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SRCE i krvni sudovi

Heart and Blood Vessels

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Original article

Who are the normotensive acute pulmonary embolism patients with right ventricle dysfunction and normal cardiac troponin blood level?

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Abstract

Background. Current guidelines for acute pulmonary embolism (PE) management classify patients with heart right ventricle dysfunction (RVD) who do not have elevated cardiac troponin (cTn) blood levels as intermediate low risk patients. The aim of this investigation is to study the characteristics of these patients and the role of pre-existing cardiovascular diseases for the RVD.

Methodology. Out of 1675 patients with acute PE from the regional PE registry, we included 353 normotensive patients who had echocardiography imaging at presentation to hospital and normal blood levels of cTn. Patients were divided into low risk PE if they hadn't RVD and intermediate-low risk if they had RVD and their characteristics were compared.

Results. A 216 patients with low risk PE were significantly younger than 137 patients with intermediate-low risk. Arterial hypertension, chronic heart failure with reduced ejection fraction, coronary disease and diabetes mellitus type 2 were all significantly more prevalent in patients with intermediate-low risk ($p \leq 0.001$ for all comparisons) compare to low risk patients (77.4% vs 47.6%, $p<0.001$ for the presence of at least one of the four mentioned cardiovascular diseases). The age and sex adjusted odds ratio to have at least one of the mentioned cardiovascular diseases and intermediate-low PE was 2.954 (95%CI 1.658-5.266).

Conclusions. The majority of normotensive acute PE patients with RVD and normal cTn are actually chronic cardiovascular patients.

Key words pulmonary embolism, right ventricle dysfunction, intermediate-low risk patients

Introduction

Treatment of acute pulmonary embolism (PE) depends on the estimation of mortality risk as soon as diagnosis is established[1]. Patients with large thrombus burden and hypotension are at highest risk for dying from acute PE with hospital mortality above 20%[1,2]. In these patients' severe obstruction of a pulmonary circulation and impaired gases exchange lead to low left heart ventricle filling with hypo-oxygenated blood, and resulted with systemic arterial hypotension and hypoxemia. Patients may have acute right ventricle (RV) dysfunction because of the pulmonary artery circulation obstruction without hypotension, usually associated with elevated cardiac troponin (cTn) blood levels, and represent intermediate-high risk patients who could deteriorate, and become the high risk patients. Hospital PE-related mortality in intermediate-high risk patients is between 5-10%[2,3] which is higher than the hospital mortality of acute ST elevation myocardial infarction. Some patients have RV dysfunction but without the cTn blood elevation. According to European Society PE guidelines, these patients should be classified as intermediate-low risk patients, with low risk of dying from acute PE. However, is it possible that acute RV dysfunction, measured with cardiac ultrasound, or computed tomography pulmonary angiography (CTPA) could be presented without the elevation of the sensitive cTn assays? Or the RV dysfunction in these pa-

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tients is actually pre-existing state which is only aggravated in some degree because of the acute PE without severe pulmonary circulatory obstruction. If it is the case, the treatment of these patients should be more oriented to the pre-existing disease, or at least it could be modified because of that.
The aim of this study is to investigated the characteristics of patients with low risk and intermediate-low risk PE, and factors that could contribute to the RV dysfunction except the acute PE.

Methods

The patients were enrolled from the regional PE registry (REPER) which was founded in 2015, and till June 2022 year 1675 patients with computed tomography pulmonary angiography (CTPA) objectively confirmed PE, were recorded from the 5 university (Military Medical Academy Belgrade, Institute for Pulmonary Diseases Vojvodina, Clinical Centers Zemun, Nis and Kragujevac) and one general hospital (Pancevo) in Serbia, and 3 university cardiology clinics, from Banja Luka (Bosnia and Herzegovina), Podgorica (Montenegro) and Skopje (North Macedonia). Patients who were included into the study were classified as intermediate-low (only according to echocardiography estimated right ventricle dysfunction with normal blood level of cardiac troponin) or low risk PE using the ESC criteria published in 2019 guidelines[1]. We did not use pulmonary embolism severity score (PESI) or simplified version of this score (sPESI)[4] for the stratification of our patients as recommended, because we wanted to avoid the classification of patients according to mixed pre-existing comorbidities, age and the consequences of acute PE which are included in the scores. All patients must have normal cTn blood level at admission, and patients who were classified as intermediate-low risk PE must have echocardiography proven RV dysfunction.
We used modified criteria (slightly enhanced) for RV dysfunction as in pulmonary embolism thrombolysis trial (PEITHO) (5). Patient defined as having RV dysfunction if he had at least one of the criteria: systolic RV pressure > 40 mmHg (using Bernoulli equation $4xV^2$-regurgitation velocity + 10 mmHg), RV end-diastolic diameter > 3.5 cm measured from the apex 4-chamber view just below the tricuspid annulus, or tricuspid annulus plane systolic excursion (TAPSE) < 16 mm. Cardiac ultrasound imaging was performed as an initial diagnostic procedure in all patients.
During the admission process, detailed status of comorbidities was recorded. Patients who positive history of arterial hypertension and diabetes mellitus, treated or not, were considered as patients with arterial hypertension and diabetes mellitus. Patients who had myocardial infarction, any kind of myocardial revascularization or angiography objectivized at least one coronary disease, were considered as patients with coronary artery disease. Patients with left ventricle ejection fraction (EF) less than 50% were considered as patients with chronic heart failure with reduced EF. Patients who had history of decompensated heart failure with EF $\geq$ 50% were diagnosed as patients with heart failure with preserved EF. Malignant disease was considered if the patient was treated because of the malignant disease in the last six months before the acute PE or if the malignant disease diagnosed at the time of acute PE. Recent surgery was defined as any kind of surgery inside 21 days from the onset of acute PE symptoms. Glomerular filtration rate was calculated using Cockroft-Gault formula with the creatinine level at admission. Overweight and obese was defined as body mass index higher than 25 kg/m^2-29.9 kg/m^2, and 30 kg/m^2 and above, respectively.
Ethical committees or local review boards gave a permission to use the patient's data and to publish the results from the investigations derived from the REPER.

Statistical analysis

Basic characteristics of the patients as continuous variables are presented as means with standard deviation or medians with interquartile range depends on the normality of the data distribution which was tested with Kolmogorov-Smirnov test. Categorical variables are presented as frequencies and the significance of difference between the distribution of the data in low risk compare to intermediate-low risk patients were tested with Chi-square test. The significance of difference between continuous variables were tested with student t-test or Man-Whitney test, again depending on the normality of data distribution. Finally, a presence of at least one of the four cardiovascular co-morbidities (arterial hypertension, coronary artery disease, diabetes mellitus type 2 and chronic heart failure with reduced EF) was tested as a predictor of intermediate-low risk status with univariate and multivariate (odds ration adjusted to age and sex) binary logistic regression. P values less than 0.05 were considered as significant.

Results

From 1675 patients who were included into the REPER, 215 patients were hypotensive and classified as high risk PE, and 516 patients had RV dysfunction and elevated cardiac troponin levels and classified as intermediate-high risk PE, and they are excluded from the study. Among 400 normotensive patients who had RV dysfunction, 125 had only the CTPA established RV enlargement, and 138 patients did not have determined cardiac troponin at admission. Among the rest 544 normotensive patients at admission, 328 had no either complete echocardiography imaging or cardiac troponin measurement at admission. Therefore, 216 low risk and 137 intermediate-low risk PE patients who had both echocardiography imaging and cTn blood level at admission were included in the study.
The basic characteristics of patients are presented in table 1. Patients in intermediate-low risk PE were significantly older than patients with low risk PE. There are no differences between the distribution of sex, chronic obstructive pulmonary disease, stroke, recent surgery, malignant disease and chronic renal failure. However, patients in intermediate-low risk group significantly more often had chronic heart failure, arterial hypertension, coronary artery disease, diabetes mellitus and

Table 1. The basic characteristics of the study group

Characteristics	Low-risk N=216	Intermediate-low risk N=137	P
Age – y ± SD	55 ± 19	63 ± 15	< 0.001
Female sex – n, %	116, 53.7	67, 48.9	0.385
Comorbidities – n, %			
COPD	14, 6.5	9, 6.6	1.000
CHF	14, 6.5	26, 18.9	0.001
CHF with EF < 50%	5, 2.3	17, 12.4	< 0.001
Arterial hypertension	93, 43.1	99, 72.3	< 0.001
Diabetes mellitus type 2	22, 10.2	32, 23.4	0.001
Coronary disease	12, 5.6	22, 16.1	0.002
Previous stroke	12, 5.6	7, 5.1	1.000
Atrial fibrillation			
Paroxysmal during aPE	7, 3.3	11, 8.0	0.055
Permanent/Persistent	9, 4.2	10, 7.3	
Obesity or overweight[1]	96, 50.5	70, 64.8	0.021
Recent surgery	42, 19.4	18, 13.1	0.146
Malignant disease	22, 10.2	18, 13.1	0.395
GFR < 60 ml/min	55, 25.6	38, 27.7	0.710
Basic parameters at admission			
Systolic arterial pressure – mean ± SD mmHg	130.2 ±17.4	136.3 ± 21.8	0.004
Heart rate – mean ± SD bpm	88.4 ± 17.4	91.4 ± 22.0	0.160
Arterial pO_2 – mean ± SD mmHg	73.1 ± 21.0	73.6 ± 23.1	0.863
Arterial pCO_2 – mean ± SD mmHg	32.2 ± 7.6	30.9 ± 6.4	0.243
SPRV – mean ± SD mmHg	29.6 ± 7.6	52.7 ± 14.3	< 0.001
RV diameter – mean ± SD cm	2.9 ± 0.4	3.5 ± 0.6	< 0.001
EBSI – median (IQR)[1]	7.0 (5.0-11.0)	10.0 (7.0-12.0)	0.001
D-dimer – median (IQR)	3.1 (1.6-6.0)	3.4 (1.5-6.7)	0.786
CRP – median (IQR) mg/dl	49.6 (12.6-99.1)	34.5 (13.1-71.6)	0.221
Glycaemia – median (IQR) mmol/l	5.9 (5.25-6.9)	6.1 (5.3-7.65)	0.102
Elevated BNP or NT-proBNP[1] – n, %	24, 17.8	32, 40.5	< 0.001
Leukocytes – mean ± SD	9.6 ± 4.7	9.7 ± 3.4	0.892
Hemoglobin – mean ± SD	129.7 ± 19.9	129.6 ± 23.4	0.968
Total cholesterol – mean ± SD mmol/l	4.68 ± 1.16	4.61 ± 1.25	0.619

Abbreviations: COPD – chronic obstructive pulmonary disease, CHF – chronic heart failure, EF – ejection fraction, GFR – glomerular filtration rate, SD – standard deviation, SPRV – systolic, RV – right ventricle diameter, EBSI – embolic burden score index, IQR – interquartile range, CRP – C reactive protein, BNP – brain natriuretic peptide. [1]Missing values greater than 5%: obesity and overweight 26 (12.0%) and 29 (21.2%), EBSI 75 (34.7%) and 78 (56.9%), elevated BNP or NT-proBNP 81 (37.5%) and 58 (42.3%) for low-risk and intermediate-low risk, respectively

overweight or obesity compare to patients in low risk group. Both paroxysmal or long-standing atrial fibrillation were borderline significantly more frequently presented in intermediate-low than in low risk PE patients. A 77.4% of patients in intermediate-low risk PE compare to 47.6% of low-risk PE had at least one of the four cardiovascular comorbidities (figure 1), chronic heart failure with reduced EF (<50%), arterial hypertension, coronary artery disease, or diabetes mellitus type 2 (p<0.001). In the univariate logistic regression analysis, the presence of at least one of the four cardiovascular comorbidities compare to none of them, resulted to increase risk of having RV dysfunction which classify patients into the intermediate-low risk PE group (OR 3.784, 95%CI 2.318-6.176, p<0.001). This increased risk is also significant when adjustment to age and sex was done (OR 2.954, 95%CI 1.658-5.266, p<0.001).
All-cause hospital mortality rate was 5.1% in intermediate low risk, and 1.4% in low risk PE. Only 1 patient (0.8%) from intermediate low risk has died from PE according to our data.

