealnom ehokardiografijom verifikovanu masu na mitralnoj valvuli, potvrđena je dijagnoza infektivnog endokarditisa. Nakon postavljenja dijagnoze, možemo hipotetisati da je upravo IE od početka bio uzrok infektivnog sindroma, a septična embolizacija uzrok CVI.

Septične embolizacije su vrlo česta komplikacija IE, koje se po literaturi javljaju kod 20-50% pacijenata i predstavljaju glavni uzrok morbiditeta i mortalita.[4] U faktore rizika za septičnu embolizaciju spadaju veličina (> 10 mm) i mobilnost vegetacije, endokarditis mitralne valvule, infekcija odredjenim mikroorganizmima (uključujući S. aureus), prethodni embolizam, godine i drugi.[4] Faktori rizika kod naše pacijentkinje predstavljali su vegetacija veća od 10 mm na mitralnoj valvuli, infekcija *S. aureusom*, kao i starija životna dob. Dodatno, navodi se da je rizik od embolijskih komplikacija IE najveći u prve dve nedelje bolesti i uvođenja antibiotske terapije.[8] Rekonstrukcijom događaja na osnovu heteroanamnestičkih podataka, možemo pretpostaviti da su simptomi IE, u

vidu zamaranja, gušenja, febrilnosti i malaksalosti, počeli nekoliko dana pre inicijalnog pregleda, a da je tek septična embolizacija CNS-a bila razlog javljanja lekaru i hospitalizacije. Neurološke komplikacije IE su relativno česte i sreću se kod 15-30% pacijenata, dok literaturni podaci upućuju da se klinički neme cerebralne embolizacije javljaju i kod 35-60% pacijenata. Najčešće se prezentuju ishemijskim centralnim događajem i to pre ili u trenutku postavljanja dijagnoze IE.[9-12] Uz druge, opšte faktore rizika za nastanak septičnih embolizacija, infekcija *S. aureusom* ima najveću tendenciju za nastanak neuroloških komplikacija. Osim što ima negativan efekat na tok bolesti i mortalitet, postojanje neuroloških komplikacija IE, prema aktuelnim vodičima, značajno utiče na dalji tok lečenja.[9,13]

Iako antibiotska terapija predstavlja osnov lečenja IE i preveniranja komplikacija, inicijalna neurološka prezentacija odložila je postavljanje dijagnoze i uvođenje adekvatnog antibiotskog režima. Naša pacijentkinja prehospitalno nije lečena antibioticima, dok je u matičnoj ustanovi lečena penicilinskim preparatima, za koje se potvrdila rezistencija na kasnije uzetoj hemokulturi. Mada je u našoj ustanovi tek osmog dana potvrđena dijagnoza IE, inicijalna uvedena antibiotska terapija predstavljala je i adekvatan izbor antibiotskog režima za lečenje IE. Iako je empirijska antibiotska terapija uvedena nedelju dana od početka simptoma bolesti bila adekvatna, odloženo postavljanje dijagnoze IE je moguće uticalo na dalji terapijski i dijagnostički algoritam. Dodatno, zbog perzistiranja povišene telesne temperature i visokih biomarkera inflamacije, u više navrata menjan je antibiotski režim, uz kontinuirano trajanje terapije vankomicinom od 6 nedelja. Perzistentna infekcija predstavlja drugu najčešću komplikaciju IE i arbitrarno se definiše kao pireksija i održavanje pozitivnih hemokultura i 7-10 dana nakon uvođenja antibiotske terapije.[4] Mada su kod naše pacijentkinje ponovljene hemokulture bile negativne i perivalvularne ekstenzije nisu viđene, temperatura je perzistirala dve nedelje lečenja u našoj ustanovi, odnosno tri nedelje od pretpostavljenog početka bolesti. Moguća objašnjenja perzistiranja temperature su naedekvatan izbor antibiotika i rezistentnost patogena, septične embolizacije, ali i postojanje pridruženih infekcija.[4]

Kardio-hiruška ustanova kontaktirana je nakon 4 nedelje lečenja u našoj ustanovi. S obzirom na teško opšte stanje pacijentkinje i perzistirajuće neurološke defekte i, u tom trenutku, nepostojanje apsolutnih indikacija za operativnim lečenjem, predložena je dalja dijagnostika u cilju ispitivanja drugih komplikacija IE i procene rizika od operativnog lečenja. Moramo napomenuti da je ovo period jednog od pikova *SARS-CoV-2* infekcije u našoj zemlji, kada su sprovođenje dijagnostike, multidisciplinarni pristup i komunikacija između ustanova bili znatno otežani.

Nakon 36 dana lečenja u našoj ustanovi, pacijentkinja u naglom pogoršanju opšteg stanja, sa gušenjem i pretećim edemom pluća. Ehokardiografski se registruje ruptura horde za zadnji mitralni kuspis sa posledičnom mitralnog regurgitacijom 4+ i opisanom *LVEF* oko 50%. Laboratorijski se registruje nagli porast biohumoralnih markera zapaljenja i markera srčane i bubrežne slabosti. Naglo nastala klinička deterioracija se može opisati mehaničkom komplikacijom IE i nastalom srčanom slabošću. Srčana slabost je najčešća komplikacija IE koja se sreće kod 42-60% pacijenata sa IE nativne valvule i uglavnom nastaje kao posledica novonastale ili pogoršanja postojeće aortne/mitralne regurgitacije. Dodatno, umereno do teška srčana slabost predstavlja najznačajniji prediktor intrahospitalnog, šestomesečnog i jednogodišnjeg mortaliteta pacijenata sa IE.[14-16] Novonastala bubrežna slabost (dvostruki porast serumskog kreatinina i razvoj oligurije - stadijum povrede po *KDIGO* klasifikaciji) može se objasniti prerenalnim (kardiorenalni sindrom tip 1), ali i renalnim, direktnim oštećenjem bubrežnog parenhima septičnom embolizacijom.[17,18]

S obzirom na razvoj situacije, kardiohirurška ustanova indikuje TEE u cilju prevoda. U sklopu rutinske pripreme, pristiže pozitivan test na *SARS-CoV-2* infekciju, te se 42. dana hospitalizacije pacijentkinja prevodi u Korona Centar. U narednih 16 dana lečena je u Korona Centru, sve vreme na oksigeno-terapiji, dezorijentisana, somnolentna, teškog opšteg stanja, gde na kraju letalno završava 58. dana hospitalizacije. Iako je direktan efekat *SARS-CoV-2* infekcije na ishod pacijentkinje diskutabilan, neminovno je uticao na terapijski algoritam IE i odlaganje kardiohiruške intervencije, koja bi potencijalno imala presudan efekat na konačni ishod.

Zaključak

IE je ozbiljno i potencijalno fatalno oboljenje, čija klinička prezentacija često nije patognomonična, naročito u inicijalnom stadijumu. S obzirom na srčane i van-srčane manifestacije bolesti, potrebno je najpre imati IE u diferencijalno dijagnostičkom algoritmu kompleksnih pacijenata, a od trenutka postavljanja dijagnoze i multidisciplinarni pristup i kontinuirano praćenje, u cilju boljeg i adekvatnijeg lečenja. Dodatno, značajan efekat *COVID-19* pandemije u prethodne dve godine na zdravstveni sistem bio je dvojak - *SARS-CoV-2* infekcija direktno je uticala na zdravlje pacijenata i osoblja, ali i indirektno negativno uticala na proces rada i lečenje ne-*COVID* patologije.

Literatura

1. Fedeli U, Schievano E, Buonfrate D, et al. Increasing incidence and mortality of infective endocarditis: a population-based study through a record-linkage system. BMC Infect Dis 2011;11:48. https://doi.org/10.1186/1471-2334-11-48
2. Wojda TR, Cornejo,K, Lin A, et al. Septic embolism: A potentially devastating complication of infective endocarditis. Contemporary challenges in endocarditis. Available from: https://www.intechopen.com/chapters/52116 doi: 10.5772/64931
3. Cahill TJ, Baddour LM, Habib G, et al. Challenges in infective endocarditis. J Am Coll Cardiol 2016;69(3):325–344.
4. Habib G, Lancellotti P, Antunes MJ, et al. 2015 ESC Guidelines for the management of infective endocarditis. Eur Heart J 2015;36 (44):3075–3128.
5. Netzer RO, Zollinger E, Seiler C, et al. Infective endocarditis: clinical spectrum, presentation and outcome. An analysis of 212 cases 1980–1995. Heart 2000;84:25-30.
6. N'Guyen Y, Duval X, Revest M, et al. Time interval between infective endocarditis first symptoms and diagnosis: relationship to infective endocarditis characteristics, microorganisms and prognosis, Ann Med 2016;49(2):117-125.

7. Dickerman SA, Abrutyn E, Barsic B, et al. The relationship between the initiation of antimicrobial therapy and the incidence of stroke in infective endocarditis: An analysis from the ICE Prospective Cohort Study (ICE-PCS), Am Heart J 2007;154(6): 1086-1094.
8. Steckelberg JM, Murphy JG, Ballard D, et al. Emboli in infective endocarditis: the prognostic value of echocardiography. Ann Intern Med 1991;114: 635–640.
9. Garcia-Cabrera E, Fernandez-Hidalgo N, Almirante B, et al. Neurological complications of infective endocarditis: risk factors, outcome, and impact of cardiac surgery: a multicenter observational study. Circulation 2013; 127:2272–2284.
10. Heiro M, Nikoskelainen J, Engblom E, et al. Neurologic manifestations of infective endocarditis: a 17-year experience in a teaching hospital in Finland. Arch Intern Med 2000;160: 2781–2787.
11. Snygg-Martin U, Gustafsson L, Rosengren L, et al. Cerebrovascular complications in patients with left-sided infective endocarditis are common: a prospective study using magnetic resonance imaging and neurochemical brain damage markers. Clin Infect Dis 2008;47:23–30.
12. Hess A, Klein I, Iung B, et al. Brain MRI findings in neurologically asymptomatic patients with infective endocarditis. AJNR Am J Neuroradiol 2013;34:1579–1584.
13. Iung B, Tubiana S, Klein I, et al. Determinants of cerebral lesions in endo- carditis on systematic cerebral magnetic resonance imaging: a prospective study. Stroke 2013;44:3056–3062.
14. Tornos P, Iung B, Permanyer-Miralda G, et al. Infective endocarditis in Europe: lesson from the Euro heart survey. Heart 2005;91:571–575.
15. Anguera I, Miro JM, Vilacosta I, et al. Aorto-cavitary fistulous tract formation in infective endocarditis: clinical and echocardiographic features of 76 cases and risk factors for mortality. Eur Heart J 2005;26:288– 297.
16. Nadji G, Rusinaru D, Remadi JP, et al. Heart failure in left-sided native valve infective endocarditis: characteristics, prognosis, and results of surgical treatment. Eur J Heart Fail 2009; 11:668–675.
17. Colen TW, Gunn M, Cook E, Dubinsky T. Radiologic manifestations of extra-cardiac complications of infective endocarditis. Eur Radiol 2008;18:2433–2445.
18. Khwaja A: KDIGO Clinical practice guidelines for acute kidney injury. Nephron Clin Pract 2012;120:c179-c184. doi: 10.1159/000339789.

Abstract

Infectious endocarditis initially presented by septic embolization of the central nervous system - a case report

Marija Popović[1], Đorđe Stevanović[1,2], Ljiljana Marić Stepanović[1], Mina Poskurica[1], Vladimir Zdravković[1,2]

[1]Cardiology Clinic, University Clinical Center Kragujevac, Serbia, [2] Department for Internal medicine, Faculty of medical sciences, University of Kragujevac, Serbia

***Introduction**. Infective endocarditis (IE) is a life-threatening condition, whose clinical presentation is often not pathognomonic, especially in the initial stage, which is why timely diagnosis can be difficult.*
***Case report**. In our report, the patient was hospitalized due to elevated body temperature, dyspnea, and altered state of consciousness. Considering the history of two previous cerebrovascular insults (CVI) and altered state of consciousness on admission, along with an ischemic zone with potential reinfarction verified by brain MSCT, the patient was initially managed as recurrent CVI and a septic state of unknown etiology. Considering the seemingly clear cause of the neurological condition and pneumonia as a potential explanation for the inflammation, the triage procedure and examination of the patient were shortened. Only after additional clinical deterioration accompanied by an increase in cardio-specific markers did the consulting cardiologist diagnose mitral valve IE, on the eighth day of hospitalization. In the following period, infective endocarditis was treated medically, and the patient, with the persistence of neurological symptoms, developed septic embolization of the kidney, a mechanical complication of IE in the form of the posterior mitral cusp chord rupture, and acute cardiorenal syndrome. The planned transfer to a cardiac surgery facility was postponed due to a positive SARS-CoV-2 antigen test, and the patient was transferred to a COVID hospital, where she deceased after two months of treatment.*
***Conclusion.** Considering the cardiac and non-cardiac manifestations of a potentially fatal disease, it is necessary to first have IE in the differential diagnostic algorithm of complex patients, and from the moment of diagnosis, a multidisciplinary approach and continuous monitoring, with the aim of a more adequate treatment.*

***Kew words:** COVID-19, infectious endocarditis, septic embolizations, stroke*

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Case report

Cardiovascular risk in psoriatic arthritis- a new plot twist in an old story: a case report

Marija Stanković[1], Marina Deljanin Ilić[2,1], Dejan Petrović[2,1], Bojan Ilić[1], Milovan Stojanović[1], Aleksa Vuković[1]

[1]Institute for Treatment and Rehabilitation "Niška Banja", Niš, Serbia, [2]University of Niš, Faculty of Medicine, Niš, Serbia

Abstract Only recently has modern medicine begun to recognize the impact of well-known rheumatological conditions on the cardiovascular system. Although the initial evidence was only related to rheumatoid arthritis, recent studies indicate that other rheumatological processes, including psoriatic arthritis, also have an impact on the initiation or acceleration of the atherosclerotic process through low-grade systemic inflammation of small blood vessels, classifying these diseases as independent risk factors for CVD. Correction of traditional cardiovascular risk factors in this group of patients does not reduce the risk of adverse cardiovascular events. As we will show in this case, the only adequate prevention of increased morbidity and mortality in these patients is routine screening for asymptomatic myocardial ischemia.