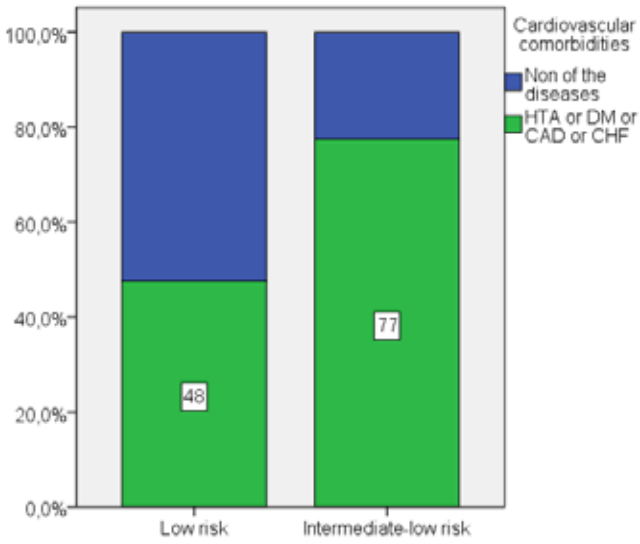

Figure 1. Frequencies of at least one cardiovascular comorbidities in low risk and intermediate-low risk aPE patients (p<0.001)

Discussion

The purpose of risk stratification in acute PE is to tailore the risk of therapy to risk of dying from PE. Therefore, patients in high risk group, who are hypotensive and have the highest risk for early dying from PE are treated with reperfusion therapy, mostly with systemic thrombolysis, if they have not absolute contraindication for that kind of therapy, which can very fast relieve the obstruction of pulmonary arteries and stabilized the patient's hemodynamics, but at the cost of almost five-time greater risk for major and fatal bleeding than anticoagulant therapy alone. Normotensive patients with RV dysfunction and elevated cardiac troponin represent the second step in the hierarchy of risk, who need close monitoring of vital parameters and in whom systemic thrombolysis can improve condition but the net advantage is doubtful taking into account that harm of major bleeding exceeds the benefit of thrombolysis. Intermediate low risk patients represent a heterogeneous group of patients. They may be defined only as sPESI score 1 and higher, and they may have either elevated cTn blood levels or RVD. Many of these patients have significantly impaired RV dysfunction which is actually not acute, and that is the reason why they have not increase of cardiac troponin which is very sensitive to acute stretching of the RV wall. Normotensive patients with acute PE and RVD without cTn blood elevation compare to patients without RVD have higher hospital mortality rate but rarely die from acute PE if they are properly anticoagulated[6].

The results from our study revealed that the majority of patients with intermediate-low risk PE, are actually chronic cardiovascular patients, and 77.4% of them had at least one cardiovascular disease, arterial hypertension, or coronary atherosclerotic disease, chronic heart failure with reduced EF or diabetes mellitus type 2. Those patients are in an increased risk of death during hospitalization because of acute PE compare to low risk patients[7]. They have diminished cardiopulmonary reserve which made them vulnerable to the less severe PE which can cause more damage in this subgroup of patients. We have already demonstrated that patients with chronic heart failure with reduced EF had higher hospital mortality than patients with normal heart independent of mortality risk estimated at admission and age[8].

The significance of define patients as intermediate low was not enough elucidated. There are only few data about the all-cause and PE-related death in this subgroup of patients. Becattini et al[2], tested the value of 2014 ESC mortality risk assessment, and the 30-day all-cause mortality was 20/333 (6.0%) of patients stratified as intermediate-low risk PE, and only 7 (2.1%) died from PE. In the smaller study of Cugno et al, mortality rate at 30 days in patients with acute PE diagnosis was 7/74 (9.5%) in the intermediate-low risk subgroup. The all-cause hospital mortality in the intermediate low risk subgroup of patients from our study was 5.1%. The presence of RV dysfunction without cTn elevation definitely mean higher early mortality in normotensive acute PE patients with OR 4.19 (95%CI 1.30-12.58) in the meta-analysis[7] of trials which studied the prognostic role of isolated cardiac troponin or RV dysfunction in low risk acute patients.

The majority of patients with RV dysfunction in our study had at least one of the four cardiovascular comorbidities. Arterial hypertension was the most common with 72.3%, following diabetes mellitus type 2 with 23.4%, coronary artery disease with 16.1% and chronic heart failure with reduced EF with 12.4%. All of this comorbidities are associated from the beginning with some degree of RV dysfunction which promote with the advanced stage of the disease.

In systemic arterial hypertension RV dysfunction began as a consequence of vascular pulmonary tree hyper-reactivity and myocardial fibrosis caused by over-reactivity of sympathetic and renin-angiotensin-aldosterone systems[9]. Left ventricle (LV) fibrosis and hypertrophy in arterial hypertension lead to progressive LV diastolic dysfunction and with time to mitral regurgitation and increase of pulmonary arterial pressure. Right and LV share interventricular septum which is very important for the normal function of RV[10]. Hypertrophic septum in arterial hypertension contribute to the dysfunction of RV. With long standing arterial hypertension, heart goes through the different stages of dysfunction, from asymptomatic phase which can be detected by the sensitive echocardiography techniques like global longitudinal strain, to heart failure with preserved EF and diastolic dysfunction of both chambers with atrial enlargement, and finely the heart failure with reduced EF and severely impairment of systolic function of both ventricles[11].

Even prediabetes is related to mild, but significant changes in RV function[12]. Overt diabetes with time is associated to heart failure which is a common evolution pathway in long-term diabetes[13]. Patients with diabetes mellitus type 2 and symptoms of heart failure with preserved EF have more frequently systolic and diastolic RV dysfunction than patients without diabetes. Finally, long-term diabetes, often associated with coronary artery disease lead to heart failure with reduced EF where RV dysfunction is even more prominent[14]. Diabetes is often associated to arterial hypertension, obesity and coronary artery disease which act synergistically and lead to myocardial fibrosis, oxidative stress, microvascular dysfunction, and resulted with impaired cardiac performance[14].

Coronary artery disease can cause necrosis and fibrosis of right heart with long-term RV dysfunction[15]. Atherosclerotic narrowing of right coronary artery may cause RV ischemia[16] which can be important for the RV failure in case of acute RV overload in acute pulmonary embolism. Heart failure with reduced EF is associated with significant RV dysfunction which is one of the main determents of the prognosis in these patients.

All these cardiovascular comorbidities, we mentioned, are in the interplay with chronic and cumulative dismal influence on RV function which can contribute to the acute RV failure in patients with acute RV afterload caused by pulmonary embolism.

Conclusion

Patients with acute PE who are normotensive and have some degree of RV dysfunction without cTn blood level elevation represent patients with high risk to suffer from

other common chronic cardiovascular diseases which could contribute to enhanced mortality risk in these patients compare to low risk PE patients.

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Sažetak

Ko su normotenzivni pacijenti sa akutnom plućnom embolijom, disfunkcijom desne komore i normalnim vrednostima troponina?

Slobodan Obradović[1,2], Boris Džudović[2,3], Bojana Subotić[1], Ivica Đuric[1], Sonja Šalinger[4,5], Jovan Matijašević[6,7], Sandra Peković[6], Tamara Kovačević Preradović[8,9], Ana Kovačević Kuzmanović[10], Irena Mitevska[11], Vladimir Miloradović[12,13], Piotr Pruszczyk[14], Marek Roik[14], Aleksandar Nešković[15,16]

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Uvod. *Aktuelne preporuke za akutnu plućnu emboliju (PE) klasifikuju normotenzivne pacijente sa disfunkcijom desne komore (DDK) koji nemaju povišen srčani troponin (cTn) u intermedijarno-nisko rizičnu grupu Cilj ovog istraživanja je da ispita karakteristike ovih pacijenata i ulogu prethodno postojeće kardiovaskulatne bolesti na DDK.*

Metodi. *Od 1675 pacijenata sa akutnom PE iz regionalnog PE regsitra, u studiju smo uključili 353 normotenzivna pacijenta koji su imali ehokardiografski imidžing na prezentaciji u bolnicu i normalne vrednosti cTn. Pacijenti su podeljeni u nisko-rizičnu PE grupu ako nisu imali DDK I intermedijarno-nisku PE grupu ako su imali DDK.*

Rezultati. *216 pacijenata sa nsikim PE rizikom su bili značajno mlađi u odnosu na 137 intermedijarno-nisko rizičnih pacijenata. Arterijska hipertenzija, hronična srčana slabost sa smanjenom ejekcionom frakcijom, koronarna bolest I dijabetes melitus tip 2 su bili značajno češći kod pacijenata sa intermedijarno-niskim rizikom ($p \leq 0.001$ za sva poređenja) u odnosu na nisko rizičnu grupu (77.4% vs 47.6%, $p<0.001$ za prisustvo najmanje jende bolesti). Prilagođeno za godine i pol, rizik da pacijenti imaju najmanje jednu dodatnu kardiovaskularnu bolest je bio 2.954 (95%CI 1.658-5.266).*

Zaključak. *Većina pnormotenzivnih pacijenata sa akutnom PE, DDK i normalnim cTn zapravo imaju akutizaciju hronične kardiovaskularne bolesti.*

Ključne reči: *plućna embolija, disfunckija desne komore, intermedijarno-nizak rizik*

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Case report

Fracture of the ventricle lead electrode of the permanent pacemaker – case presentation

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Abstract

Introduction. Lead fracture is common late complication of permanent pacemaker implantatiton, and is refered as one of the most important causes of pacemaker malfunction. The most demanding step in the treatment is proper diagnostics, as the clinical presentation can be various. ECG, electrophysiology and imaging methods should be done (chest X-ray, CT scan). The treatment includes a new operation and a new electrode placement.

Case presentation. A 91-year-old female has came in the Emergency Room because of dizziness, fainting and fatigue that she felt earlier that day. ECG showed third degree AV block with pacemaker and registered pacemaker activity without capture. On the chest X-ray, infraclavicular lead fracture was registered. After diagnosis, the patient was admitted to the hospital, and a new lead was placed after cephalic vein cutdown.

Conclusion. When performing pacemaker implantation, the most important step is to choose the vein access carefully, due to relation of subclavian vein access and lead fracture. It is important to educate a patient about risk factors in order to prevent lead fracture. The most important step in the treatment is an early diagnose and a proper patient management thereafter.

Key words permanent pacemaker, lead fracture

Background

Electrode fracture is one of the late, technical complications of permanent pacemaker implantation. Etiological factors include: trauma, the aging process, ossification of the costoclavicular ligament, twisting of the generator itself, resulting in a break in the continuity of the pacemaker electrode (Twiddler's syndrome, Reel's syndrome), etc. The main symptoms and signs of electrode fracture are reflected in the dysfunction of the pacemaker itself and, consequently, heart rhythm disorders. Symptomatology is often variable, from completely asymptomatic patients to the development of atypical symptoms. Anamnestic data are important in the diagnosis of electrode fracture, and it is necessary to control the operation of the pacemaker and check the electrodes, as well as one of the imaging methods (X-ray p/c, CT chest). Once the diagnosis is made, it is necessary to address adequately the problem. The patient is brought into the operating room, and under local infiltrative anesthesia, a new electrode is placed, along with the isolation of the existing one. In exceptional cases, extirpation of the existing electrode is performed, with special caution, because the risk of damage to the blood vessel is high.

Case presentation

A 91-year-old patient was admitted to the Coronary care unit of general hospital Uzice due to dizziness, fainting, feeling of increased fatigue. The complaints started on the day of admission, she had no complaints in the previous days. She denies the increased physical effort of the previous days, as well as the trauma. On the day of admission, she reported to the Emergency Service, bradycardia verified on ECG, average frequency up to 30/min, for which reason she was referred to the Emergency Department of our hospital. Personal history: in 2000, a permanent pacemaker VVI stimulation mode was implanted at Medical Military Academy, the last pacemaker control was 5 months before admission (May 2020), then PM parameters were optimally programmed. The patient is otherwise being treated for hypertension, cardiomyopathy (on the last ultrasound of the heart, ejection fraction was estimated at 45%), Parkinson's disease, without drug allergies.

On admission, the patient was conscious, oriented, afebrile, eupnoic, acyanotic, with normal discoloration of the skin and visible mucous membranes, without lymphadenopathy and signs of hemorrhage. Auscultatory findings on the heart and lungs: cardiac action rhythmic, calm, tones clear, systolic murmur at the top of the heart. On the lungs, vesicular breathing without accompanying pathological findings. TA at the time of admission 150/80mmHg, SpO2 93% without oxygen therapy. Without pretibial edema, deformities and varicose veins.

On the ECG at the time of admission to the Coronary care unit, a complete AV block with average frequency of 40/min, with pacemaker activity and without capture was observed.

After admission, a complete laboratory work-up, coagulation status, chest X-ray was performed. There were no

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significant deviations in laboratory findings, except for elevated values of urea (13.4 mmol/L), AST 41 U/L, CRP 5.08 mg/L, uric acid 612 µmol/L. In the repeated laboratory findings, there were no deviations from the reference values. On the chest radiograph: The patient is tilted and rotated to the left. The cardiac shadow is enlarged, in the lung parenchyma the interstitial drawing is accentuated on both sides. In the area of the middle lung field on the left, an oval shadow of metal intensity corresponding to the pacemaker generator can be observed. The tip of the electrode positioned in the apex of the right ventricle. In the area of the upper lung field on the left, immediately next to the lower edge of the medial border of the clavicle, a break in the continuity of the electrode can be observed.

Immediately after admission, the pacemaker was checked, after which a decision was made to replace the pacemaker generator. After adequate preoperative preparation (repeated laboratory findings, coagulation status, urine culture taken), on the second day of hospitalization, with previously prescribed prophylactic cephalosporin antibiotic of the first generation, under local infiltrative anesthesia, the intervention of replacement of the pacemaker generator and placement of a new ventricular electrode through the prepared v. cephalic, with isolation of the previously placed electrode. The intervention was without complications.

Upon admission to the Coronary Unit, ECG: rhythm PM, fr 65/min, proper captures and sensing.

The early perioperative period passed without complications. The wound is calm, dry, without signs of inflammation and presence of hematoma. The patient in the further course of hospitalization is in a stable general condition, hemodynamically stable, cardiopulmonary compensated, without repeated complaints. She was discharged home 3 days after the intervention, with previously repeated ECG, laboratory findings, coagulation status in which there were no deviations compared to previous findings. On discharge, in addition to regular therapy, a cephalosporin antibiotic of the first generation was prescribed, with the expected duration of therapy up to 5 days. The sutures were removed on the tenth postoperative day, the wound was calm, dry, without signs of inflammation and the presence of hematoma. On the same day, the pacemaker control was performed, the parameters optimally programmed. The next control is planned for 6 months.

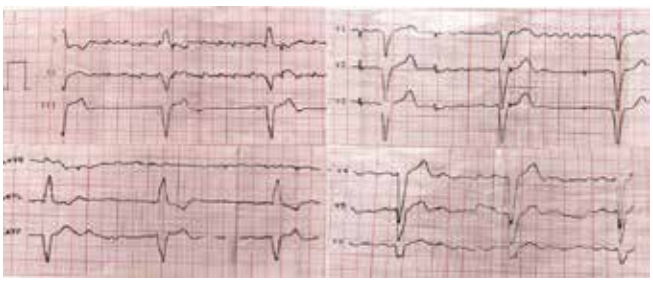

Figure 1. ECG on admission to Coronary care unit (AV dissotiation, activation of PM without capture)

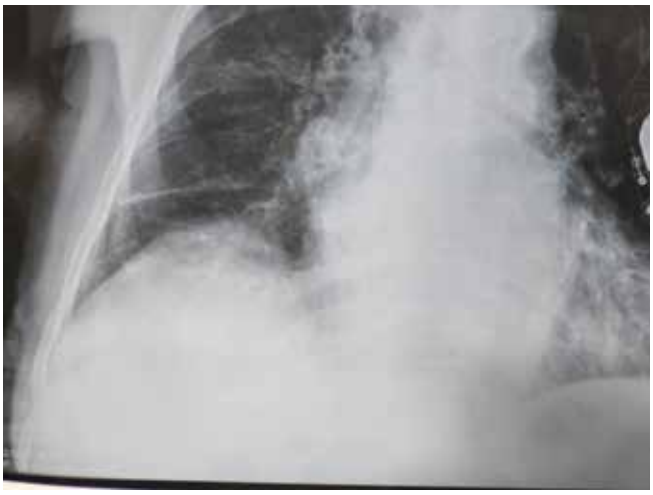

Figure 2. RTG p/c during hospitalization where discontinuity of the electrode can be observed, immediately next to the lower edge of the medial border of the clavicle

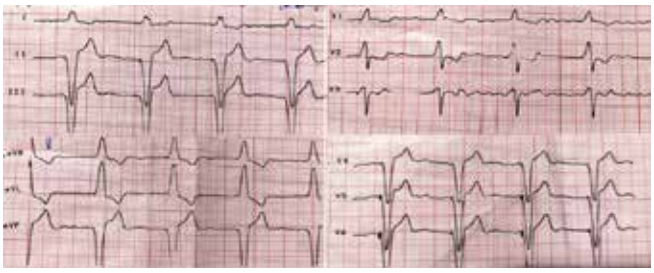

Figure 3. ECG on admission to coronary care unit after placement of the new electrode and changing of the generator (ventricular rhytm of pacing, fr 65/min, normal capture)

Discussion

Implantation of a permanent pacemaker is an interventional procedure that has significantly contributed to the treatment of rhythm disorders. However, like all interventional procedures, pacemaker implantation can be accompanied by numerous complications, which can be classified into two groups:

- In relation to the time of origin (early and late)
- In relation to the mechanism of origin (biological and mechanical - generator/electrode)

Early complications arise during the intervention itself or immediately after the operation. Early complications could include: pneumothorax, hematoma in the wound area, perforation of the myocardium with the electrode, thrombosis of the vein through which the electrode is placed, infection of the pacemaker box... Some of the late complications that occur several months and even several years after the operation are electrode disorders (displacement, fracture) or pacemaker generator disorders (most often due to electronics failure). Considering that the patient from our presentation suffered a fracture of the ventricular lead of the permanent pacemaker 20 years after the primary implantation, we decided to analyze in more detail the complications related to the pacemaker lead, in order to see the reasons why this happened, as well as the possibilities that would give us help avoid and overcome this problem in the future.

Electrode fracture is a common complication after implantation of a permanent pacemaker. It can be partial or complete. In the case of a partial one, the conductor is most often damaged, and in the case of a complete one, there is a complete break in the continuity of the electrode. When establishing a diagnosis, anamnestic data must be taken into account, because the clinical picture varies from asymptomatic to completely atypical symptoms. Of course, the most common are patients with typical symptoms, such as chest pain, dizziness, fainting, syncope, fatigue, weakness, a feeling of heart skipping, which was also the case with our patient. However, patients with atypical symptoms, such as tingling and involuntary jerks of the hand due to stimuli, are not rare. brachialis, hiccups and abdominal pulsations due to irritation of the diaphragm and n. phrenicus[1]. Also, data on potential etiological factors can be obtained from the anamnestic.

During the diagnosis, it is necessary to control the pacemaker operation and check the electrode, especially in asymptomatic patients in whom changes are observed in the ECG record (Table 1).

Tabla 1. Most prevalent isorders of pacing in permanent pacemakers[1]

NO CAPTURE	NO OUTPUT
Displacement of electrode Subthreshold programmed output Increased threshold of pacing Damage of isolated material Partial damage od the conductance Failure of electricity circle, air in battery, after defibrillation	Depletion of battery Elsctrode fracture Damage of electricity circle Inhibition of pacemaker Nonfunctioning connection between battery and electrode Bipolar programming of unipolar electrode

If an electrode disturbance is observed, attention should be paid to the impedance and the pacing threshold (Table 2):

Tabla 2. Diagnostic approach for the most prevalent electrode failure using values of impedance and threshold[1]

IMPEDANCE	THRESHOLD	STATUS OF THE ELECTRODE
Normal	**Normal**	**Normal**
↓	**normal**	**Lack of electricitz**
↓	↑	**Displacement**
↑	↑	**Fracture**
Normal	↑	**Microdisplacement**

Although an elevated impedance and an elevated pacing threshold are almost pathognomonic of a lead fracture, a chest radiograph should be performed to confirm the diagnosis.