Key words psoriatic arthritis, non-traditional risk factor, asymptomatic myocardial ischemia

Introduction

Psoriatic arthritis (PsA) is a chronic inflammatory immune-mediated arthropathy that accompanies or precedes a psoriatic cutaneous manifestation. Approximately 30% of patients with psoriasis (PsO) suffer from PsA[1-3]. The annual incidence is diversified, ranging from 0.1 to 23.1 per 100,000, while the prevalence ranges from 1 to 420 per 100,000[1,4].

Clinical presentation of PsA is heterogeneous and includes diverse variants of joint and skin conditions in terms of disease progression and outcomes. Therefore, patients may present with limited disability over time due to relatively benign articular inflammation. A more severe form of PsA is associated with progressive erosive and deforming joint damage[5,6], with a prognosis similar to rheumatoid arthritis (RA)[7].

In addition to articular and cutaneous involvement, there is increasing evidence from numerous epidemiologic studies, meta-analyzes, and systematic reviews that patients with PsA are also at higher risk for subclinical and clinical cardiovascular and cardio-metabolic disease compared with the general population, primarily due to accelerated atherosclerosis[8,9]. In particular, patients with psoriatic arthritis have a three- to fourfold higher prevalence of coronary atherosclerosis[10]. Compared to other chronic inflammatory arthritic diseases such as rheumatoid arthritis (RA) and ankylosing spondylitis, this association is much stronger[11-13].

On the other hand, extensive literature data have shown that mortality rates are higher in PsA patients due to the increased incidence of traditional cardiovascular risk factors (TRFs), including hypertension, dyslipidemia, and type 2 diabetes mellitus, in addition to the ongoing chronic inflammation of the underlying PsA disease[13,14]. Therefore, patients with PsA might be in what amounts to be a double cardiovascular risk: TRFs at the one end, and an ongoing, body-wide inflammation, on the other. This imposes the question of whether PsA should be considered as an independent cardiovascular risk factor and whether better knowledge of the association between PsA and cardiovascular score risk may help to treat and modify risk factors early, minimizing the impact of cardiovascular comorbidities, thus improving patients' long-term outcome[15-16].

Case presentation

We present the case of a 70-year-old man who was diagnosed with psoriasis shortly after the first appearance of skin manifestations in 2014.

In August 2016, the patient was for the first time admitted to the Rheumatology Clinic of the Institute "Niška Banja" for examination and evaluation of pain and swelling of the wrist and small joints of the hands and feet. On admission, he reported arterial hypertension, diabetes on oral anti-diabetic therapy, and smoking, with no food or drug allergies in his personal history.

Based on clinical, laboratory, and additional diagnostic tests, he was diagnosed with psoriatic arthritis and started on methotrexate 15 mg per week as a treatment regimen.

Corresponding author: Stanković Marija*, e-mail: ranmarrah@gmail.com, phone: +381692124162, address: Dragiše Cvetkovića 66/5, 18108, Niš, Srbija

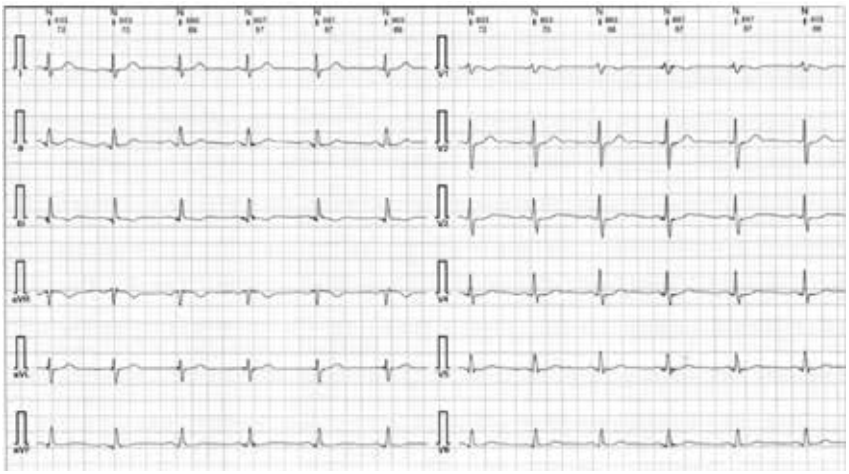

Figure 1. ECG before the start of the exercise treadmill test

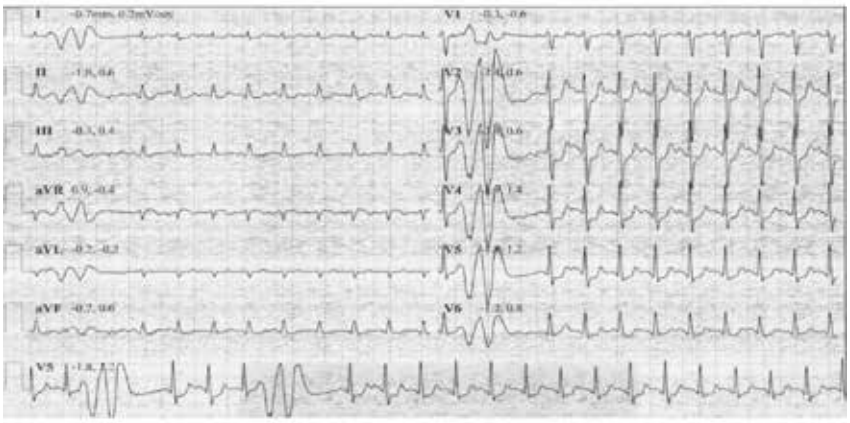

Figure 2. Descending ST segment depression of 1.5 mm in leads V2-V5 ventricular extrasystoles with R- on-T phenomenon during ECG exercise treadmill test monitoring

At his regular checkup in November 2017, radiological findings included narrowing of the spaces between the metacarpophalangeal (MCP), proximal interphalangeal (PIP), and distal interphalangeal (DIP) joints, bone proliferates at the level of the PIP and DIP joints, and periostitis, with no recommended change in Methotrexate dosage.

In January 2018, he was enrolled in a balneophysical rehabilitation program at the Institute "Niška Banja". During hospitalization, a treadmill stress test was performed. Continuous electrocardiogram (ECG) monitoring recorded a descending ST segment depression of 1.5 mm in leads V2-V5 with premature ventricular contractions (PVCs) and PVCs with an "R-on-T phenomenon" (*Figure 1 and 2*), without chest pain.

Six months later, he underwent a stress echocardiography test. Finally, after the finding of segmental motion abnormalities of the apicomedial segment of the lateral wall and the apical part of the septum, an invasive examination of the coronary arteries was indicated.

Coronary angiography was performed in February 2019, and multivessel coronary artery disease was found (*Figure 3*). Percutaneous coronary intervention with implantation of 3 stents in the left circumflex artery was performed in May 2019.

In October 2020, he was again enrolled in the a specialized cardiovascular rehabilitation at the Institute "Niška Banja". On admission, he denied chest pain, shortness of breath, joint pain, swelling, and stiffness. Routine laboratory tests revealed normal lipid and glycemic levels. Inflammatory parameters indicated low activity of the underlying disease (PsA).

The patient performed treadmill stress, the patients didn't have chest pain but the ECG was susceptive of myocardial ischemia in lateral leads (*Figure 4*). His anti-anginal therapy was intensified, and he was again scheduled for coronography. In November 2021, repeated coronarography demonstrated the new stenosis in the second obtuse marginal artery (OM2), and further continuation of drug therapy was recommended.

Discussion

The association between inflammatory arthropathies and cardiovascular disease (CVD) is well established. Despite the abundant research on this relationship, representatives of this group, with the exception of RA (17, 18), are still not recognized as risk factors for the development of CVD in everyday clinical practice.

Although is PsA mostly considered to be a milder arthropathy than RA, CVD mortality is almost the same in these two groups[19,20].

Recent mortality studies suggest increased mortality in patients with PsA compared with the general population. The increased mortality in PsA patients is predominantly due to cardiovascular disease[13], with the risk ratio for a cardiovascular event in the PsA patient group exceeding 43%[15,16].

Cardiovascular morbidity between the general population and PsA patients resembles polarization-alike mortality rates in these two groups.

Available data on the increased prevalence of TRFs with at least one cardiovascular event-including angina, myocardial infarction, cardiomyopathy, and heart failure in PsA patients compared with the general population is consistent[21-23].

Moreover, there is a negative outcome correlation between the number of TRFs and disease activity in these patients[24], contributing not only to overt but also to subclinical CVD[25]. These findings are consistent with the personal history of our patient, who had diabetes and hypertension, was dyslipidemic, and smoked.

Of concern, an increased prevalence of cardiovascular mortality and morbidity in PSA patients remains significant even after medical treatment and correction of TRFs, as is our patient's case. In this particular case, the progression of coronary artery disease was demonstrated by new stenosis (*OM2 60%)* by coronagraphy.

This raises the question of why patients with the relatively benign musculoskeletal disease are almost as likely to have CVD morbidity and mortality in percentage terms as patients with RA, which is considered an independent cardiovascular risk factor in modern medicine[19,26].

In the work of Husted et al, it was pointed out that diseases associated with inflammatory properties, such as PsA, tend to accelerate atherosclerosis via endothelial dysfunction and vascular stiffness at the functional level. Holistically, inflammation itself could be apprehended as an independent CVD risk factor across the group of inflammatory arthropathies[18] and a precursor to higher CV risk that precedes overt cardiovascular events and mortality[22,26].

And although there is ample evidence, including Ari Polaček's observational study involving 32 973 patients with PsA[15,16,26,27], to suggest that PsA is an independent risk factor for cardiovascular disease, most clinicians do not recognize it as such.

This bivalent approach is of concern considering that, as Lihi points out[28], there may be failures to treat traditional factors, which on the one hand increases the burden on the hospital system and the resulting economic burden on society, while on the other reduces the quality of life of PsA patients.

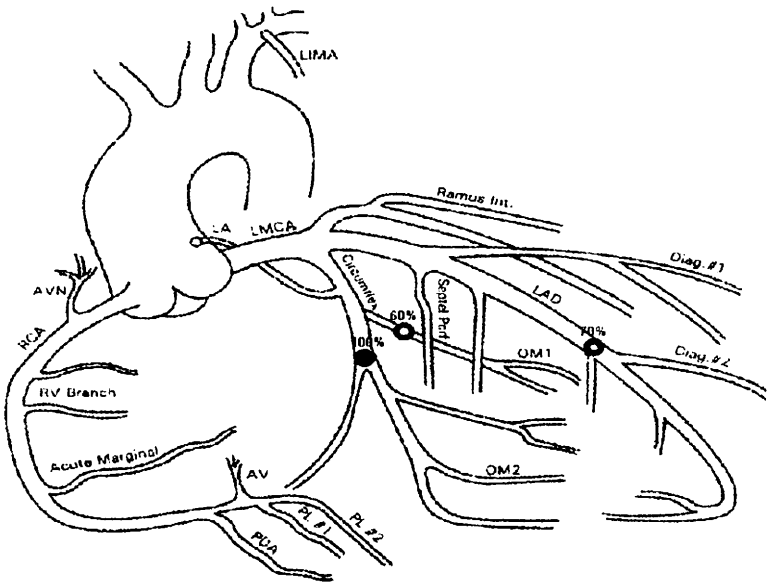

Figure 3. Coronarography findings (left main without stenosis, left anterior descending artery (LAD) medially stenosis 70%, left circumflex artery (LCx) medially occluded, first obtuse marginal artery (OM1) narrowed 60%), right coronary artery without stenosis

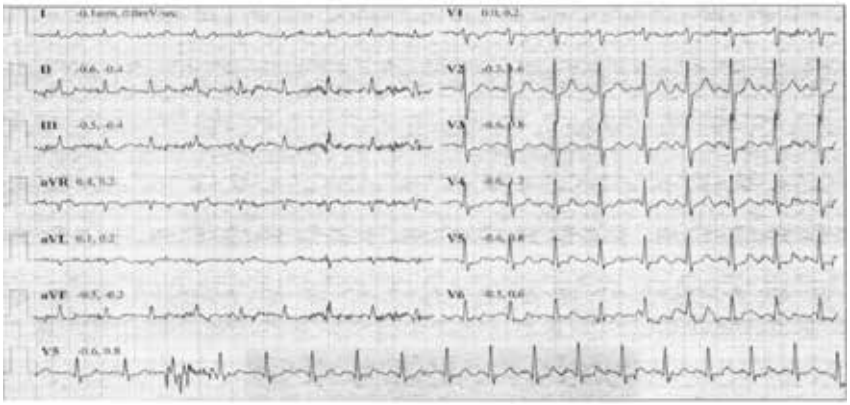

Figure 4. The susceptive mild ST changes in leads V5 and 6 during ECG treadmill stress test exercise treadmill test monitoring

Conclusion

We presented a case report of a PsA patient with asymptomatic coronary artery disease. PsA as an inflammatory autoimmune inflammatory disease represents an independent risk factor for CAD. Therefore, we believe that these patients should be routinely screened of CAD.

References

1. Alamanos Y, Voulgari PV, Drosos AA. Incidence and prevalence of psoriatic arthritis: a systematic review. *J Rheumatol* 2008; 35(7):1354–1358.
2. Tiwari V, Brent LH. Psoriatic Arthritis. [Updated 2021 Aug 11]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan; Available from: https://www.ncbi.nlm.nih.gov/books/NBK547710/
3. Hope C. Medically reviewed by Stephanie S. Gardner, MD on April 14, 2021. Psoriatic Arthritis Stages and Progression. Stages of Psoriatic Arthritis: How It Progresses (webmd.com)
4. Alinaghi F, Calov M, Kristensen LE, et al. Prevalence of psoriatic arthritis in patients with psoriasis: A systematic review and meta-analysis of observational and clinical studies. J Am Acad Dermatol 2019;80(1):251-265.e19. doi: 10.1016/j.jaad.2018.06.027. Epub 2018 Jun 19. PMID: 29928910.
5. Gladman, Dafna D. et al. Psoriatic arth*ritis (PSA)--an analysis of 220 patients.* Quarter J Med *1987;62:127-141.*
6. McHugh NJ, Balachrishnan C, Jones SM. Progression of peripheral joint disease in psoriatic arthritis: a 5-yr prospective study, Rheumatol 2003;*42 (6):778–783.*
7. Mok CC, Kwok CL, Ho LY, Chan PT, Yip SF. Life expectancy, standardized mortality ratios, and causes of death in six rheumatic diseases in Hong Kong, China (2011). Arthritis Rheum 2011; 63:1182-1189.
8. Sule B, Umut K, Abdulsamet E, et al. Assessment of subclinical atherosclerosis in psoriatic arthritis patients without clinically overt cardiovascular disease or traditional atherosclerosis risk factors. Turk Kardiyoloji Dernegi arsivi: Turk Kardiyoloji Derneginin yayin organidir 2018;46:358-365.
9. Lihi E, Vinod C, Dafna G. The Framingham Risk Score underestimates the extent of subclinical atherosclerosis in patients with psoriatic disease. Ann Rheum Dis 2013;73:10.1136/annrheumdis-2013-203433.
10. Crist C (January 17, 2017). Psoriatic Arthritis Linked to Increased Heart Disease Risk - The Rheumatologist (the-rheumatologist.org)
11. Galarza-Delgado DÁ, Azpiri-López JR, Colunga-Pedraza IJ, et al. AB1212 Prevalence of Carotid subclinical atherosclerosis in patients with Psoritatic Arthritis VS Rheumatoid Arthritis: A Case Control Srudy. Ann Rheum Dis 2020;**79:**1897.
12. Peters MJ, van der Horst-Bruinsma IE, Dijkmans BA, et al. Cardiovascular risk profile of patients with spondylarthropathies,

particularly ankylosing spondylitis and psoriatic arthritis. Seminar Arth Rheum 2004;34 (3):585-592.
13. Arumugam R, McHugh NJ. Mortality and causes of death in psoriatic arthritis. J Rheumatol Suppl 2012;89:32-35.
14. Ramonda R, Lo Nigro A, Modesti V, et al. Atherosclerosis in psoriatic arthritis, Autoimmun Rev 2011;10 (12):773-778.
15. Polachek, A., Touma, Z., Anderson M et al. Risk of cardiovascular morbidity in patients with psoriatic arthritis: A meta-analysis of observational studies. Arth Care Res 2017;69: 67-74.
16. Pappas S. (May 24, 2016). Psoriatic Arthritis: Independent Risk Factor for Cardiovascular Disease (rheumatologynetwork.com).
17. Fazeli MS, Khaychuk V, Wittstock K, et al. Cardiovascular disease in rheumatoid arthritis: Risk factors, autoantibodies, and the effect of antirheumatic therapies. Clinical medicine insights. Arthr Musculoskel Dis 2021;14: 11795441211028751. https://doi.org/10.1177/11795441211028751
18. Hannawi SM, Hannawi H, Al Salmi I. Cardiovascular risk in rheumatoid arthritis: Literature review. Oman Med J 2021;36(3):e262. https://doi.org/10.5001/omj.2021.25
19. Saalfeld W, Mixon AM, Zelie J, et al. Differentiating psoriatic arthritis from osteoarthritis and rheumatoid arthritis: A narrative review and guide for advanced practice providers. Rheumatol Ther 2021;8(4):1493–1517. https://doi.org/10.1007/s40744-021-00365-1
20. John H, Kitas G. Inflammatory arthritis as a novel risk factor for cardiovascular disease. Eur J Intern Med 2012;23(7):575-579. doi: 10.1016/j.ejim.2012.06.016. Epub 2012 Jul 28. PMID: 22841864.
21. Husted JA, Thavaneswaran, A, Chandran V, et al. Cardiovascular and other comorbidities in patients with psoriatic arthritis: A comparison with patients with psoriasis. Arthritis Care Res 2011;63:1729-1735. https://doi.org/10.1002/acr.20627
22. Gruev I, Staneva M, Karamfilof KK, et al. Psoriatic arthritis and subclinical atherosclerosis. Cr Acad Bulg Sci 2015;68:1199-1204.
23. Verhoeven F, Prati C, Demougeot C, et al. Cardiovascular risk in psoriatic arthritis, a narrative review, Joint Bone Spine 2020;87(5):413-418.
24. Ferraz-Amaro I, Prieto-Peña D, Palmou-Fontana N, et al. The number of traditional cardiovascular risk factors is independently correlated with disease activity in patients with psoriatic arthritis. Medicina (Kaunas) 2020;56(8):415. doi: 10.3390/medicina56080415. PMID: 32824666; PMCID: PMC7466182.
25. Zhu TY, Li EK, Tam LS. Cardiovascular risk in patients with psoriatic arthritis. Int J Rheumatol 2012;2012:714321. doi:10.1155/2012/714321
26. Popescu C, Pintilie AM, Bojinca V, Balanescu A, Ionescu R. Cardiovascular risk in psoriatic arthritis - a cross-sectional study. Maedica 2014;9(1):19-24.
27. Ramírez J, Azuaga-Piñango AB, Celis R, et al. Update on cardiovascular risk and obesity in psoriatic arthritis. Front Med Rheumatol 2021;8:742713. https://doi.org/10.3389/fmed.2021.742713
28. Lihi E, et al. Gaps in diagnosis and treatment of cardiovascular risk factors in patients with psoriatic disease: An International Multicenter Study. J Rheumatol 2018;45:378-384.

Sažetak

Kardiovaskularni rizik u psorijaznom artritisu- novi obrt u staroj priči: prikaz slučaja

Marija Stanković[1], Marina Deljanin Ilić[2,1], Dejan Petrović[2,1], Bojan Ilić[1], Milovan Stojanović[1], Aleksa Vuković[1]

[1]Institut za lečenje i rehabilitaciju "Niška Banja", Niš, Srbija, [2]Univerzitet u Nišu, Medicinski fakultet, Niš, Srbija

Relativno od skora, moderna medicina je počela da prepoznaje uticaj dobro poznatih reumatoloških stanja na kardiovaskularni sistem. Iako se prvobitni dokazi odnose na reumatoidni arthritis, sve je više studija da I drugi reumatološki procesi među kojima je i psorijazni artritis, takođe imaju uticaja na inicijaciju i akceleraciju ateroskleroskog procesa preko sistemske inflamacije malih krvnih sudova niskog gradusa, svrastavajući ove bolesti u nezavisni faktor rizika za nastanak kardiovaskularnih bolesti. Korekcija tradicionalnih kardiovaskularnih faktora rizika u ovoj grupi bolesnika ne smanjuje rizik incidence nepovoljnog kardiovaskularnog događaja. Kao što ćemo prikazati u slučaju, jedina adekvatna prevencija povećanja morbiditeta I mortaliteta kod ovih bolesnika je rutinski skrining na asimptomatsku miokardnu ishemiju.

***Ključne reči**: psorijazni artritis, netradicionalni faktori rizika, asimptomatska miokardna ishemija*

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Case report

Peripheral artery disease - contemporary approach through case report

Milan Nikolić[1], Vladimir Mitov[1], Aleksandar Jolić[1], Dragana Adamović[1], Marko Dimitrijević[1], Milan A. Nedeljković[2], Milena Nikolić[3], Fahrat Fouldevand[4], Oktaj Maksudov[5]

[1]Department of invasive cardiology, Health center Zaječar, [2]Clinic of cardiology, University Clinical center of Serbia, [3]Anestesiology and reanimatiology department, Health center Zaječar, [4]Clinica polispecialistica San Carlo, Paderno Dugnano, Italy, [5]Bulgarian cardiac institut, Bugras, Bulgaria

Abstract

Introduction. Peripheral arterial disease (PAD) of the lower extremities is an atherosclerotic disease of the arteries of the legs. Due to the frequent overlap of PAD and ischemic heart disease, cardiologists are in a unique position to screen, diagnose, and treat PAD. The aim of the paper is to present the initial results of the Department of Invasive Cardiology of Health center Zaječar in the diagnosis and treatment of patients with PAD of the lower extremities.

We present the initial results of the Department of Invasive Cardiology, including screening, non-invasive and invasive (angiographic) diagnosis of PAD of the lower extremities. Starting from March 2020, the Department of Invasive Cardiology is performing diagnostic invasive peripheral angiography in patients selected by non-invasive diagnostics from the territory of Eastern Serbia. In 2020 there were 3 and in 2021 5 more invasive peripheral angiographies performed. The number of these procedures is gradually increasing and during the first 10 months of 2022, 10 peripheral angiographies were performed. A total of 6 percutaneous angioplasties were performed as part of the endovascular treatment of PAD of the lower extremities, two of them within the Department of Invasive Cardiology Health center Zaječar symposium - ZASINK 2021. A complex patient with numerous comorbidities who was successfully treated with percutaneous angioplasty in our center is also presented.

Case report. A 67-year-old female patient with intermittent claudication at a distance of less than 10 meters after a physical examination was referred to ABI, which indicated a hemodynamically significant disease of the left leg (1.02 right; 0.68 left). Peripheral angiography was performed, which showed short segment stenosis of the left common iliac artery of about 80% and endovascular treatment was planned for the second act. During the following angiography, the mentioned segment was occluded. Percutaneous angioplasty was performed with the implantation of two balloon-expandable bare metal stents, with an excellent immediate angiographic result. After the procedure, the patient had significant symptomatic improvement. Dual antiplatelet therapy was continued for 6 months. During the follow-up period of 8 months, there were no clinically significant events in the patient. **Conclusion**. In a health center with experience in the treatment of various forms of coronary artery disease, the diagnosis and treatment of patients with PAD of the lower extremities can be successfully done with low procedural risk, as shown by our experience with 17 peripheral angiographies and 6 peripheral angioplasties performed, with a tendency to further increase the number and complexity of procedures performed.

Key words peripheral artery disease; PAD; ABI, angioplasty; peripheral angiography

Introduction

Peripheral arterial disease (PAD) of the lower extremities is an atherosclerotic disease of the arteries of the legs[1]. As a manifestation of systemic atherosclerosis, PAD is associated with significantly increased cardiovascular morbidity, mortality and reduced quality of life. Due to the frequent overlap of PAD and ischemic heart disease, cardiologists are in a unique position to screen, diagnose, and treat PAD. Clinical evidence is not as robust in patients with PAD compared to patients with coronary artery disease. However, the treatment goals in both groups are the same: to prevent ischemic cardiovascular events by changing lifestyle, medical therapy management and weighing the risks and benefits of revascularization procedures[2].

The aim of this study is to present of the initial results of the work of the Department of Invasive Cardiology Health center Zaječar in the diagnosis and treatment of patients with PAD of the lower extremities.

Address for correspondence: Dr Milan Nikolic, Department of invasive cardiology, Health center Zaječar. E-mail: nikolic.milan988@gmail.com.

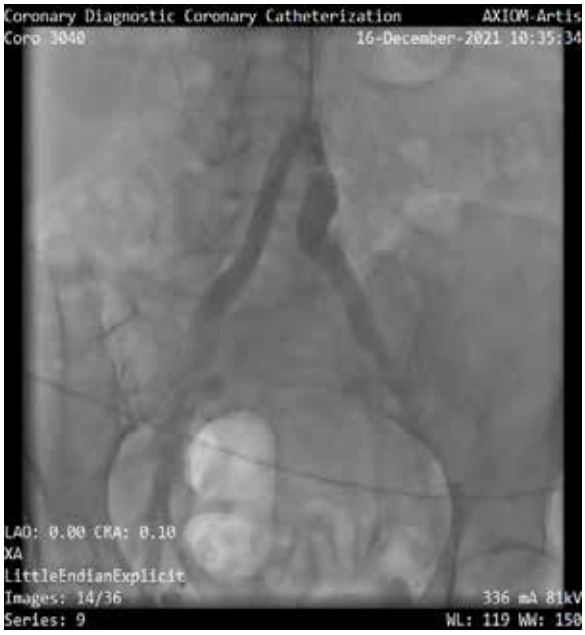

Figure 1.

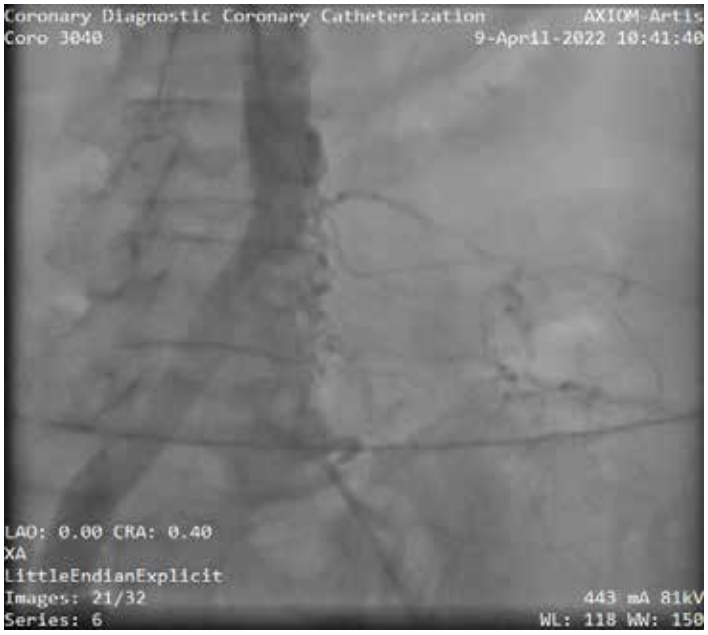

Figure 2.