An important etiological factor for electrode fracture is trauma. The literature describes numerous cases of electrode fracture, caused by blunt trauma to the chest wall, most often during traffic accidents. Cases were also described where the fracture was caused by some innocuous actions, e.g. extending or raising the arm, etc. An interesting case was also recorded, where after displacement of the electrode on several occasions, a guide was left in the ventricular electrode, which later led to a fracture of the electrode and injury to the lung parenchyma[2].

By inspecting the discharge list of a patient from the Military Medical Academy in Belgrade, we learn that in 2000 the patient was implanted with a permanent pacemaker of the VVI mode of stimulation. The chamber electrode was placed by puncturing the subclavian vein, which may also have an impact on the subsequent fracture of the electrode, due to the very localization of the puncture site and the process of ossification of the costoclavicular ligament, given that various studies have determined that the fracture of the electrode most often occurs precisely at the point of entry of the electrode into the subclavian vein[3].

There are different approaches for the placement of lead electrode during PM implantation[4,5]:

- V. cephalica - in the most cases (60%) this approach is utilized, still representing a gold standrad, and encompases preparation and venotomy, and than lead electrode placement,
- V. subclavia - puncture of intrathoracic (21%) or extrathoracic part of the vein (19%),
- V. axillaris - puncture of v. axillaris, lately more utilized in many centers.

Preparation and venotomy of v. cephalice is the approach used in the largest number of cases and still represents the gold standard in a large number of world centers[4,5]. The biggest advantage of this approach is the avoidance of complications that occur during v. puncture. subclaviae (Table 3). Also, with this approach, access is simultaneously provided for not only one, but for several electrodes, which is useful when implanting a two-chamber pacemaker. However, there are also situations when it is not possible to provide access through v. cephalicu, most often due to anatomical variations in patients (obese people, tortuosity...). In those situations, it is necessary to consider an alternative approach, and operators most often decide to puncture v. subclaviae.

Table 3. Advantages and limitations of v. cephalicu i v. subclaviu approach[7,8]

	Punction of V. SUBCLAVIAE	Preparation of V. CEPHALICAE
Advanatges	Easy apprach, following failure of v. cephalicae approach	Tortuosity Anatomic variations Small caliber of the vessel
Limitations	Pneumotorax Hemopneumotorax Artery puncture Hematoma Bleeding Air embolism Damage of pl. brachialis Damage of ductus thoracicus “Subclavian crush syndrome” Fracture of electrode Periosteal reaction around electrode	

Immediately before the puncture, the venous system must be visualized fluoroscopically due to the anatomical proximity of v. subclaviae with surrounding structures. Then, a needle is introduced through a horizontal cut at the junction of the medial border and the middle third of the clavicle, which is then passed through the muscle, horizontally, to the vein between the clavicle and the first rib, which is why there is a danger of the electrode being "pinched" in that small space (" subclavian crush syndrome")[4,5]. Unfortunately, this is not the only complication that can occur during this procedure. Due to its position and anatomical closeness v. subclaviae with surrounding structures, bleeding and hematoma due to subclavian artery puncture, brachialis plexus injury, as well as tension pneumothorax due to proximity to the apex of the lung wing may occur. Also, due to its proximity to the costoclavicular ligament, there is a risk of infraclavicular fracture, due to its ossification during the aging process. An infraclavicular fracture can occur due to multiple bending due to the contraction of the pectoral muscle, or due to "trapping" of the electrode by the soft tissue of the subclavian muscle (5). When puncturing the left subclavian vein, there is a risk of trauma to the thoracic duct. When choosing this procedure, the potential risks must be taken into account[4,7,8].

Another alternative, increasingly used approach is puncture of v. axillaris. By using this method, the risk of iatrogenic pneumothorax is decreased. Also, the risk of electrode damage is reduced in relation to puncture of v. subclaviae[4,9]. In some clinical trials, puncture v. axillaris was performed "blindly", without previous venography or ultrasonography in order to detect this vein[9]. Regardless of the impossibility of visualization, no serious complications were recorded, nor were there any deviations in the results compared to the preparation of the v. cephalicae, and the duration of the procedure was less, because the preparation of the vein requires a lot more time and surgical skills. Also, the time of personnel exposure to radiation was significantly shorter[9]. In some studies, comparing the frequency of electrode fracture between v. subclavian and v. axillaris approaches, it was observed that electrode fracture was twice as common in patients in whom the electrode was implanted through v. subclavian approach, and that the most common location of the fracture was precisely at the point of puncture c. subclaviae (52% of cases), while less often it was in the middle of the electrode (6%), as well as at the point of connection to the pacemaker generator (10%)[3].

Although some research has proven that the most common localization of electrode fracture is at the point of v. subclaviane puncture, it is not its only localization. Sometimes, after implantation of a permanent pacemaker, a fracture occurs in the middle of the electrode, in the cavity of the right ventricle, at the point of connection to the generator, which is not related to the choice of venous access. Sometimes it happens that the generator box expands, which can lead to rotation of the pacemaker generator[10]. This happens less often in obese people, especially women, due to the larger amount of fat tissue. If there is manipulation of the generator by the patient, the probability of rotation is even higher. The generator can rotate in two ways, around its horizontal and vertical axis, and depending on that, we distinguish 2 syndromes:

- Twiddler syndrome – rotation of the pacemaker generator around the longitudinal (vertical) axis, resulting in twisting of the electrode. Twisting can lead to displacement, but also to fracture of the electrode, which can be partial or complete. The diagnosis is made on the basis of a chest radiograph where a break in the continuity of the electrode can be observed. When placing a new electrode, the existing electrode is isolated, but not removed, because there is a high risk of injury to the blood vessel when pulling out the «twisted» electrode. The tying of the pacemaker box is also performed so that the generator does not rotate again. It is interesting that patients with Twiddler's syndrome can be asymptomatic, and depending on the location of the fracture of the electrode and the movement of its free end, abdominal pulsations due to stimulation of the n. phrenicus, as well as hand jerks due to stimulation pl. brachialis[1,10],
- Reel syndrome - rotation of the generator around the transverse (horizontal) axis, which often leads to displacement of the electrode. No case of fracture has been reported yet.

After the electrode fracture is diagnosed, the problem is solved in the operating room. In local infiltrative anesthesia, a new electrode is placed, with careful selection of venous access. The previous electrode is isolated. Its extirpation is rarely performed due to the high risk of damage to the blood vessel and surrounding structures, and the impossibility of removing the distal end. After the intervention, before discharge from the hospital, the pacemaker must be checked and the parameters rechecked. It is necessary to educate the patient about the lifestyle with a pacemaker in order to prevent future complications.

Conclusion

Lead fracture is a common complication after permanent pacemaker implantation. In order to overcome the problem of electrode fracture, it is necessary to pay attention to a series of steps, from the very implantation of the pacemaker to the discharge of the patient from the hospital and his lifestyle after that. During implantation, the most important step is the choice of venous access. Since the subclavian approach is more often associated with lead fracture, it is advised to avoid it whenever possible. Although the approach through the v. cephalica is still the gold standard when implanting a permanent pacemaker, the axillary approach should not be neglected either. With the development of medicine, new ideas are also being developed in the era of pacemakers. Although the first pacemaker was implanted almost 60 years ago, single-chamber, double-chamber pacemakers and CRT (cardiac resynchronization therapy) developed relatively quickly. Recently, the so-called "leadless" pacemakers are available. There is a chance that using these pacemakers can avoid numerous

complications, including electrode fractures. Nevertheless, research on the evaluation of the balance between benefits and risks in the application of these pacemakers is still ongoing.

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Sažetak

Fraktura komorske elektrode trajnog pejsmejkera - prikaz slučaja

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Uvod. *Fraktura elektrode je česta kasna komplikacija nakon ugradnje trajnog pejsmejkera i predstavlja jedan od vodećih faktora koji dovodi do nefunkcionisanja pejsmejkera. Najzahtevniji korak u tretmanu bolesnika sa frakturom elektrode je postavljanje dijagnoze, obzirom na širinu kliničke slike, zbog čega je potrebno uraditi EKG zapis, elektrofiziološka ispitaivanja, neke od imidžing metoda (RTG p/c, CT grudnog koša). Lečenje se odvija u operacionoj sali, plasiranjem nove elektrode.*

Prikaz slučaja. *Bolesnica stara 91 godinu javila se u službu hitne pomoći zbog nesvestice, vrtoglavice, osećaja zamaranja koji su se javili ranije tog dana. Na EKG zapisu je zabeležen kompletan AV blok, frekvencije 40/min, sa beleženjem aktivnosti pejsmejkera bez kapture. Na radiografiji grudnog koša uočen je prekid kontinuiteta elektrode u infraklavikularnoj regiji. Nakon postavljanja dijagnoze, bolesnici je plasirana nova komorska elektroda, preparacijom v. cephalicae.*

Zaključak. *Prilikom implantacije pejsmejkera potrebno je pažljivo odabrati venski pristup, obzirom na učestalost frakture elektrode nakon subklavijalnog pristupa. Bitan faktor u prevenciji ima edukacija bolesnika. Bitno je na vreme postaviti dijagnozu, a nakon toga adekvatno zbrinuti bolesnika.*

Ključne reči: *trajni pejsmejker, fraktura elektrode*

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Case report

Asymptomatic aortic regurgitation: recommendations and dilemmas

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Abstract Aortic regurgitation (AR) is the third most common valvular disease, which more often affects younger people, mostly men. Untreated severe AR leads to advanced left ventricular (LV) remodeling, which results in LV systolic dysfunction, which consequently leads to the heart failure. There is no clear consensus for the management of asymptomatic patients with hemodynamically significant AR who do not meet guideline-defined echocardiographic criteria. In these patients, there is a debate about the optimal therapeutic approach, that is, whether to replace the aortic valve in an early, asymptomatic phase, or wait for the symptom onset and/or systolic dysfunction and LV enlargement in order to intervene. Through this case, we present the approach to the patient from his first visit to the doctor, as well as the diagnostic process that led to the diagnosis of severe AR and pericarditis, which turned out to be the case of the patient's symptoms, as well as the dilemma in the further treatment of the patient.

Key words asymptomatic aortic regurgitation, echocardiography, cardiac MRI, cardiopulmonary exercise testing, pericarditis

Introduction

Aortic regurgitation (AR) is the third most common valvular disease, occurring more frequently in younger patients, predominantly men[1]. The most common cause of AR is a degenerative process affecting the valve leaflets, following with a bicuspid aortic valve[1,2]. Infective or rheumatic endocarditis and aortic dissection are less frequent causes of AR. Hemodynamically significant AR leads to volume overload of the left ventricle (LV). Untreated severe AR results in advanced remodeling of the LV, characterized by dilation and eccentric hypertrophy, leading to LV systolic dysfunction and consequently to the development of heart failure[3]. The main indication for interventional treatment are symptoms caused by Arm most commonly dyspnea and fatigue[2]. On the other hand, there is no clear consensus on intervention for asymptomatic patients with hemodynamically significant AR who do not meet echocardiographic criteria defined by guidelines. Among these patients, there is a debate about the optimal therapeutic approach, whether to proceed with aortic valve replacement in the early asymptomatic stage or wait for the onset of symptoms and/or systolic failure and LV enlargement and then intervening. We present the case accentuating the dilemmas faced by cardiologists/cardiac surgeons dealing with this issue.

Case presentation

A 41-year-old male presented to the Emergency Centre of the University Clinical Center due to sudden severe chest pain, sharp and tearing in nature, propagating to the neck, and towards the shoulders. The patient reports history of hypertension, which is treated with an ACE inhibitor. Physical examination revealed a rough diastolic murmur over the entire precordium, with the punctum maximum over the aortic orifice. An electrocardiogram showed sinus rhythm with a heart rate of 97 beats per minute, without ischemic ST and T wave changes. Blood samples were taken for laboratory tests, and due to suspicion of acute aortic syndrome, the patient underwent multi-slice computerised tomography (MSCT), which showed no signs of acute aortic syndrome. Previously taken laboratory analyses (including troponin and D-dimer) were within reference ranges. After ruling out acute aortic syndrome, acute coronary syndrome, and pulmonary embolism, and as the symptoms had meanwhile alleviated, the patient was discharged home with advice to follow up with a cardiologist for echocardiography or stress testing if necessary. The patient returned for the scheduled outpatient visit stating that the pain still occasionally occurs but with slightly less intensity, and resolves with analgetics (Ibuprofen). Echocardiography revealed mild aortic dilation in the thoracic segment, bicuspid aortic valve, and significant aortic regurgitation of 4+ (Figure 1), with an enlarged left ventricle (end-diastolic diameter 7.0,

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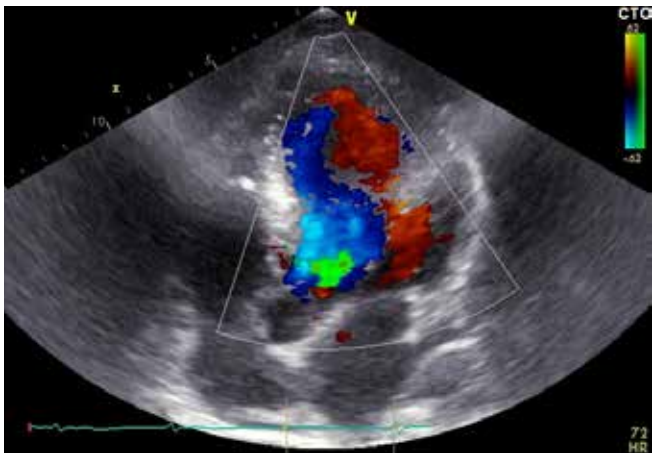

Figure 1. Echocardiographic image showing aortic regurgitation

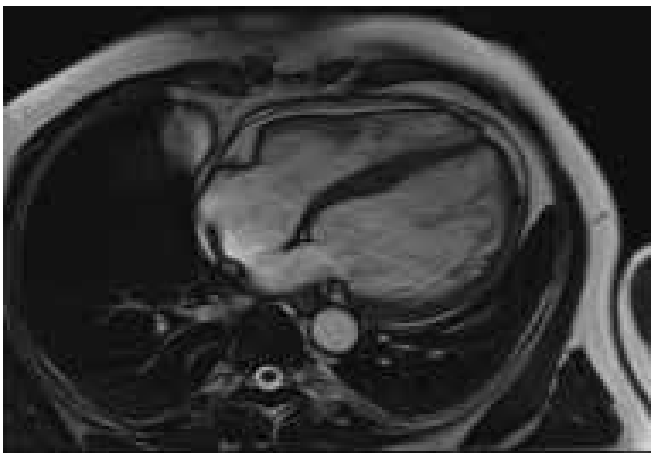

Figure 2. MRI image showing pericarditis

end-systolic diameter 4.8) and preserved overall systolic function (left ventricular ejection fraction 65%), without clear abnormalities in kinetics. Subsequently, the patient underwent cardiometabolic evaluation in the form of cardiopulmonary exercise testing (CPET) on a semi-supine ergobicycle to assess functional capacity and symptomatic status. A maximal CPET was performed as the test was terminated at fifth stage V at 150 W load, reaching anaerobic threshold (peak O_2 consumption achieved 24 mL/(kg·min), which is 52% of predicted), during which the patient remained asymptomatic. Other parameters of the cardiopulmonary exercise testing are listed in Table 1. Finally, in order to determine the severity of AR and the degree of LV burden more precisely, cardiac MRI was performed in three standard planes without contrast enhancement and after contrast enhancement. The MRI findings showed an enlarged left ventricle, no signs of myocardial fibrosis, and confirmed a degenerative bicuspid aortic valve with severe aortic regurgitation up to 4+ (regurgitant volume 31 ml, regurgitant fraction 39%). Additionally, circumferential pericarditis (Figure 2) was observed during this examination, which most likely was the cause of the patient's chest pain.

Table 1. Cardiopulmonary exercise testing parameters

	Load (W)	HR (/min)	BP (mmHg)	Sp O_2 (%)
	/	76	147/80	97
	15	92	159/91	97
	45	93	158/86	96
	90	112	184/87	99
	135	140	205/97	96
Max	150	141	210/94	99
5th rest minute	/	97	147/82	89

Legend: HR – heart rate, BP – blood pressure, Sp O_2 - oxygen saturation

After reviewing all the performed tests and the patient's clinical condition, as well as having a detailed discussion with the patient, Ibuprofen was advised at therapeutic doses for treating pericarditis. As there is no consensus on when to intervene in asymptomatic patients with severe AR who do not fulfill echocardiographic criteria for intervention, the patient was advised with conservative treatment and frequent monitoring to detect promptly any symptom onset or deterioration in echocardiographic parameters, which are clear indication for surgical aortic valve replacement.

Discussion

Considering that patient was entirely asymptomatic, as confirmed by exercise testing, and diagnostic methods (CPET, echocardiography, MRI) showed borderline preserved cardiopulmonary capacity, as well as borderline dimensions and LV ejection fraction, the decision whether to refer the patient for surgical treatment or further diagnostic monitoring is extremely challenging, given that current guidelines, due to insufficient evidence, are unclear for asymptomatic patients with chronic severe AR and without significant diataion of the ascending aorta. Watchful waiting and regular echocardiographic follow-up until meeting any of the aforementioned criteria is recommended by guidelines.

The optimal timing for surgical treatment of patients with severe chronic asymptomatic AR has not been precisely established, and the current approach is based on a combination of symptom onset time, echocardiographic assessment of AR severity, and LV remodeling (LV ejection fraction ≤50% or left ventricular end-systolic diameter >50 mm or indexed left ventricular end-systolic diameter >25 mm/m^2 in patients with small body surface area)[2]. Since percutaneous aortic valve replacement in patients with AR is not yet recommended (studies evaluating this method are ongoing), surgical aortic valve replacement is currently the only interventional method used.

Relying solely on echocardiographic criteria for setting indications for surgical treatment, a number of patients undergoing aortic valve surgery already have irreversible myocardial fibrotic changes at the time of intervention[4]. On the other hand, cardiac MRI has high precision in determining the severity of AR and selecting patients for surgical treatment. There is data indicating that to determine the optimal timing for surgical treatment, before irreversible myocardial damage occurs, it is

crucial to determine parameters indicating AR severity (echocardiographically determined vena contracta, left ventricular end-diastolic volume index - EDVI, as well as AR volume and regurgitation fraction determined by MRI), then parameters indicating remodeling and subclinical left ventricular failure (MRI-determined EDVI or left ventricular global longitudinal strain determined by echocardiography), serum levels of natriuretic peptides, as well as the patient's age[5,6]. These parameters are independent predictors of early disease progression, and their combination has a higher predictive value than individual parameters in determining the risk of decompensation in the early stages of the disease and selecting patients for early surgical treatment while still in the asymptomatic phase[5,6]. Timely surgical treatment has been shown to be associated with significant reverse remodeling and normalization of LV structure and function, while perioperative mortality is significantly reduced using new surgical techniques[7-9].

Although previous guidelines favored a conservative approach in patients with severe asymptomatic AR and preserved left ventricular ejection fraction, there is increasing evidence supporting early surgical treatment of this specific valvular disease. For this reason, the multicenter randomized ELEANOR trial (Early aortic vaLve surgEry versus wAtchful waitiNg strategy in severe asymptomatic aOrtic reguRgitation; NCT 05438862) has been initiated, aiming to compare outcomes in two groups of asymptomatic patients with severe asymptomatic AR and preserved left ventricular systolic function, one in which patients undergo early surgical treatment of the AR and one in which patients are conservatively treated and intensively monitored to detect symptoms and signs of heart failure or a decrease in LV ejection fraction, when they are promptly referred for surgical treatment according to class I of the current recommendations for valvular disease treatment[2]. The results of this trial are expected in 2026.

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Sažetak

Asimptomatska aortna regurgitacija: preporuke i dileme

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Aortna regurgitacija (AR) je treća po učestalosti valvularna bolest, koja se češće javlja kod mlađih osoba, pretežno muškaraca. Nelečena teška AR dovodi do uznapredovalog remodelovanja leve komore (LK), što za posledicu ima sistolnu disfunkciju LK i nastanak srčane insuficijencije. Ne postoji jasan konsenzus za lečenje asimptomatskih pacijenata sa hemodinamski značajnom AR koji ne ispunjavaju vodičem definisane ehokardiografske kriterijume. Kod ovih pacijenata vodi se debata o optimalnom terapijskom pristupu, to jest da li pristupiti zameni aortnog zaliska u ranoj, asimptomatskoj fazi, ili čekati na pojavu tegoba i/ili sistolnog popuštanja i uvećanja LK kako bi se intervenisalo. Kroz ovaj slučaj prikazan je pristup pacijentu od njegovog prvog javljanja lekaru, kao i dijagnostički proces koji je doveo do postavljanja dijagnoza teške aortne regurgitacije i perikarditisa, za koji se ispostavilo da je uzrok tegoba, kao i dileme u daljem tretmanu pacijenta.