We present the initial results of the Department of Invasive Cardiology, including screening, non-invasive and invasive (angiographic) diagnosis of PAD of the lower extremities. Starting from March 2020, the Department of Invasive Cardiology is performing diagnostic invasive peripheral angiographies in patients selected by non-invasive workup from the territory of Eastern Serbia. In 2020, there were 3 and in 2021 five more invasive peripheral angiographies performed. The number of these procedures is gradually increasing and during the first 10 months of 2022, 10 peripheral angiographies were performed. A total of 6 percutaneous angioplasties were performed as part of the endovascular treatment of PAD of the lower extremities, two of them within the Department of Invasive Cardiology Health center Zaječar symposium - ZASINK 2021. A complex patient with numerous comorbidities who was successfully treated with percutaneous angioplasty in our center is also presented.

Case presentation

A 67-year-old patient was referred to the Council of the Department of Invasive Cardiology due to intermittent claudication at a distance of less than 10 meters. In the medical history review she had a colour duplex scan examination of the major arteries, and an occlusion of the left anterior tibial artery was wound. After that, she was referred to a vascular surgeon at a tertiary health care level, where she was prescribed pentoxifylline and later cilostazol. In addition medical hystory is remarkable for arterial hypertension, chronic obstructive pulmonary disease and essential thrombocythemia, on cytoreductive therapy with hydroxyurea. After a physical examination with pulse palpation, the ankle brachial index (ABI) was performed: 1.02 on the right and 0.68 on the left. Acetylsalicylic acid and a high dose statin were prescribed to the patient and peripheral angiography was indicated. An angiographically significant lesion of the left common iliac artery of an estimated 80% diameter narrowing was appreciated (Figure 1). An endovascular treatment was indicated. In the second act dated 9/4/2022. during the planned PTA procedure performed through the right radial artery, there is an ostial occlusion of the left common iliac artery (Figures 2 and 3). Terumo straight stiff type wire 0.035 260cm passes through the lesion. Predilatation of the lesion was performed with Allunga PTA 5x40mm balloons at 4 atm and with the same type of 6x10mm balloon at 6 atm. Bare metal stents Omnilink Elite 7x59mm and Omnilink 8x59mm were implanted. Stent overlap was optimized with a balloon stent carrier and an excellent final angiographic finding was obtained (Figure 4). Dual antiplatelet therapy was continued for 6 months, after which clopidogrel was discontinued. After percutaneous angioplasty, there is no more claudication and walking is limited only partially by osteomuscular disease.

Discussion

Despite the fact that PAD of the lower extremities affects about 230 million people worldwide[2], a recent survey found that 61% of general practitioners screen patients for PAD and only 6% are familiar with evidence-based therapy guidelines[3]. After detailed history, every examination of a patient with suspicion of PAD should be supplemented with a targeted physical examination, because certain clinical findings have prognostic significance: the difference in arterial blood pressure in the arms over 15 mmHg is a marker of vascular disease and mortality[4]; murmur over the femoral artery is an independent prognostic marker of future ischemic coronary events[5]. Following that in the non-invasive diagnostic algorithm comes ABI (ankle brachial index). The limited availability of this method is considered one of the reasons for the underdiagnosis of PAD, even in countries such as the United States of America[6]. ABI of one side of the body represents the highest systolic pressure measured by inflating the cuff over the ankle with the Doppler blood flow signal registered over a. dorsalis pedis and a. tibialis posterior and then divided by the highest systolic pressure obtained over the ipsilateral brachial artery by

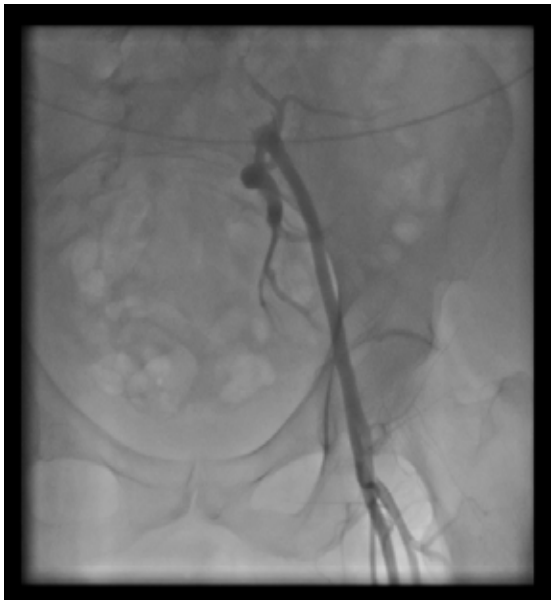

Figure 3.

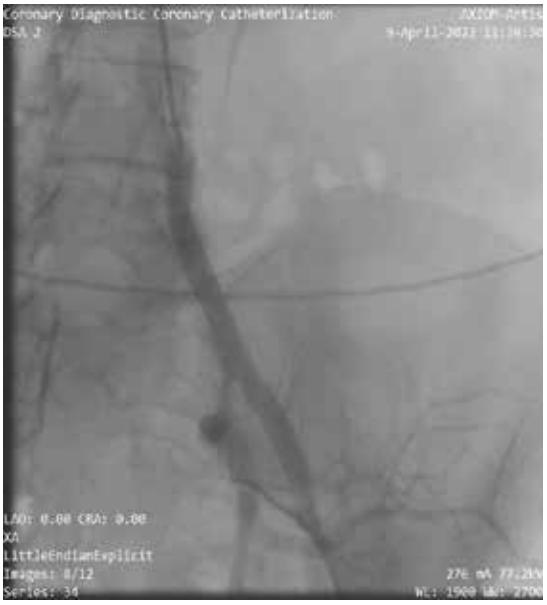

Figure 3.

inflating the cuff on the upper arm. It is determined individually for each side of the body. Values below 0.9 are suggestive of PAD of the lower extremities; 0.9-1.4 are considered normal: values over 1.40 indicate stiff/non compressible arteries and are caused by medial calcinosis, occurring more often in the elderly and patients with chronic kidney disease. In unclear cases, ABI can be performed after Treadmill exercise, increasing the sensitivity of the test[2]. The sensitivity and specificity of ABI in the detection of stenosis over 50% compared to imaging diagnostics as the gold standard is 61-73% and 83-96% respectively[1]. ABI is slightly lower in women, on average 0.017, which is not clinically significant[7]. This test shows lower reliability (proportion of true positive plus true negative patients out of the total population tested) in diabetics - 66%, compared to 81% in non-diabetic individuals. In diabetics, a better indicator, as well as in a population where greater arterial stiffness is expected, a better diagnostic indicator is TBI (toe-brachial index), because the small arteries of the fingers are very rarely affected by medial calcinosis (8). In the case of borderline ABI 0.9-1 and typical PAB symptoms in the lower extremities, exercise ABI is proposed, preferably on a treadmill. A drop in ABI below 0.9 or more than 20% of the pretest value or a drop in leg systolic pressure greater than 30 mmHg are considered diagnostic[9].

A color duplex scan can be used in non-invasive diagnostics. This method is non-invasive, there is no radiation exposure but is largely operator dependent. With this method, the femoropopliteal segments can generally be adequately examined, while the aortoiliac segments are less accessible due to intestinal gas and body habitus, especially in obese individuals[1].

MDCT angiography of the aorta and lower extremity arteries considered the "gold standard" in the definitive non-invasive diagnosis of PAD in order to assess the anatomical complexity of the disease and decide on revascularization modality. The sensitivity of the method in comparison with conventional angiography is about 90%. The advantage is a short acquisition time of only a few seconds, as well as the avoidance of vascular access site complications during diagnostic procedures, while the disadvantage is ionizing radiation exposure and the interference of calcified lesions with the findings obtained[1,10].

MR angiography has excellent sensitivity in the diagnosis of PAD - 90-100%[11]. The advantages of MR angiography over CT angiography are the absence of ionizing radiation and no interference with calcium in the diagnostic study. The disadvantage is the considerably longer time required for examination[1]. There is also a risk of nephritogenic systemic fibrosis in patients with significantly reduced renal function. Studies with newer paramagnetic contrast agents indicate that this risk is virtually non-existent[11]. Despite all the advantages, MR angiography is a less available diagnostic method in our country and worldwide.

In Healt center Zaječar, after the targeted anamnestic data collection and physical examination of the patient with pulse palpation and auscultation of possible murmurs over the peripheral arteries, determination of ABI is carried out. For these purposes, an automated ABI (MESI ABPI MD) device is used, which simultaneously determines the systolic pressure in all four extremities, and the acquisition period is about one minute. The system uses an automated Doppler signal delivered via pre-positioned cuffs on the upper arms and above the ankles and has a measurement error detection system. Patients with an index below 0.9 on one or both sides of the body are referred for peripheral invasive angiography.

Invasive peripheral angiography has long been considered the gold standard in the diagnosis of PAD, but nowdays is mainly used in the planning of endovascular procedures in patients with already performed anatomical non-invasive diagnostics[12]. Due to the local specifics of the health care system (unavailability of CT and MR angiography) and availability of trained medical personne workingl in the field of interventional cardiology in Health center Zaječar after positive ABI finding is appreciated, peripheral invasive angiography is indicated for patients as a diagnostic and, depending on the findings, therapeutic procedure in the same or subsequent act.

Invasive peripheral angiography is based on the acquisition of angiographic images after the injection of an

iodinated contrast agent, usually diluted with normal saline because of the local irritation it produces. Since the image of blood vessels in the environment of bones and large surrounding muscle mass is obtained, the method of subtraction (digital subtraction angiography - DSA) of the surrounding structures is used to obtain angiographic images of blood vessels of the legs with excellent resolution. Usually, the common femoral artery is used as a vascular access with the placement of a 5 or 6F vascular introducer. Then, the blood vessels of the ipsilateral leg are visualized by contrast injection through the vascular sheet and then a crossover is performed with a diagnostic catheter to the contralateral common iliac artery to visualize the blood vessels of the other leg[13]. In our center, the first angiograms were performed using a transfemoral approach. In the later course, diagnostic procedures are carried out by cannulation of the radial or ulnar artery, at first using a pigtail catheter, and then the JR4 5F 125 cm catheter (longer than the standard catheter for cannulation of the right coronary artery) becomes the standard in diagnosis, which can be used to reach the bifurcation of the aorta in most people with a standard stature. The first angiographic record is usually with the tip of the catheter before the aortic bifurcation to visualize the distal aorta and common iliac arteries and then the left and right common iliac arteries are selectively cannulated. A system of manual injection of diluted iodine contrast agent is used. When obtaining angiographic images of the infrapopliteal arterial segments , slight angulation of the C arch laterally up to 10 degrees and internal rotation of the patient's hip joint is used to avoid superposition of the lower leg bones. The total amount of aplicated contrast agent usually does not exceed 150-200ml and so far there have been no cases of contrast-induced nephropathy. Due to the transition to transradial vascular access, local vascular complications of the puncture site have been avoided so far.

Revascularization of PAD of the lower extremities is recommended in case of failure of medical therapy and supervised physical training and when symptoms of PAD significantly impair the patient's daily living acivities[14]. The presented patient had a claudication distance of less than 10 m, so it was decided to plan revascularization along with the introduction of drug therapy. Isolated iliac lesions (stenoses or occlusions) shorter than 5 cm have excellent long term outcome with endovascular treatment, with a five-year patency >90% with a low risk of complications[15]. The first peripheral angiography showed a short iliac stenosis in our patient, which corresponds to a TASC II type A lesion in which the recommended treatment is endovascular, so percutaneous transluminal angioplasty is indicated in the second act, for technical reasons. The subsequent peripheral angiography performed three months later, in which endovascular treatment was intended, revealed occlusion of the diseased segment of the artery. This corresponds to a TASC II type B lesion in which endovascular treatment is also recommended[16], so percutaneous angioplasty was performed using right radial and left femoral access simultaneously. Balloon-expanding bare metal stents were used, the main advantages of which are greater radial strength and more predictable positioning compared to self-expanding stents, and they are preferred in ostial and calcified lesions. In a study with the treatment of 222 lesions, the Omnilink stent showed excellent results with 93.1% of lesions successfully treated (less than 30% residual stenosis) with a total of 5.4% major adverse events in the 9-month follow-up period and 91% of lesions without clinically guided target lesion revascularization in a 3 years follow-up period (only 9% of clinically detected in-stent restenosis)[17]. After successful endovascular revascularization, at least one month of dual antiplatelet therapy is recommended, regardless of the type of stent used[14], although in some trials, dual antiplatelet therapy was used for 2 months[18] or one year[19]. However, the aforementioned studies were performed with drug-eluting stents or drug-coated balloons, which were not used in our procedure. Our patient has chronic myeloproliferative disease - essential thrombocythemia in which there is an increased risk of both ischemic and hemorrhagic complications[20-22], so the question of the optimal duration of dual antiplatelet therapy arose. Given that the patient is on cytoreductive therapy with hydroxyurea and the platelet count is well controlled, it was estimated that the ischemic risk outweighted the hemorrhagic one, so she was treated with dual antiplatelet therapy for 6 months, after which she was switched to monotherapy with aspirin.

Conclusion

In a center with experience in the treatment of various forms of coronary artery disease, the diagnosis and treatment of patients with peripheral arterial disease of the lower extremities can be successfully done with low procedural risk, as shown by our experience with 17 peripheral angiographies and 6 peripheral angioplasties performed, with a tendency to further increase the number and complexity of procedures performed.

References

1. Gerhard-Herman MD, Gornik HL, Barrett C, *et al*. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines.*Circulation* 2017;135:726–779.
2. Tran B. Assessment and management of peripheral arterial disease: what every cardiologist should know. *Heart* 2021; 107:1835–1843.
3. Bridgwood BM, Nickinson AT, Houghton JS, et al. Knowledge of peripheral artery disease: what do the public, healthcare practitioners, and trainees know? *Vasc Med* 2020; 25:263–273.
4. Clark CE, Taylor RS, Shore AC, *et al*. Association of a difference in systolic blood pressure between arms with vascular disease and mortality: a systematic review and meta-analysis. *Lancet* 2012;379:905–914.
5. Cournot M, Taraszkiewicz D, Cambou JP, *et al*. Additional prognostic value of physical examination, exercise testing, and arterial ultrasonography for coronary risk assessment in primary prevention. *Am Heart J* 2009;158:845–851.
6. Pradhan AD, Aday AW, Beckman JA. The Big MAC attack on peripheral artery disease.*Circulation* 2020; 141:1211–1213.
7. Aboyans V, Criqui MH, McClelland RL, et al. Intrinsic contribution of gender and ethnicity to normal ankle-brachial index values: the Multi-Ethnic Study of Atherosclerosis (MESA). *J Vasc Surg*. 2007;45:319–327.
8. AbuRahma AF, Adams E, AbuRahma J, *et al*. Critical analysis and limitations of resting ankle-brachial index in the diagnosis of symptomatic peripheral arterial disease patients and the role of

diabetes mellitus and chronic kidney disease.*J Vasc Surg 2020*; 71:937–945.
9. Aboyans V, Criqui MH, Abraham P, et al.; on behalf of the American Heart Association Council on Peripheral Vascular Disease; Council on Epidemiology and Prevention; Council on Clinical Cardiology; Council on Cardiovascular Nursing; Council on Cardiovascular Radiology and Intervention, and Council on Cardiovascular Surgery and Anesthesia. Measurement and interpretation of the ankle-brachial index: a scientific statement from the American Heart Association.*Circulation* 2012; 126:2890–2909.
10. Takahashi EA, Kinsman KA, Neidert NB, *et al*. Guiding peripheral arterial disease management with magnetic resonance imaging. *Vasa* 2019; 48:217–222.
11. Woolen SA, Shankar PR, Gagnier JJ, *et al*. Risk of nephrogenic systemic fibrosis in patients with stage 4 or 5 chronic kidney disease receiving a group II gadolinium-based contrast agent: a systematic review and meta-analysis.
12. Sun Z. Digital Variance Angiography: A promising alternative technology to traditional angiography for improvement of image quality with reduction of radiation and contrast medium doses. *Cardiovasc Interv Radiol* 2021;44:460–461.
13. Posa, A.; Tanzilli, A.; Barbieri, *et al*. Digital subtraction angiography (DSA) technical and diagnostic aspects in the study of lower limb arteries. *Radiation* 2022;2:376–386.
14. Aboyans V, Ricco JB, Marie-Louise EL, *et al*. ESC Scientific Document Group, 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries.Endorsed by: the European Stroke The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS), *Eur Heart J* 2018;39(9):763–816.
15. Indes JE, Pfaff MJ, Farrokhyar F, *et al*. Clinical outcomes of 5358 patients undergoing direct open bypass or endovascular treatment for aortoiliac occlusive disease: a systematic review and meta-analysis. *J Endovasc Ther* 2013;20:443–455.
16. Hardman RL, Jazaeri O, Yi J, *et al*. Overview of classification systems in peripheral artery disease. *Semin Intervent Radiol* 2014; 31(4):378-388.
17. Aggarwal V, Waldo SW, Armstrong EJ. Endovascular revascularization for aortoiliac atherosclerotic disease. *Vasc Health Risk Manag* 2016;12:117-127.
18. Dake MD, Ansel GM, Jaff MR, *et al*. Durable clinical effectiveness with paclitaxel-eluting stents in the femoropopliteal artery: 5-year results of the Zilver PTX randomized trial. *Circulation* 2016; 133:1472–1483.
19. Laird JR, Schneider PA, Tepe G, *et al*. Durability of treatment effect using a drug-coated balloon for femoropopliteal lesions: 24-month results of IN.PACT SFA. *J Am Coll Cardiol* 2015;66:2329–2338.
20. Fenaux F, Simon M, CAulier MT, *et al*. Clinical course of essential thrombocythemia in 147 cases.*Cancer* 1990;66(3):549-556.
21. Pósfai É, Marton I, Borbényi Z, *et al*. Myocardial infarction as a thrombotic complication of essential thrombocythemia and polycythemia vera. *Anatol J Cardiol* 2016;16(6):397-402.
22. Palandri F, Polverelli N, Ottaviani E, *et al*. Long-term follow-up of essential thrombocythemia in young adults: treatment strategies, major thrombotic complications and pregnancy outcomes. A study of 76 patients. *Haematologica*. 2010;95(6):1038-1040.

Sažetak

Periferna arterijska bolest – savremen pristup kroz prikaz slučaja

Milan Nikolić[1], Vladimir Mitov[1], Aleksandar Jolić[1], Dragana Adamović[1], Marko Dimitrijević[1], Milan A. Nedeljković[2], Milena Nikolić[3], Fahrat Fouldevand[4], Oktaj Maksudov[5]

[1]Odeljenje invazivne kardiologije, Zdravstveni centar Zaječar, [2]Klinika za kardiologiju, Univerzitetski Klinički centar Srbije
[3]Anesteziologija i reanimacinioni odeljenje, Zdravstveni centar Zaječar, [4]Clinica polispecialistica San Carlo, Paderno Dugnano, Italija
[5]Bulgarian cardiac institut, Bugras, Bugarska

Uvod. *Periferna arterijska bolest (PAB) donjih ekstremiteta je aterosklerotsko oboljenje arterija nogu. Zbog čestog preklapanja PAB i ishemijske bolesti srca kardiolozi su u jedinstvenoj prilici da sprovedu skring, dijagnostiku i lečenje PAB. Cilj rada je priikaz početnih rezultata rada Odeljenja invazivne kardiologije ZC Zaječar u dijagnostici i lečenju bolesnika sa PAB donjih ekstremiteta.*

Metode*. U radu su prikazani početni rezultati rada Odeljnjenja invazivne kardiologije, uključujući skrining, neinvazivnu i invazivnu (angiografsku) dijagnostiku PAB donjih ektremiteta. Počev od marta 2020. godine na Odeljenju invazivne kardiologije sprovode se dijagnostičke invazivne periferne angiografije kod pacijanata selektovanih neinvazivnom dijagnostikom sa teritorije istočne Srbije. U 2020. godini urađeno je 3 i u sledećoj 2021. još 5 invazivnih perifernih angiografija. Postepeno dolazi do povećanja broja ovih procedura i tokom prvih 10 meseci 2022. godine urađeno je 10 perifernih angiografija. Ukupno je urađeno 6 perkutanih angioplastika u sklopu lečenja PAB donjih ekstremiteta, od toga dve u okviru simpozijuma Odeljenja invazivne kardiologije ZC Zaječar - ZASINK 2021. godine. Prikazana je i kompleksna bolesnica sa brojnim komorbiditetima koja je uspešno lečena perkutanom angioplastikom u našem centru.*

Prikaz slučaja. *Bolesnica starosti 67 godina sa intermitentnim klaudikacijama pri distanci kraćoj od 10 metara nakon fizikalnog pregleda upućena je na ABI koji je ukazao na hemodinamski značajnu bolest leve noge (1.02 desno; 0.68 levo). Urađena je periferna angiografija na kojoj je viđena stenoza leve zajedničke ilijačne arterije oko 80% u kraćem segmentu i za drugi akt planirano endovaskularno lečenje. Pri narednoj angiografiji navedeni segment je okludiran. Urađena je perkutana angioplastika sa implantacijom balon oslobađajuća 2 bare metal stenta, uz odličan neposredni angiografski rezultat. Nakon procedure pacijentkinja ima značajno simptomatsko poboljšanje. Sprovedena je dvojna antirombocitna terapija u trajanju od 6 meseci. U periodu praćenja od 8 meseci nije bilo kliničkih događaja od značaj kod bolesnice.*

Zaključak.*U centru sa iskustvom u lečenju različitih oblika prezentacije koronarne arterijske bolesti može se uspešno ogranizovati dijagnostika i lečenje bolesnika sa perifernom arterijskom bolešću donjih esktremiteta uz nizak proceduralni rizik što pokazuju naša iskustva sa 17 urađenih perifernih angiografija i 6 perifernih angioplastika, sa tendencijom daljeg povećanja broja i kompleksnosti izvedenih procedura.*

Ključne reč*i: periferna arterijska bolest donjih ekstremiteta; PAB; angioplastika, ABI, periferna angiografija*

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Case Report

Empagliflozin-associated euglycemic ketoacidosis

Ivona Vranić[1], Ivan Stanković[1,2], Miloš Panić[1], Predrag Miličević[1], Aleksandar N. Nešković[1,2]

[1]Clinical Hospital Centre Zemun, Department of Cardiology, Vukova 9, Belgrade, Serbia, [2]Faculty of Medicine, Belgrade University, Dr Subotića 8, Belgrade, Serbia

Abstract We present a case of euglycemic ketoacidosis in a 69-year-old patient with diabetes mellitus type 2 treated with insulin and empagliflozin who was hospitalised for high-intermediate risk pulmonary thromboembolism. After initial clinical improvement with conservative therapy, on the fifth day of hospitalisation the patient became dyspnoeic (Kussmaul type), with nausea and fatigue, but without other significant physical, electrocardiographic or echocardiographic findings. Laboratory results revealed metabolic acidosis with increased anion gap and significant ketonuria, but without marked hyperglycemia. We suspected the occurrence of euglycemic ketoacidosis, stopped empagliflozin and proceeded with treatment protocol for diabetic ketoacidosis. After 36 hours the patient was stabilised with normal acid-base status, but glycosuria was observed the following seven days, as a prolonged effect of empagliflozin.

Key words empagliflozin, SGLT2 inhibitor, euglycemic ketoacidosis

Introduction

Sodium glucose cotransporter 2 inhibitors (SGLT2 inhibitors) represent an important therapeutic group that is widely used owing to their anti-diabetic, cardiovascular and renoprotective effects, a favourable safety profile and no need for dose titration[1,2]. Side effects are rare, with genitourinary infections (3-10%) and volume depletion (9.4%) being most commonly observed[3,4]. Euglycemic ketoacidosis is described as a rare adverse effect of SGLT2 inhibitors that can develop in circumstances of absolute or relative lack of insulin, during acute infections, surgery, pregnancy, fasting, dehydration, strenuous physical exertion or high alcohol consumption[5]. All of these scenarios can cause relative insulin deficiency and insulin glucagon ratio inversion leading to ketoacidosis[6]. Euglycemic ketoacidosis is a rare, life-threatening condition, that can be difficult to diagnose, thus leading to a delay in treatment. It is therefore important to recognise the conditions that might trigger this metabolic disorder in order to prompt early diagnosis and treatment[7]. We present a case of euglycemic ketoacidosis in patient with type 2 diabetes treated with insulin and empagliflozin who was hospitalised for high-intermediate risk pulmonary thromboembolism.

Case presentation

A 69-year-old woman presented to emergency room with progressive dyspnoea, malaise, fever and chest pain. She reported arterial hypertension, hyperlidipemia and diabetes mellitus type 2 (on insulin therapy and empagliflozin) in her medical history. One month prior to current admission, she had a cardiac surgery (a coronary artery bypass grafting) for unstable angina pectoris. After uncomplicated surgery with unremarkable perioperative period, the patient was inactive at home. On the day of admission to our department, the patient was conscious but adynamic, subfebrile and dyspnoeic with oxygen saturation of arterial blood of 87% on room air. Physical examination revealed no breath sounds in the basal portion of the left lung and occasional bilateral late inspiratory crackles. An electrocardiogram revealed sinus tachycardia and negative T-waves in the lateral leads, while echocardiographic examination showed the signs of right ventricular overload, including a dilated right ventricle, McConnell's sign and early systolic notching in pulmonary artery Doppler flow signal. Chest X ray showed signs of congestion and a large left sided pleural effusion (Figure 1), while computed tomography pulmonary angiography showed the signs of massive pulmonary thromboembolism, unilateral left pleural effusion with subsequent atelectasis (Figure 2). The patient was hemodynamically stable and was started on low-weight molecular heparin and also dual antibiotic therapy because of clinical and laboratory markers of infection (C-reactive protein 130 mg/L, fibrinogen 7.1 g/L). After the initial clinical improvement, on the fifth day of hospitalisation, the patient became dyspnoeic (with Kussmaul breathing), nauseous and lethargic. Laboratory results showed metabolic acidosis with increased anion gap (pH 7.19, bicarbonate 6.1 mmol/L, anion gap 31 mmol/L) and marked ketonuria with only slightly elevated blood glucose levels (9.5 mmol/L). Since the findings were consistent with an euglycemic ketoacidosis, empagliflozin was immediately stopped and protocol for diabetic

Address for correspondence: Ivona Vranić, Clinical Hospital Centre Zemun, Department of Cardiology, Vukova 9, 11080 Belgrade, Phone: +381 62 260 803, e-mail: ivona-26@hotmail.com

ketoacidosis initiated. The acid-base balance and patient clinical status gradually improved and eventually normalized in the ensuing 36 hours (Figure 3). Although empagliflozin was immediately stopped, its prolonged effect (glycosuria and ketonuria) was observed over the next 7 days, but without acidosis. The patient was recovered and discharged from hospital 3 weeks later.