Ključne reči: *asimptomatska aortna regurgitacija, ehokardiografija, magnet srca, ergospirometrija, perikarditis*

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Review article

Treatment of patients with spontaneous coronary artery dissection - is there a difference?

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Abstract Patients with spontaneous coronary artery dissection (SCAD) do not differ from any other acute coronary syndrome (ACS) patients from the first medical contact to coronary angiography; the diagnostic approach and therapy are the same. SCAD patients are identified only based on coronary angiography findings. Perhaps the "SCAD Patient Model" can help. By analyzing registries of SCAD patients, we can see that 90% are women, with 87-95% aged 44-53 years, who may have a personal or family history of fibromuscular dysplasia, and may be correlated with the use of hormone therapy or with changes in hormonal status during pregnancy. Based on this data, we can identify a model of SCAD patient, which is presented by a young woman suggesting a SCAD patient with clinical presentation of ACS. This is almost certain if we have a young pregnant woman or a woman in the postpartum period with ACS. Considering that the use of fibrinolytic therapy in SCAD patients is absolutely contraindicated, and that the diagnosis of SCAD is made only by coronary angiography, it should be considered whether patients with a possible SCAD pattern should not receive fibrinolytic therapy but should be transported to an available PCI center. PCI is indicated in patients with SCAD in cases of TIMI 0 flow on coronary angiography, significant reduction in blood flow in the vessel and persistent chest pain, or hemodynamically unstable patients. The pathophysiological mechanism in SCAD patients is not atherosclerotic disease but an intramural hematoma in the coronary artery wall. Medical treatment of SCAD patients is different from that of patients with an atherosclerotic form of acute coronary syndrome. Dual antiplatelet therapy is administered for a duration of 12 months only in the group of patients undergoing PCI, while others are taking it for a duration of 1 month. Statins, ACE inhibitors are given only to selected patients. It is recommended that beta-blocker therapy be applied to all patients who can tolerate the medication.

Key words spontaneous coronary artery dissection, acute coronary syndrome, therapy

Introduction

According to guidelines for the diagnosis and treatment of patients with acute coronary syndrome (ACS), 4% of patients with clinically manifested ACS on coronary angiography are diagnosed with spontaneous coronary artery dissection (SCAD). Out of this number, 22-35% are women under the age of 60 (1). Patients with SCAD do not differ from any other ACS patients from the first medical contact to coronary angiography; the diagnostic approach and therapy are the same. SCAD patients are identified only based on coronary angiography findings. According to current guidelines, ACS patients receive dual antiplatelet therapy (DAPT) after the first medical contact, consisting of acetylsalicylic acid (ASA) with the addition of Clopidogrel, Ticagrelor, or Prasugrel in loading doses. It should be noted that according to guidelines, Ticagrelor and Prasugrel, as more potent drugs, are preferred over Clopidogrel. The same patients also receive low molecular weight heparin (LMWH) in therapeutic doses[2]. If the first medical contact is in a PCI center, LMWH is often not given, and unfractionated heparin (UFH) is used during the procedure itself. This therapeutic approach has been used for almost 20 years and has shown a significant difference in survival, with fewer recurrent infarctions during hospitalization and within the first year in patients with ACS and primarily due to atherosclerotic disease[3].
Unlike atherosclerotic lesions, SCAD is pathophysiological characterized by the occurrence of an intramural hematoma within the tunica media of the coronary artery, which, by its propagation and enlargement, partially or completely, in shorter or longer artery segments reduces blood flow in the infarcted coronary artery (Figure 1.).

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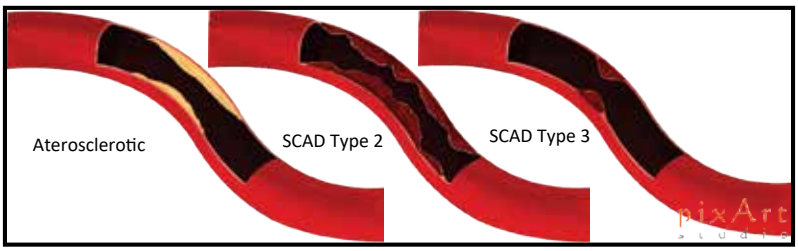

Figure 1. Aterosclerotic vs SCAD Type 2 and Type 3 lesion oronarne aerterije

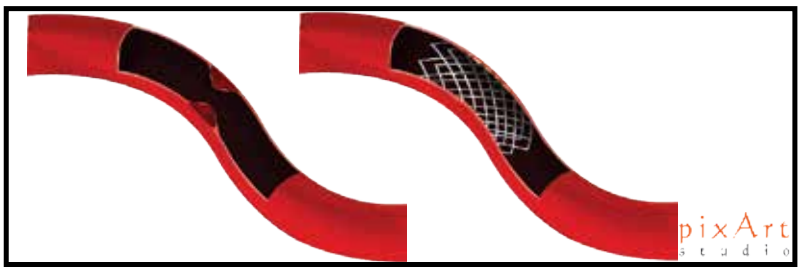

Figure 2. PCI with single stent implantation

Knowing that SCAD is fundamentally characterized by hemorrhage and the occurrence of a hematoma within the wall of the coronary artery, rather than atherosclerosis, it is clear that the application of standard ACS therapy from the first medical contact to coronary angiography and definitive diagnosis of SCAD can be problematic. How can we differentiate SCAD patients at this stage of clinical presentation? Perhaps the "SCAD Patient Model" can help. By analyzing registries of SCAD patients, we can see that 90% are women, with 87-95% aged 44-53 years[1], who may have a personal or family history of fibromuscular dysplasia[4], and may be correlated with the use of hormone therapy or with changes in hormonal status during pregnancy[5]. Based on this data, we can identify a model of SCAD patient, which is presented by a young woman without traditional risk factors for atherosclerosis (except smoking and hypertension), suggesting a SCAD patient with clinical presentation of ACS. This is almost certain if we have a young pregnant woman or a woman in the postpartum period with ACS.

The aim of this study is to point out the difference in therapeutic approach between patients with an atherosclerotic disease and patient with spontaneous coronary artery dissection that both present themselves clinically with acute coronary syndrome.

If we go back to the fact that only 4% of patients with ACS have SCAD as the underlying cause, it is not expected that the therapeutic strategy for patients with ACS will change from the first medical contact to coronary angiography. However, the therapy for patients with SCAD has its specificities.

Fibrinolytic therapy

A portion of patients with SCAD who clinically present as ACS are treated in centers where PCI is not available as a therapeutic option. According to the protocol for patients with STEMI ECG presentation, these patients receive fibrinolytic therapy. According to data from the Can SCAD registry, 29.7% of patients present as STEMI patients at the first medical contact, and 11% received fibrinolytic therapy[6]. Considering that the use of fibrinolytic therapy in SCAD patients is absolutely contraindicated[7,8], and that the diagnosis of SCAD is made only by coronary angiography, it should be considered whether patients with a possible SCAD pattern should not receive fibrinolytic therapy but should be transported to an available PCI center.

Percutaneous coronary intervention (PCI)

After coronary angiography and definitive diagnosis of SCAD based on lesion characteristics and TIMI flow, a decision is made regarding further conservative medical treatment or PCI[1]. According to the CanSCAD registry of 750 patients, 86.4% were treated conservatively. Their conclusion is that in the most experienced centers, the majority of patients are treated conservatively, and in 95% of patients, complete recovery of the coronary artery was found on follow-up coronary angiography after 30 days[6,9]. Coronary artery recovery is high, with low mortality, 1% during a 3-year follow-up period, but a large number of patients continue to experience frequent symptoms and poor quality of life even after the acute phase of the disease[10].

PCI is indicated in patients with SCAD in cases of TIMI 0 flow on coronary angiography, significant reduction in blood flow in the vessel and persistent chest pain, or hemodynamically unstable patients[1]. PCI techniques in SCAD patients include:

1. PCI with a single stent - suitable for patients with SCAD Type 3, when the affected part of the coronary artery is short. Primo-implantation of a stent placed in the middle of the lesion is used, and the upper and lower edges of the stent need to be 5-10mm longer than the lesion. (Figure 2.).

2. PCI with multiple stents (Sandwich technique) - suitable for patients with Type 2, when a longer segment of the coronary artery is affected by hematoma. Stents are deployed without prior balloon dilatation, if possible. The first stent is positioned in the proximal part of the

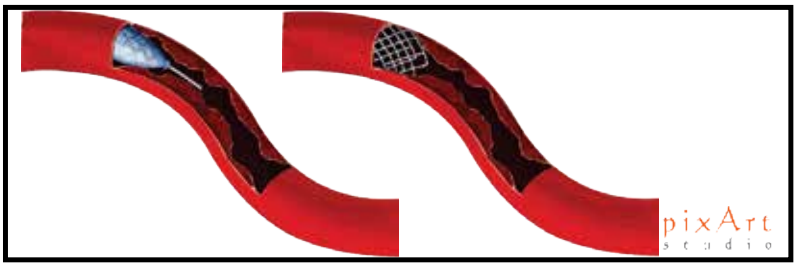

Figure 3a. Sandwich technique - proximal stent implantation

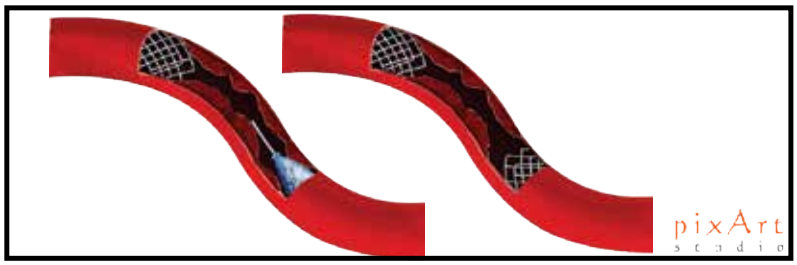

Figure 3b. Sandwich technique - distal stent implantation

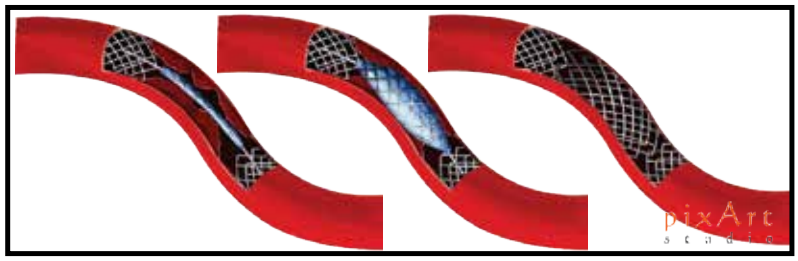

Figure 3c. Sandwich technique - middle stent implantation

Figure 4. PCI with Cutting Balloon

artery, with at least 5-10mm of the stent overlapping the lesion onto the healthy part of the artery (Figure 3a.). This stent localizes the hematoma propagation towards the proximal part of the artery. The second stent is positioned in the distal part of the artery, with 5-10 mm of the stent extending beyond the lesion into the healthy part of the artery (Figure 3b.). This stent isolates the hematoma and prevents its propagation into the distal part of the artery. The third stent is positioned in the central part of the lesion, overlapping with both the proximal and distal stents (Figure 3c.).