Discussion

Euglycemic ketoacidosis is an acute, life-threatening emergency that requires prompt diagnosis and treatment with an incidence of 2.6 – 3.2% of all admissions with diabetic ketoacidosis[8]. It was first described by Munro et al. in 1973 in patients with diabetes mellitus type 1[9] and is characterised by ketoacidosis and mildly elevated serum glucose (less than 14 mmol/L)[10]. It is diagnosed by excluding other causes of metabolic acidosis with increased anion gap such as excessive alcohol consumption, methanol or polyethylene glycol ingestion, sepsis, lactic acidosis, drug overdose (salicylate or tricyclic antidepressants), ketosis due to prolonged starvation and/or strenuous physical exertion, as well as glycogen storage diseases[5,10,11]. Common causes of euglycemic ketoacidosis are use of SGLT2 inhibitors, pregnancy, and prolonged starvation[5].

SGLT2 inhibitors reduce serum glucose by inhibiting 80-90% glucose reabsorption in the proximal renal tubule, subsequently leading to osmotic diuresis[5]. In the conditions of stress (e.g. acute myocardial infarction, acute decompensated heart failure, acute infection, surgery, trauma, fasting, strenuous physical exertion) there is an excess of counterregulatory hormones (catecholamines, cortisol and glucagon), leading to a relative deficiency of insulin in diabetes type 2, an absolute insulin deficiency in diabetes type 1 and ketogenesis and ketoacidosis[6]. The lack of carbohydrates and dehydration associated with SGLT2 inhibitor use (trough glycosuria and osmotic diuresis) plays a pivotal role in the development of euglycemic ketoacidosis[6]. Additionally, SGLT2 inhibitors stimulate pancreatic alpha cells promoting glucagon secretion and reduce the excretion of ketone bodies in the proximal tubule, thus facilitating the occurrence of euglycemic ketoacidosis in stress situations[12,13].

This rare, but life-threatening side effect of SGLT2 inhibitors was the reason American Association of Clinical Endocrinologists and American College of Endocrinology recommended that SGLT2 inhibitors should be omitted 24 hours prior to elective surgery[14]. There are some published data about the

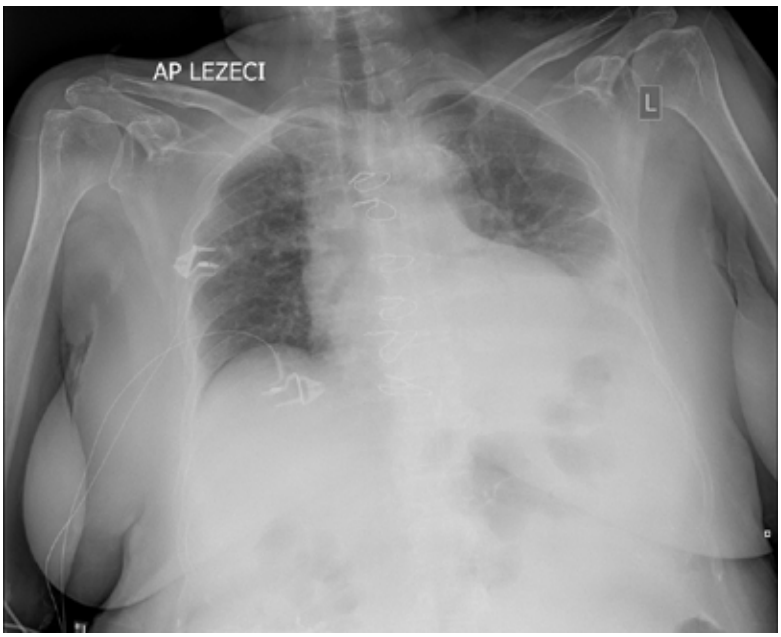

Figure 1. Chest X ray showing the signs of pulmonary congestion and a large left-sided pleural effusion

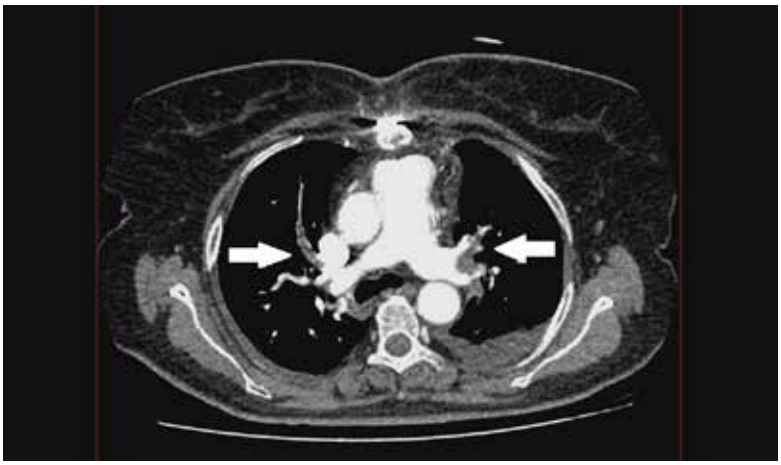

Figure 2. Computed tomography pulmonary angiography showing thrombi in both pulmonary artery branches and their lobar and segmental branches (arrows)

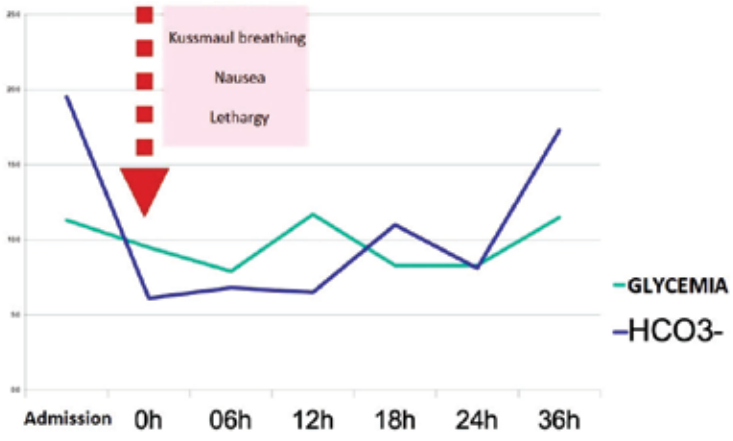

Figure 3. Temporal changes of bicarbonate and blood glucose levels from the occurrence of ketoacidosis (0h) and over the following 36 hours

possibility of prolonged SGLT2 inhibitors effect, that can last up to 8 to 10 days after drug discontinuation[15]. In some cases, even after drug omission 2-3 days prior to elective surgery, prolonged glycosuria with ketonemia was observed due to decelerated drug pharmacokinetics[16,17,18]. Given the long terminal half-lives of SGLT-2 inhibitors, the U.S. Food and Drug Administration recommends discontinuing canagliflozin, dapagliflozin, and empagliflozin at least three days before, and ertugliflozin at least four days before scheduled surgery[19]. In acidosis, SGLT2 inhibitors are highly bound to plasma proteins (80-90%), and their dissociation is possible only after acid-base normalisation, which is a necessary step in order for drug to be eliminated from the body[20].

In euglycemic ketoacidosis associated with SGLT2 inhibitors, immediate drug discontinuation is required followed by correction of hypovolemia and electrolytes, as well as insulin and glucose replacement[21]. Since drug prolonged effect has been observed, longer acid-base and electrolyte status follow-up is advisable.

SGLT2 inhibitors are used in treatment of diabetes mellitus, chronic heart failure and chronic kidney disease. In comparison to numerous beneficial effects, there is a fairly low occurrence of side effects (urinary tract infections, genital mycotic infections, dehydration, ketoacidosis), most of which are preventable. While the EMPEROR-PERSERVED study reported 4 cases (0.1 %) of ketoacidosis, there was no observed cases of ketoacidosis in the EMPEROR- REDUCED trial (22, 23). Furthermore, in a study investigating the effects of dapagliflozin in heart failure with reduced ejection fraction (DAPA-HF), only two cases (0.1 %) of diabetic ketoacidosis were observed (24). Additional 2 cases (0,1%) of diabetic ketoacidosis were reported in DELIVER study which investigated the effects of dapagliflozin in heart failure with preserved ejection fraction (25).

To prevent euglycemic ketoacidosis, temporary SGLT2 inhibitor discontinuation should be considered in acute illnesses, metabolic disturbances and infections.

References

1. Zelniker TA, Wiviott SD, Raz I, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet 2019; 393: 31-39.
2. Neuen BL, Young T, Heerspink HJL, et al. SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: a systematic review and meta-analysis. Lancet Diabetes Endocrinol 2019; 7: 845-854.
3. Halimi S, Vergès B. Adverse effects and safety of SGLT-2 inhibitors. Diabetes Metab 2014; 40(6 Suppl 1): S28-34.
4. Vukadinović D, Abdin A, Anker SD, et al. Side effects and treatment initiation barriers of sodium-glucose cotransporter 2 inhibitors in heart failure: a systematic review and meta-analysis. Eur J Heart Fail 2022; 24(9): 1625-1632.
5. Nasa P, Chaudhary S, Shrivastava PK, Singh A. Euglycemic diabetic ketoacidosis: A missed diagnosis. World J Diabetes 2021; 12(5): 514-523.
6. Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. Diabetes Care 2009; 32: 1335-1343.
7. Mahfooz RS, Khan MK, Al Hennawi H, Khedr A. SGLT-2 Inhibitor-Associated Euglycemic Diabetic Ketoacidosis: A Case Report and a Literature Review. Cureus 2022; 14(6): e26267.
8. Yu X, Zhang S, Zhang L. Newer Perspectives of Mechanisms for Euglycemic Diabetic Ketoacidosis. Int J Endocrinol 2018; 2018: 7074868.
9. Munro JF, Campbell IW, McCuish AC, Duncan LJ. Euglycaemic diabetic ketoacidosis. Br Med J 1973; 2: 578-580.
10. Modi A, Agrawal A, Morgan F. Euglycemic Diabetic Ketoacidosis: A Review. Curr Diabetes Rev 2017; 13: 315-321.
11. Barski L, Eshkoli T, Brandstaetter E, Jotkowitz A. Euglycemic diabetic ketoacidosis. Eur J Intern Med 2019; 63: 9-14.
12. Taylor SI, Blau JE, Rother KI. SGLT2 inhibitors may predispose to ketoacidosis. J Clin Endocrinol Metab 2015; 100: 2849-2852.
13. Thomas MC, Cherney DZI. The actions of SGLT2 inhibitors on metabolism, renal function and blood pressure. Diabetologia 2018; 61: 2098-2107.
14. Handelsman Y, Henry RR, Bloomgarden ZT, et al. American Association of Clinical Endocrinologists and American College of Endocrinology position statement on the association of SGLT-2 inhibitors and diabetic ketoacidosis. Endocr Pract 2016; 22(6): 753-762.
15 Pujara S, Ioachimescu A. Prolonged Ketosis in a Patient With Euglycemic Diabetic Ketoacidosis Secondary to Dapagliflozin. J Investig Med High Impact Case Rep 2017; 5(2): 2324709617710040.
16. Nishida A, Ogawa O, Takizawa H. Detection of Euglycemic Diabetic Ketoacidosis During Thoracic Surgery 75 Hours After Empagliflozin Discontinuation. Cureus 2022; 14(10): e29974.
17. Goldenberg RM, Berard LD, Cheng AYY, Gilbert JD, Verma S, Woo VC, Yale JF. SGLT2 Inhibitor-associated Diabetic Ketoacidosis: Clinical Review and Recommendations for Prevention and Diagnosis. Clin Ther. 2016 Dec;38(12):2654-2664.e1.
18. Aggarwal A, Jain A, Sachdeva S, Kulairi ZI. Prolonged Glucosuria With Sodium-Glucose Cotransporter-2 (SGLT2) Inhibitors: A Case Report and Review of Literature. Cureus 2020; 12(11):e11554.
19. U.S. Food and Drug Administration [Internet]. FDA revises labels of SGLT2 inhibitors for diabetes to include warnings about too much acid in the blood and serious urinary tract infections; 2022 Mar 15 [cited 2022 Nov 20]. Available from: https://www.fda.gov/drugs/drug-safety-and-availability/fda-revises-labels-sglt2-inhibitors-diabetes-include-warnings-about-too-much-acid-blood-and-serious?utm_medium=email&utm_source=transaction
20. Hinderling PH, Hartmann D. The pH dependency of the binding of drugs to plasma proteins in man. Ther Drug Monit 2005; 27: 71-85.
21. Bonora BM, Avogaro A, Fadini GP. Euglycemic ketoacidosis. Curr Diab Rep. 2020; 20(7): 25.
22 Anker SD, Butler J, Filippatos G, et al. EMPEROR-Preserved Trial Investigators. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. N Engl J Med 2021; 385(16): 1451-1461.
23. Packer M, Anker SD, Butler J, et al. EMPEROR-Reduced Trial Investigators. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. N Engl J Med 2020; 383(15): 1413-1424.
24. McMurray JJV, Solomon SD, Inzucchi SE, et al. DAPA-HF Trial Committees and Investigators. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med 2019 Nov 21;381(21):1995-2008.
25. Solomon SD, McMurray JJV, Claggett B, et al. DELIVER Trial Committees and Investigators. Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. N Engl J Med 2022; 387(12): 1089-1098.

Sažetak

Euglikemijska ketoacidoza povezana sa empagliflozіom: prikaz slučaja

Ivona Vranić[1], Ivan Stanković[1,2], Miloš Panić[1], Predrag Miličević[1], Aleksandar N. Nešković[1,2]

[1]Kliničko-bolnički centar Zemun, Odeljenej kardiologije, Vukova 9, Belgrade, Serbia
[2]Medicinski fakultet, Univerzitet u Beogradu, Dr Subotića 8, Belgrade, Serbia

Prikazujemo slučaj euglikemijske ketoacidoze u bolesnice stare 69 godina, sa poznatim dijabetesom melitusom tip 2 na terapiji insulinom i empagliflozinom, koja je hospitalizovana zbog tromboembolije pluća visokog-intermedijarnog rizika. Ubrzo po prijemu, na primenjenu terapiju stanje pacijentkinje se stabilizuje, ali petog dana hospitalizacije dolazi do razvoja otežanog disanja Kussmaul-ovog tipa, mučnine i malaksalosti, bez drugih promena u fizikalnom, elektrokardiografskom i ehokardiografskom nalazu. U laboratorijskim analizama je registrovana metabolička acidoza sa povišenim anjonskim zjapom, izražena ketonurija bez značajne hiperglikemije. Postavljena je sumnja na euglikemijsku ketoacidozu, nakon čega je obustavljen empagliflozin i ordinirana terapija za dijabetesnu ketoacidozu. Nakon 36 sati dolazi do normalizacije acido-baznog statusa i stabilizacije stanja pacijentkinje, ali se odložen efekat empagliflozina u vidu glikozurije prati tokom narednih nedelju dana.

***Ključne reči**: empagliflozin, SGLT2 inhibitor, euglikemijska ketoacidoza*

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Review article

Clinical application of cardiopulmonary exercise stress test for the recommendations for physical activity in patients with chronic heart failure

Ivana Nedeljković[1,2], Vojislav Giga[1,2], Marko Banović[1,2], Ana Djordjević Dikić[1,2], Nikola Bošković[2], Marina Ostojić[2], Nenad Radivojević[2], Marija Zdravković[1,3], Tamara Stojmenović[4], Nenad Dikić[4], Olga Petrović[1,2], Emilija Nestorović[1,4], Svetozar Putnik[1,5], Katarina Matejić Gaćeša[2], Marija Ristić[2], Branko Beleslin[1,2]

[1]Medical Faculty, University of Belgrade, [2]Cardiology Clinic, University Clinical center of Serbia, Belgrade, [3]KBC "Bežanijska Kosa", Belgrade, [4]Faculty for physical culture and management in sport - University Singidunum, Belgrade, [5]Clinic for cardiosurgery, University Clinical center of Serbia, Belgrade

Abstract Physical activity (PA) according to current guidelines is an important adjunctive therapy for patients with chronic heart failure (CHF) with reduced and preserved ejection fraction (HFrEF and HFpEF) which is level of evidence class 1A. However, as with any therapy, PA must be dosed according to the patient's own characteristics, so an individual assessment and prescription of exercise intensity is necessary. Different types of PA (endurance and resistance) and intensity levels (mild, mild to moderate, and high to moderate) are used in programs in patients with CHF.
The assessment can be carried out through indirect (heart rate reserve) or direct metabolic measures (VO2 reserve, anaerobic threshold) where precision is ensured by direct assessment of VO2 kinetics at constant work speed protocols of various loads - ergospirometry. Ergospirometry enables a direct assessment of the occurrence of anaerobic metabolism and real fatigue of the patient towards the limits of his position under different loads. In addition, the effect of exercise can be monitored on the basis of control tests. In this way, evidence-based efforts are prevented that a person with CHF cannot sustain or that would not lead to progress and improvement in symptoms and effort tolerance. Also, it enables a gradual increase in intensity and further progress in exercise.

Key words chronic heart failure, cardiopulmonary exercise test, functional capacity, anaerobic threshold, oxygen consumption, training prescription

Exercise is a key element in the prevention and treatment of cardiovascular diseases (CVD), and leads to improved quality of life, mortality, disability and prevention of comorbidities. Therefore, regular physical activity (PA) with at least 150 minutes of moderate-intensity aerobic exercise or at least 75 minutes of high-intensity exercise per week is recommended, with additional health benefits as minutes per week increase[1].

According to the current guidelines, PA is also adjunctive therapy for patients with chronic heart failure (CHF) with reduced and preserved ejection fraction (HFrEF and HFpEF), which is the level of evidence class 1A. However, like any therapy, it must be dosed according to the CHF severitiy and the capabilities of the patient himself, so individual assessment and prescription of exercise intensity is necessary. Different types of PA (endurance and resistance) and intensity levels (mild, mild to moderate, and moderate to high) are used in programs in patients with CHF[1-5].

For the objective assessment and determination of functional capacity, the gold standard is cardiopulmonary exercise test- ergospirometry (CPET)[6]. On the basis of CPET, patients with CHF are precisely stratified, which is the starting point for prescribing PA and monitoring the effects of exercise (Table 1).

CPET-based parameters for the assessment of the degree of CHF

Improvement in functional capacity is the most immediate and objective result of an effective training program for patients with CHF. [6,7.]

Peak oxygen consumption - maximum functional capacity (PeakVO_2)[7]. VO2max is a parameter that describes the maximum amount of energy that can be produced from aerobic metabolism in a unit of time (aerobic power). Normal values of VO2max depend on age, sex, and are influenced by body weight, level of physical activity and genetic predisposition. In patients it is represented as a

Address for correspondence: Ivana Nedeljković, Cardiology Clinic, University Clinical center of Serbia, Višegradska 26, 11000 Beograd, Serbia;
E-mail: ivannanedeljkovic@yahoo.com; Phone:063232696

Table 1. Prognostic and diagnostic stratification of patients with heart failure[9]

<table>
<tr><th colspan="4">PRIMARY PARAMETERS CPET</th></tr>
<tr><td>VE/VCO$_2$ slope</td><td>PeakVO^2</td><td>EOV</td><td>PetCO$_2$</td></tr>
<tr><td>Ventilatory class I
VE/VCO$_2$ slope <30</td><td>Weber class A
PeakVO$_2$ >20 ml/kg/min</td><td rowspan="2">Bez EOV</td><td rowspan="2">PetCO$_2$ at rest ≥33 mmHg
Increase 3-8mmHg during CPET</td></tr>
<tr><td>Ventilatory class II
VE/VCO$_2$ slope = 30-35.9</td><td>Weber class B
Peak VO$_2$= 16-20 ml/kg/min</td></tr>
<tr><td>Ventilatory class III
VE/CO$_2$ slope = 36-44.9</td><td>Weber class C
PeakVO$_2$= 10 – 15.9 ml/kg/min</td><td rowspan="2">Sa EOV</td><td rowspan="2">PetCO$_2$ at rest < 33 mmHg
<3mmHg increase during CPET</td></tr>
<tr><td>Ventilatory class IV
VE/VCO$_2$ slope ≥ 45.0</td><td>Weber class D
PeakVO$_2$ < 10 ml/kg/min</td></tr>
<tr><td colspan="4">Standardni paremetri testa fizičkim opterećenjem</td></tr>
<tr><td>Hemodynamic</td><td colspan="2">EKG</td><td>Oporavak srčane frekvence</td></tr>
<tr><td>Normal increase in SBP during CPET</td><td colspan="2">Without rhythm disturbances; No ST segment changes during the test</td><td>>12 bpm at 1 min recovery</td></tr>
<tr><td>Poor response of SBP during CPET</td><td colspan="2">Rhythm disorders; ST-segment changes not due to test termination</td><td rowspan="2">≤ 12 bpm at 1 min recovery</td></tr>
<tr><td>SBP drop during CPET</td><td colspan="2">Arrhythmias and/or ST-segment changes that are the reason for stopping the test</td></tr>
<tr><td colspan="4">Subjective reasons for stopping the test</td></tr>
<tr><td>Leg fatigue</td><td colspan="2">Angina</td><td>Dyspnea</td></tr>
<tr><td colspan="4">Interpretation of CPET
• Green color: excellent prognosis in the next 1-4 years (≥90% event-free survival)
- Optimal drug therapy and control test for 4 years.
• A greater number of CPET parameters and standard TFO red/yellow/orange indicates a progressively poor prognosis.
– All CPET parameters in red: risk for fatal outcome extremely high in the next 1-4 years (>50%)
• A greater number of parameters of CPET and standard TFO red/yellow/orange indicate an increase in the degree of heart failure
– All CPET parameters in red: significantly low cardiac output, elevated neurohormones, high potential for secondary pulmonary hypotension are expected.
• A greater number of parameters of CPET and standard TFO red/yellow/orange indicates a progressively poor prognosis and warns to consider more aggressive treatment and the option of surgical treatment</td></tr>
</table>

VE/VCO$_2$, ratio of minute ventilation vs carbon dioxide production; VO$_2$, oxygen consumption; EOV, oscillatory ventilation; PETCO2, partial pressure of end-tidal CO$_2$; SBP, systolic blood pressure; CPET, cardiopulmonary exercise test; ECG, electrocardiogram; TFO, physical load test; HRR, heart rate recovery; RER, respiratory gas exchange index.

peakVO$_2$ as a maximal achieved valueof VO2 during the test. Pathological disturbance of the response of minute volume to physical load leads to a reduction of peakVO2 in relation to predicted values of VO2max.

Anaerobic threshold (VAT)[8]. When the metabolic needs during the exercise exceed the supply of oxygen to the working musculature, anaerobic metabolism is activated, which is also confirmed by the increase in lactate concentration. The ventilatory anaerobic threshold (VAT) is revealed by the metabolic increase in VCO$_2$ and VE in relation to VO$_2$. Usually, VAT occurs between 47% and 64% of predicted VO$_2$max of untrained healthy individuals and increases with training. VAT is the most important parameter in prescribing training and rehabilitation in patients with CHF because VO2 at AT indicates the ability to perform submaximal effort and daily activities, but also the degree of fitness and decreases with deconditioning. The effort up to the anaerobic threshold is a mild effort, defining the limit of mild and moderate effort for that patient (50-60% of peak VO$_2$), and the second anaerobic threshold (at the moment of intensive hyperventilation) is the limit of moderate to high intensity (60-80% of peak VO$_2$).

Work efficiency[7]. During symptom-limited exercise, the increase in VO2 is linearly related to the incremental workload (expressed in Watt/min) accurately reflecting the degree of aerobically regenerated adenosine triphosphate (ATP) and is called work efficiency. Under physiological conditions, the linearity of VO2 corresponds to an increase of 10 ml/min per watt, regardless of the load imposed and changes slightly depending on the duration of exercise. In addition, the change in VO2 intensity at the anaerobic threshold is monitored in terms of increasing the capacity for greater efforts and increasing peakVO2. In patients with CHF, this parameter is reduced depending on the severity of the disease, because the load is not accompanied by an increase in cardiac output, which results in the appearance of dyspnea, fatigue and exercise intolernce. In addition, the ECG and hemodynamic response are monitored during the test, so that in addition to symptoms, the symptomatic drop in pressure and the appearance of arrhythmias during exertion have prognostic significance.

Ventilatory efficiency (ventilation to CO$_2$ elimination ratio - VE/VCO$_2$ slope)[7] This parameter is perhaps the most important unique characteristic of CPET as the objective assessment of the ventilatory status - the ability of adequate ventilation and CO2 elimination. In the presence of pulmonary hypertension of varying degrees, this parameter is abnormal which allows the stratification. Improvement can be registered by reducing VE/VCO2slope in as the sign of improving ventilatory gas exchange. The mechanisms involved in this beneficial effect may be multifactorial, including modulating activity on chemoreflex sensitivity and improved perfusion of lung microvessels.

Table 2. Level of exercise intensity based on CPET[6]

Intensity	%VO_2peak	%HR_{max}	HRR	RPE scale	Trening zone
Low	<40	<55	<40	10-11	aerobic
Mild	40-60	55-74	40-69	12-13	aerobic
Moderate to high	70-85	75-90	70-85	14-16	aerobic -lactates
Very high	>85	>90	>85	17-19	Aerobna-anaerobic

HR_{max} = maximum pulse frequency; HRR = heart rate reserve; RPE = subjective feeling of exertion; VO_2peak = peak oxygen consumption.

Oscillatory ventilation (EOV)[7]. Another important parameter in stratification is oscillatory ventilation, a phenomenon characterized by cyclical fluctuation of ventilation and expired gas kinetics, which occurs in approximately 20-30% of patients with HF. When it is present, it is a sign of a worse prognosis. The proposed etiology includes prolonged circulation time with the absence of an adequate increase in cardiac output during exertion, causing a delay in circulation time and a decrease in chemoreflex sensitivity to blood gases. Studies have shown that physical activity has a better effect on improving EOV compared to drug therapy, suggesting that EOV is a phenomenon that may not respond to standard CHF therapy.

Determination of exercise intensity in CHF

The methodology for determining exercise intensity (EI) for exercise prescription is still being improved, especially in patients with CHF. Recently, the new 2020 ESC sports cardiology guidelines proposed a new classification of EI based on the exercise stress test[6] (Table 2). Of all the essential elements of exercise prescription in CHF, EI is considered to be the most critical for achieving aerobic fitness and to have the most beneficial effect on risk factors[6,7]**.** Absolute EI refers to the rate of energy expenditure during exercise and is usually expressed in kcal/min or metabolic equivalents (METs). Relative EI is usually prescribed as a % of maximal aerobic capacity (VO2max or VO2peak) based on CPET. Training intensity can also be expressed as a % of maximum heart rate (HRmax). during the exercise test or predicted based on the equation [HRmax = 220 - age]. There are caveats regarding the use of HR to prescribe and assess exercise intensity in individuals using beta-blockers. Intensity is also usually monitored using a rate of perceived exertion (eg 12 - 14 on Borg's 6 - 20 scale) or a 'talk test', eg 'to be able to talk while exercising'[6].