3. PCI with Cutting Balloon - in the case of patients with SCAD Type 3, a cutting balloon is positioned at the center of the lesion, while in patients with SCAD Type 2, it is necessary for the cutting balloon to be positioned and expanded at 2 or 3 sites. A cutting balloon with a diameter no greater than 2mm is used and expanded with no more than 2-4 atmospheres. This minimally invasive approach fenestrate the vessel's intima, facilitates drainage of the hematoma into the vessel lumen, and reduces the risk of periprocedural complications on the vessel wall. After the cutting balloon is expanded and an adequate TIMI flow is achieved, the procedure can be terminated or continued with stent implantation (Figure 4.). There is a group of authors who suggest the use of bioresorbable scaffold stents for this purpose (11). This recommendation may be justified given that we know SCAD resolves spontaneously within a few months, and bioresorbable stents completely degrade in about 2 years. After this period, a healthy vessel remains without a metallic stent.

Coronary angiography/PCI in SCAD patients has its specificities:

- Femoral access is recommended for SCAD patients since radial artery dissection is three times more common with radial access[12],
- Manual contrast injection is recommended, avoiding the use of contrast pumps whenever possible.
- If dilation or expansion of the stent is performed near a significant side branch, it is necessary to protect the side branch with an additional coronary wire in case of hematoma propagation towards the side branch.
- "Soft" atraumatic coronary wires should be used.

• After a successful PCI procedure with stent implantation over the hematoma, repeat coronary angiography is recommended after one month, expecting complete hematoma resorption. Assessment with intravascular imaging (IVUS, OCT) is necessary to determine if there is free space between the coronary artery wall and the stent, with eventual post-dilation of the stent using a balloon to correct any stent malposition that may occur after hematoma resorption.

Coronary artery bypass grafting

According to guidelines for treatment of ACS without ST elevation, coronary artery bypass grafting (CABG) can be performed in specific cases (1). This primarily applies to patients with extensive dissections, dissections of the left main, or after unsuccessful PCI attempts (inability to pass the wire through the true lumen of the coronary artery) (11). The issue with this treatment method lies in the pathophysiological characteristic of SCAD, where in 95% of cases, the dissected artery spontaneously recovers within 1-3 months. After artery recovery, there is competitive flow through the coronary artery, either through venous or arterial grafts. Therefore, there is a risk of graft thrombosis after several months. The experiences of SCAD patients treated with bypass surgery are limited to individual cases.

Medical therapy

1. LMWH and UFH
As noted, patients with clinical and ECG presentations of ACS before coronary angiography routinely receive LMWH. After coronary angiography and the diagnosis of SCAD, further use of any form of heparin is absolutely contraindicated during the course of patient treatment.

2. DAPT (Acetylsalicylic acid and Clopidogrel)
The DAPT therapeutic approach differs for SCAD patients since the underlying pathology is a hematoma within the vessel wall rather than atherosclerotic disease. Based on the TIMI flow on coronary angiography, a decision is made whether the patient will undergo PCI or continue with conservative treatment. The difference lies in the DAPT therapy, which involves the use of ASA in combination only with Clopidogrel. Ticagrelor and Prasugrel, being more potent, are not indicated for this patient population due to a higher risk of new intramural bleeding within the vessel. DAPT with Clopidogrel is recommended for all SCAD patients at discharge, with differences in duration: for patients with SCAD and after PCI, DAPT therapy is recommended for 12 months, while for all others, DAPT therapy lasts for 1 month, followed by ASA alone. In everyday clinical practice, differences are observed compared to the recommended therapy. In the DISCO registry, 66% of patients used DAPT for longer than one month, even without undergoing PCI procedures, leading to twice the frequency of MACE compared to the group of patients using only one drug (13). In the Vancouver registry, 83.1% of patients were treated without PCI procedures. At discharge from the hospital, 62.2% of patients had DAPT, and in 25.4% of cases, this treatment continued after 3 years of follow-up.(14)

3. Statins
The use of statins is not indicated for all SCAD patients since the cause of this disease is not the presence of atherosclerotic plaque. Therefore, statins are only given to selected patients. Statins are indicated for patients with proven hyperlipoproteinemia, type II diabetes mellitus, or previously known atherosclerotic disease. According to the Can SCAD registry, 346 out of 750 patients, or 46.1%, had these indications for the safe long-term use of statins. However, a review of registries reflecting daily clinical practice shows that the majority of patients receive statins after hospital treatment. In the DISCO registry, 70% of patients received statins at discharge, and interestingly, statin use depended on antiplatelet therapy. In the group that received DAPT at discharge, 81.8% also received statins, while in patients who received only one antiplatelet drug, 50.7% received statins (13). In the Vancouver registry, statins were given to only 54.2% of patients at discharge, which is approximately the number of patients with a real indication for their use, but in 36.7% of cases, statins continued to be used after 3 years of therapy (14).

4. Beta-blockers
Beta-blockers are indicated for all SCAD patients with heart failure and reduced ejection fraction. They have been observed to have a favorable effect even in patients with preserved ejection fraction due to reducing shear stress on the vessel wall, thereby reducing the risk of SCAD propagation (a mechanism similar to aortic dissection). Beta-blockers also have a favorable effect due to reducing heart rate, thereby having an anti-arrhythmic effect, and also in lowering blood pressure. There is evidence that beta-blockers significantly reduce the risk of recurrent events in SCAD patients (13). A limitation for the use of beta-blockers may be that SCAD patients are usually young women who often have hypotension and may not tolerate the medication well. In the Vancouver registry, 83% of patients had beta-blockers at discharge, and 80.4% continued their use after 3 years of follow-up (12).

5. ACE Inhibitors
ACE inhibitors should be used in all SCAD patients in the presence of heart failure with reduced ejection fraction. In the Vancouver registry, 57.6% of patients had ACEIs in their therapy at discharge, and 49.2% continued their use after 3 years of follow-up. In the same registry, a very small number of patients had heart failure during hospital treatment or during the follow-up period. The justification for the use of ACEIs can only be if they were used in the treatment of arterial hypertension, which was present in 32.1% of SCAD patients (14).

Conclusion

Patients with spontaneous coronary artery dissection are part of the population of patients who clinically present with acute coronary syndrome. The pathophys-

iological mechanism in SCAD patients is not atherosclerotic disease but an intramural hematoma in the coronary artery wall. Medical treatment of SCAD patients is different from that of patients with an atherosclerotic form of acute coronary syndrome. Dual antiplatelet therapy is administered for a duration of 12 months only in the group of patients undergoing PCI, while others are taking it for a duration of 1 month. Statins, ACE inhibitors are given only to selected patients. It is recommended that beta-blocker therapy be applied to all patients who can tolerate the medication.

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Sažetak

Terapija pacijenata sa spontanom disekcijom koronarnih arterija - da li ima razlike?

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Pacijenti sa sponatnom disekcijom koronarne arterije (SCAD) se od prvog medicinkog kontakta do koronarografije ne razlikuju od bilo kojih pacijenata sa akutnim koronarnim sindromom (AKS), isti je dijagnostički pristup, ista je terapija. Tek na osnovu nalaza koronarografje identifikujemo SCAD pacijente. Možda može pomoći „Model SCAD pacijenta". Analizom registara sa SCAD pacijentima uočavamo da su 90% žene, i to 87-95% starosti 44-53 godine života, da mogu imati ličnu ili porodinu anamezu o postojanju fibromuskularne displazije, da može biti u korelaciji sa upotrebom hormonske terapije ili zbog promene hormonskog statusa za vreme trudnoće. Na osnovu ovih podataka možemo uočiti model SCAD pacijenata gde imamo mladu ženu, što nam može sugerisati da se radi o SCAD pacijentu sa kliničkom prezentacijom AKS. Ovo je skoro izvesno ukoliko imamo mladu ženu u trudnoći, ili u postpartalnom periodu sa AKS. S obzirom da je upotreba fibrinolitičke terapije kod SCAD pacijenata apsolutno kontraindikovana, a da se dijagnoza SCAD postavlja upravo na koronarografiji, razmotriti mogućnost da pacijenti sa mogućim SCAD modelom možda ne treba da dobijaju fibrinolitičku terapiju, već da se transportuju u dostupni PCI centar. PCI je indikovana kod pacijenata sa SCAD u slučaju TIMI 0 protoka na koronarografiji, kod značajne redukcije protoka na krvnom sudu, ako perzistira bol u grudima, kod hemodinamski nestabilnih pacijenata. Patofiziološka osnova kod ovih pacijenata nije aterosklerotska bolest već intramuralni hematom u zidu koronarne arterije. Medikamentno lečenje SCAD pacijenata nije isto kao kod pacijenata sa aterosklerozom. Dvojna antitrombocitna terapija se daje u trajanju od 12 meseci samo u grupi pacijenata sa PCI dok ostali imaju u trajanju od 1 meseca. Statini, ACEI daju se samo kod selektovanih pacijenata. Preporučuje se da hronična terapija beta blokatorima bude primenjena kod svih pacijenata koji lek mogu da tolerišu.

***Ključne re**či: sponatna disekciaj koronarne arterije, akutni koronarni sindrom, terapija*

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Review article

The importance of recognizing the harmful effects of hyperoxia in the treatment of cardiac patients

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Abstract Non-selective use of oxygen therapy can lead to the development of hyperoxia, which is known to cause harmful consequences on multiple organ systems through various mechanisms. Besides its detrimental effects on pulmonary parenchyma, the cardiovascular system represents another target where the detrimental effects of hyperoxia manifest. The pathogenetic mechanism of hyperoxia is based on reducing the bioavailability of NO, increasing systemic vascular resistance, inducing vasoconstriction, reducing oxygen supply to tissues, and inducing additional cellular mechanisms that lead to apoptosis of myocardial cells, decreased stroke volume, and cardiac output. These pathogenetic changes can worsen the clinical condition, especially in patients with myocardial infarction and heart failure. Clinicians need to pay attention to optimal oxygen therapy in specific indications and appropriate dosing (dosage), and highlight the potential harmful effects of hyperoxia that can significantly affect the clinical course of patients.

Key words hyperoxia, cardiovascular diseases

In clinical practice, oxygen therapy is often used non-selectively in patients with myocardial infarctions, heart failure, and other acute cardiac conditions. Oxygen is frequently administered in doses higher than necessary, which not only fails to improve the clinical condition but can also have negative consequences under certain conditions. Despite the knowledge of the harmful effects of oxygen dating back to the 1960s and well-documented recent literature on the adverse effects of hyperoxia in all categories of patients, including those treated on an outpatient basis, in the prehospital and hospital phases, as well as during rehabilitation, there persists an inertia in applying outdated oxygen therapy regimens. [1-8]

To highlight to clinicians the pathogenetic mechanisms underlying the development of harmful effects and clinical manifestations of hyperoxia.

Hyperoxia refers to a condition of elevated oxygen supply to tissues and organs, whereas the toxic effects of oxygen manifest when the partial pressure of alveolar oxygen exceeds that inspired under normal conditions. With continuous exposure to supraphysiological concentrations of oxygen, a state of hyperoxia develops.[6] Based on arterial blood gas analysis, hyperoxia is defined as a finding of partial pressure of oxygen (PaO_2) greater than 100 mmHg to 125 mmHg (13.3- 16.7kPa) depending on the literature.[3]

Hyperoxia exhibits adverse effects on the entire organism, and the adverse effects on the cardiovascular system can be evaluated only as part of the mutual and additive multi-organ action. Table 1 illustrates the pathophysiological mechanisms of hyperoxia on the major organ systems. [2-6]

The negative effects of hyperoxia on hemodynamics and the cardiovascular system as a whole occur via two key systemic effects, including direct vasoconstriction and the generation of toxic reactive oxygen species (ROS).[4] Supraoptimal oxygen level used with the aim of improving tissue oxygenation in hypoxic patients, paradoxically leads to the opposite effect, resulting in reduced oxygen release to tissues. The main mechanism by which hyperoxia leads to this phenomenon is based on vasoconstriction. This leads to increased systemic vascular resistance and decreased blood flow by 10-30% in the coronary, cerebral, and vascular systems.[2] It is logical that the reduction in oxygen release to tissues leads to an increase in the ischemic zone in acute myocardial infarction, and it may lead to arrhythmias, recurrent myocardial infarction, and negative cardiac remodeling.[3] The mechanism via the negative effects of reactive oxygen species (ROS), mitochondrial stress, leads to cellular apoptosis and myocardial cell death. It is also important to consider the role of hyperoxia in activating the parasympathetic nervous system and the onset of bradycardia, which further has significant implications for clinical management and drug administration.[6] The reduction in the bioavailability of nitric oxide (NO) induced by hyperoxia affects the onset of endothelial dysfunction,

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Table 1. Pathophysiology mechanisms of the occurrence of adverse effects of hyperoxia[3-6]

PATHOPHYSIOLOGY MECHANISMS OF THE OCCURENCE OF ADVERSE EFFECTS OF HYPEROXIA	
Cardiovascular system	• ↓ cardiac output and stroke volume • ↑ systemic vascular resistance • ↓ NO bioavailability • ↓ heart rate
Respiratory system	• Lung inflammatic edema • Hyperoxic acute lung injury • Bronchopulmonary dysplasia • Absorption atelectasis • ARDS • COPD; • Hypercapnia
Central nervous system	• Direct neurotoxicity • Reduced myelination • Activation of parasympathetic nervous system • *Paul Bert effect (toxic CNS effects)*
Renal function	• Reduced renal blood flow • Tubular necrosis • Glomerular dysgenesis • Acute kidney injury
Cellular level	• Reactive oxygen species • Mitochondrial stress • Cellular injury • Apoptosis • Cell death • Pro-inflammatory signaling (NF-kB, IL-6, TGF-B, ET-1) (Lipid peroxidation, sulfhydryl protein oxidation, DNA damage, reduction of cellular reducing agents)

which represents the fundamental pathogenetic mechanism of the development and acceleration of atherosclerosis, the primary cause of coronary artery disease.[3-6]

It has been found that the earlier routine use of oxygen therapy in patients with acute myocardial infarction is not only not beneficial in normoxemic patients but can also lead to harmful effects.[5-8]

The AVOID study (*Australian Air Versus Oxygen in Myocardial Infarction*) randomized 441 patients with STEMI type of myocardial infarction, registering larger infarct areas on magnetic resonance imaging, increased cardiac biomarkers, and a higher incidence of recurrent myocardial infarctions in patients who used oxygen therapy at 8 L/min via nasal mask compared to those who did not receive oxygen therapy. In contrast, the SOCCER study (*Supplemental Oxygen in Catheterized Coronary Emergency Reperfusion*), which randomized 100 normoxemic STEMI patients prescribed oxygen therapy at 10 L/min and those on room air, did not find a statistically significant difference in the size of the infarct zone or the myocardial salvage index examined with CMR (Cardiac magnetic resonance).[2] The DETO2X-AMI randomized study of 6629 patients during the administration of 6 L/min over 6-12 hours did not reveal a change in overall mortality, hospitalization due to heart failure, or cardiovascular death within one year.[2]

According to the latest recommendations of the European Society of Cardiology, oxygen therapy is justified in patients with acute myocardial infarction if oxygen saturation is below 90% (Class I). Otherwise, in patients who are not significantly hypoxic (SaO2 >90%), oxygen therapy is not recommended and may be considered harmful (Class III).[9]

Hyperoxia in patients with heart failure also leads through the mechanism of vasoconstriction to an increase in afterload, systemic vascular resistance, and thereby a decrease in stroke volume and cardiac output.[6,10,11] It is important to emphasize the additional effect of hyperoxia on reducing oxygen distribution to tissues and consequent cellular changes. Routine oxygen therapy is not recommended in patients with acute heart failure. Hyperoxygenation can disrupt the matching of ventilation and perfusion and thereby suppress ventilation, leading to hypercapnia. Therefore, in this patient group, caution should be exercised with the use of oxygen therapy, with monitoring of acid-base balance, SaO2, and SaCO2.[9,10,11] The ELSO registry (*Extracorporeal Life Support Organization*) found that patients with hyperoxemia, defined as PaO2 > 100mmHg within 24 hours after initiation, have a higher degree of in-hospital mortality.[2]

Conclusion

In clinical practice, attention should be paid to the rational use of oxygen therapy, which undoubtedly has a beneficial effect in therapy, especially in those with SaO2 below 90%. However, it must be kept in mind that the use of oxygen in unjustified indications or in excessive doses in justified indications can cause more harmful effects and worsen the prognosis of patients. Additional basic and clinical studies are expected to determine the precise detection of hyperoxia within a time-limited interval and highlight its significance in everyday practice.

Table 2. Summary effect size of acute hyperoxia-induced changes of different clinical state[4]

Summary effect size of acute hyperoxia-induced changes of different clinical state						
	Heart rate	Stroke volume	Cardiac output	Mean arterial pressure	Systemic vascular resistance	Oxygen delivery
Healthy volonteers	↓↓	↓	↓↓	NS	↑↑	NS
Coronary artery disease	↓	NS	↓↓	↑	↑↑	-
Heart failure	NS	↓↓	↓↓	NS	↑↑↑	-
CABG	↓	-	NS	NS	↑↑	-
Sepsis	NS	-	NS	NS	NS	NS

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Sažetak

Značaj prepoznavanja štetnih efekata hiperoksije u lečenju kardioloških bolesnika

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Neselektivna primena oksigenoterapije može uzrokovati nastatanak hiperoksije za koju je poznato da preko brojnih mehanizama uzrokuje štetne posledice na više organskih sistema. Pored štetnog dejstva na plućni parenhim, kardiovaskularni sistem predstavlja drugo ciljno mesto na kome se ispoljavaju detrimentalni efekti hiperoksije.
Patogenetski mehanizam hiperoksije zasniva se na smanjenju bioraspoloživosti NO, povećanju sistemske vaskularne rezistencije, nastanku vazokonstrikcije, redukciji snadbevanja kiseonika tkivima i indukovanju dodatnih celularnih mehanizama koji dovode do apoptoze ćelija, smanjenja udarnog i minutnog volumena srca. Navedene patogenetske promene mogu uzrokovati pogoršanje kliničkog stanja, naročito kod bolesnika sa infarktom miokarda i srčanom insuficijencijom.
Kliničarima je potrebno skrenuti pažnju na optimalizaciju terapije kiseonikom u određenim indikacijama i adekvatnoj dozi i ukazati na potencijalne štetne efekte hiperoksije koji mogu značajno uticati na klinički tok bolesnika.

Ključne reči: *hiperoksija, kardiovaskularne bolesti*


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DUGOROČNIJA PLOVIDBA U TERAPIJI HIPERTENZIJE

NOSILAC DOZVOLE HEMOFARM AD VRŠAC Beogradski put bb, Vršac

BROJEVI DOZVOLA ZA STAVLJANJE LEKA U PROMET

Prilinda® Duo, 5 mg+5 mg, kapsule, tvrde: 515-01-03838-20-001;
Prilinda® Duo, 10 mg+5 mg, kapsule, tvrde: 515-01-03840-20-001
Prilinda® Duo, 5 mg+10 mg, kapsule, tvrde: 515-01-03839-20-001;
Prilinda® Duo, 10 mg+10 mg, kapsule, tvrde: 515-01-03841-20-001

DATUM PRVE DOZVOLE I DATUM OBNOVE DOZVOLE ZA STAVLJANJE LEKA U PROMET

Datum prve dozvole: 28.06.2022.
Datum revizije teksta SmPC-a: Jun, 2022.

Pre propisivanja leka, proučiti kompletan tekst odobrenog SmPC-a.

SAMO ZA STRUČNU JAVNOST

Prilinda® Duo

ramipril, amlodipin

Cor Tensec®

bisoprolol

1,25 mg 2,5 mg 3,75 mg

film tablete

ZA FINA PODEŠAVANJA

u terapiji stabilne hronične srčane insuficijencije

NOSILAC DOZVOLE: HEMOFARM AD VRŠAC, Beogradski put b.b., Vršac
BROJ(EVI) DOZVOLE(A) ZA STAVLJANJE LEKA U PROMET:
Cor Tensec®, 1,25 mg, film tablete: 515-01-00148-21-002
Cor Tensec®, 2,5 mg, film tablete: 515-01-00149-21-002
Cor Tensec®, 3,75 mg, film tablete: 515-01-00150-21-002
DATUM VAŽEĆE DOZVOLE ZA STAVLJANJE LEKA U PROMET:
20.11.2022.DATUM REVIZIJE TEKSTA: Mart, 2023.

Lek se može izdati samo uz lekarski recept.
Samo za stručnu javnost.
Pre propisivanja leka, detaljno proučiti kompletan tekst odobrenog SmPC-a.

Hemofarm
STADA GRUPA