Risk stratification and training prescription

Physical activity in patients with CHF is initiated in a clinically stable individual after medical therapy for CHF has been optimized [6-10]. The main components before starting an exercise program and participating in sports include[6]:
(1) Exclusion of contraindications to exercise: hypotension or hypertension at rest or during exercise, unstable heart disease, worsening CHF symptoms, myocardial ischemia despite therapy (exercise may be allowed up to ischemic threshold), or severe and suboptimally treated lung disease.
(2) Detailed cardiology evaluation: assessment of comorbidities and severity of CHF (eg, by blood natriuretic peptide assessment and echocardiography). Mandatory exercise test - recommended just ergospirometry to assess functional capacity, exercise-induced arrhythmias and hemodynamic abnormalities. Based on the obtained anaerobic threshold and peak VO2 on the test, the exercise intensity is prescribed. When doing only ECG exercise test, prescription is based on the maximum HR achieved or Borg's rating of perceived exertion (RPE).
(3) Optimization of medical therapy: All persons with CHF should be treated according to current guidelines, including device implantation when necessary.
Based on CPET results, aerobic exercise is prescribed for stable patients [New York Heart Association (NIHA) Class I-III], due to its effectiveness and safety. In patients in NIHA class III, exercise intensity should be maintained at a lower intensity (<40% VO2peak), according to observed symptoms and clinical status during the first 1-2 weeks. This should be followed by a gradual increase in intensity up to 50-70% VO2peak, and if tolerated, up to 85% VO2peak which is the primary goal[6,7]. (Table 3)
Strength/resistance exercises are not prohibited and are complementary because they recover and maintain the mass of skeletal muscles, but without significant strain on the heart. The intensity level is adjusted so that the CHF patient can do 10 to 15 repetitions with an RPE on the Borg scale of up to 15[6]. (Table 3)

Identification of post-program progress/deterioration based on CPET results

Some patients do not show improvement after the PA program in terms of exercise tolerance and PeakVO2 increase and represent perhaps the most important population for analysis and correction of treatment approaches. There are studies addressing the clinical relevance of poor response to PA. They showed that PeakVO2 and natriuretic peptides are the most important for monitoring. Absence of improvement after PA programs was defined in those who:

- did not improve peakVO2 by > 5%
- did not increase workload by > 10%,
- did not reduce the VE/VCO2 slope by > 5%.

The one of the best predictors was HR recovery in 1 min (in patients without atrial fibrillation), and people who did not meet at least one of the mentioned criteria were classified as non-responders (less than 30 beats/min for HR, less than 6 beats/min for HR recovery and less than 101 rpm for maximum HR).
Follow-up according to recommendations should be carried out for 3 to 6 months, more precisely depending on the severity of CHF, comorbidities, age and symptomatic status[6].

Conclusion

Ergospirometry represents the gold standard in the assessment of functional capacity and stratification of patients with CHF and is therefore a guide for prescribing physical activity. Because of its repeatability and

Table 3. Recommendations for physical activity in patients with CHF[6]

	Aerobic	resistance/strength
Frequency	3-5 days/week, Or every day	2-3 days/week, Or every day
Intensity	40-80%VO2peak	Up to RPE<15 40-60% , 1 RM
Duration	20-60 min	10-15 repetitions At least 1 set, with 8-10 upper and lower body exercises
Mode	Continuous or intermittent	
Progress	Progressive increase in intensity based on monitoring and evaluations at 3 to 6 months depending on effort tolerance	Progressive increase in intensity based on monitoring and evaluations at 3 to 6 months depending on effort tolerance

RM - the maximum load that a person can lift in one repetition; RPE = subjective feeling of exertion; VO_2peak = peak consumption of oxygen.

safety, it is also used to monitor the effects of training and further increase in intensity as fitness and clinical status progress. Thanks to that, for the last 10 years it has become an integral part of recommendations for heart failure, rehabilitation and sports cardiology.

References

1. Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice: Developed by the Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies With the special contribution of the European Association of Preventive Cardiology (EAPC) Eur Heart J 2021;42(34):3227–3337.
2. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2021;42 (36):3599–3726.
3. Corrà U, Agostoni PG, Anker SD, et al. Role of cardiopulmonary exercise testing in clinical stratification in heart failure. A position paper from the Committee on Exercise Physiology and Training of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail 2018;20(1):3-15.
4. Carriere C, Corrà U, Piepoli M, et al. Anaerobic threshold and respiratory compensation point identification during CPET in chronic heart failure. Chest 2019;156(2):338-347.
5. Sato T, Yoshihisa A, Kanno Y, et al. Cardiopulmonary exercise testing as prognostic indicators: comparisons among heart failure patients with reduced, mid-range and preserved ejection fraction. Eur J Prev Cardiol 2017;24:1979-1987.
6. Pelliccia A, Sharma S, Gati S, et al. 2020 ESC Guidelines on sports cardiology and exercise in patients with cardiovascular disease The Task Force on sports cardiology and exercise in patients with cardiovascular disease of the European Society of Cardiology (ESC). Eur Heart J 2020;
7. Mezzani A. Cardiopulmonary exercise testing: Basics of methodology and measurements. Ann Am Thorac Soc 2017;14(Suppl 1):S3-S11.
8. Anselmi F, Cavigli L, Pagliaro A, et al. The importance of ventilatory thresholds to define aerobic exercise intensity in cardiac patients and healthy subjects. Scand J Med Sci Sport. 2021;31:1796–1808. |
9. Guazzi M, Adams V, Conraads V, et al. EACPR/AHA Joint Scientific Statement Clinical Recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. Eur Heart J 2012; doi:10.1093/eurheartj/ehs221
10. Guazzi M, Arena R, Halle M, et al. 2016 focused update: clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations Eur Heart J 2018; 39(14):1144–1161.

Sažetak

Klinička primena kardiopulmonalnog testa fizičkim opterećenjem u propisivanju fizičke aktivnosti kod bolesnika sa hroničnom srčanom insuficijencijom

Ivana Nedeljković[1,2], Vojislav Giga[1,2], Marko Banović[1,2], Ana Djordjević Dikić[1,2], Nikola Bošković[2], Marina Ostojić[2], Nenad Radivojević[2], Marija Zdravković[1,3], Tamara Stojmenović[4], Nenad Dikić[4], Olga Petrović[1,2], Emilija Nestorović[1,4], Svetozar Putnik [1,5], Katarina Matejić Gaćeša[2], Marija Ristić[2], Branko Beleslin[1,2]

[1]Medicinski fakultet Univerziteta u Beogradu, [2]Klinika za kardiologiju, Univerzitetski Klinički centar Srbije, [3]KBC "Bežanijska Kosa" u Beogradu, [4]Fakultet za fizičku kulturu i menadžment u sportu-Univerzitet Singidunum, [5]Klinika za kardiohirurhiju, Univerzitetski Klinički centar Srbije

Fizička aktivnost (FA) prema važećim smericama predstavlja nezaobilaznu pomoćnu terapiju za pacijente sa hroničnom srčanom insuficijencijom (HSI) sa redukovanom i sa očuvanom ejekcionom frakcijom (HFrEF i HFpEF) što je nivo dokaza i klase 1A. Medjutim ka oi svaka terapija, FA se mora dozirati prema spsoosbnostima samog pacijenta, tako da je neophofdna indivisualna procena i propisivanje intenziteta vežbanja. Različiti tipovi FA (izdržljivost i otpor) i nivoi intenziteta (blagi, blagi do umereni i visoki do umereni) se koriste u programima kod pacijenata sa HSI.

Procena se može se izvesti putem indirektnih (rezerva otkucaja srca) ili direktnih metaboličkih mera (VO_2 rezerva, anaerobni prag) gde je preciznost obezbedjena direktnom procenom kinetike VO_2 pri protokolima konstantne brzine rada različitih opterećenja- ergospirometrijom. Ergospirometrija omogućava direktnu procenu pojave anaerobnog metabolizma i realnog zamora pacijenta kao i granica njegove tolerancije na napor. Pored toga, na osnovu kontrolnih testova može se pratiti efekat vežbanja. Na taj način se, zasnovano na dokazima, sprečava primena napora koji bi doveo do pogoršanja CHF ili koja ne bi dovela do napretka i poboljšanja simptoma/tolerancije napora. Takodje, omogućava postepeno povećanje intenziteta i dalji napredak u vežbanju.

***Ključne reči**: hronična srčana insuficijencija, kardiopulmonalni test fizičkim opterećenjem, funkcionalni kapacitet, anaerobni prag, potrošnja kiseonika, propisivanje treninga*

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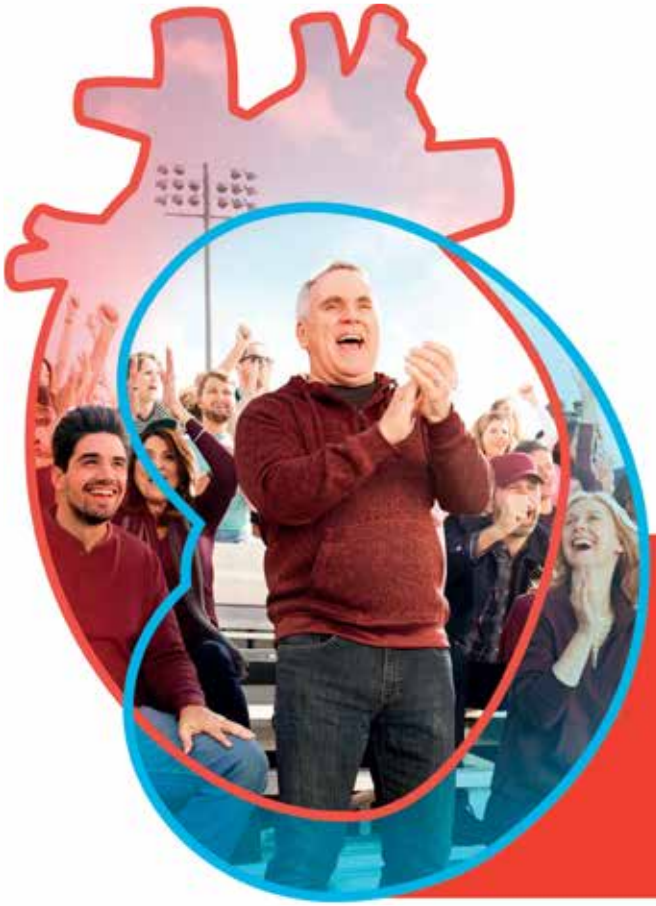

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Reference: 1. Sažetak karakteristika leka Forxiga®, poslednja revizija teksta decembar 2021. **2.** McMurray JJV, et al. *N Engl J Med* 2019;381:1995–2008 **3.** M. Packer et al. NEJM 383;15, October 2020. **4.** Docherty kf et al. eur heart j. 2020;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

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

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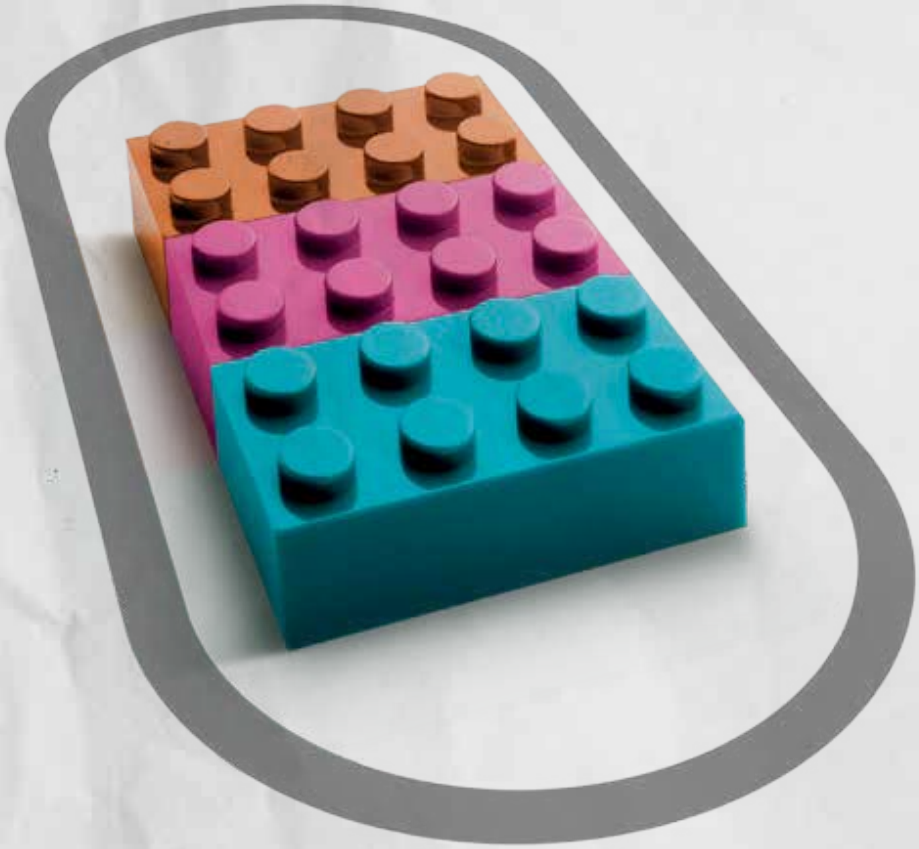

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Datum rešenja: 13.05.2020.

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

Datum pripreme materijala: Mart 2022. | PC-RS-100347

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