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Heart and Blood Vessels

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Review article

Carcinoma associated pulmonary embolism: summary and treatment challenges

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Abstract Cancer-associated venous thromboembolism (VTE) represents one of the major causes of increased morbidity and mortality in cancer patients. It is very important to determine the risk level in order to adequately treat the patients, but also select the patients for primary and secondary prevention of VTE and assess the risk of early death in case of acute pulmonary embolism. Nowadays the significant development in the VTE treatment in cancer patients is evident. Novel oral anticoagulants (NOACs) simplified the treatment of VTE compared to low-molecular-weight heparin (LMWH) due to their characteristics, way of administration, fixed - dose regimens and lower cost. However, their prescription requires additional caution, especially in patients with gastrointestinal malignancies. The latest available data on reperfusion therapy emphasize the importance of individual approach to each cancer patient with VTE.

Kew words carcinoma, pulmonary thromboembolism, risk stratification, therapy

Cancer-associated venous thromboembolism (VTE), which includes deep vein thrombosis, pulmonary embolism, and central venous catheter-related VTE, is the second leading cause of death in patients with cancer after progression. The prevalence of cancer-associated thrombosis is increasing because of numerous factors, including prolonged patient survival, anticancer therapies, an enhanced detection of incidental VTE during surveillance imaging, and broader use of central venous catheters.[1]
The risk of developing VTE in cancer patients is increased up to seven-fold as compared to the general population.[2] However, VTEs are incidentally detected in about one-half of all cancer patients without any clinical suspicion of VTE at the time of diagnosis.[3] Patients with cancer-associated thrombosis are at high risk of recurrent VTE and anticoagulant-related bleeding, which are associated with high morbidity and resource use.[1] The occurrence of VTE in patients with cancer may interfere with planned chemotherapy regimens, increase the risk of mortality, and result in increased costs compared with patients without cancer.[4] More than 50% of thrombotic events occur within 3 months of the cancer diagnosis, the time when most cancer treatments will be underway.

Risk factors for VTE

VTE risk factors in cancer patients can be grouped into 3 general categories: intrinsic and extrinsic patient-related factors, cancer-related factors and treatment- related factors.[2] The risk for VTE and recurrent VTE is highest among certain hematologic malignancies, such as lymphoma, acute leukemia and multiple myeloma. Patients with high-grade lymphoma and acute promyelocytic leukemia appear to be at higher risk than other forms of lymphoma or leukemia. Lung cancer, gastrointestinal cancer (stomach/colon), pancreatic cancer, kidney cancer, bone cancer, myelodysplastic disorder and patients with distant metastasis are also susceptible.[5]
Several risk factors for developing venous thrombosis usually coexist in cancer patients including surgery, hospital admissions, immobilization; and the presence of the central catheter, older age, platelet count ≥ 350X109 /L, hemoglobin<100 g/L or use of red cell growth factors, and leukocyte count ≥ 11 X 109 /L 35 kg/m^2.[2,6]
The risk of VTE increases with age and is also associated with malignancy. Among cancer patients undergoing surgery, advanced age, disability, prolonged and difficult surgery, and a lengthy and complicated postoperative course add to the risk of DVT.[2,5,6] The extent of cancer impacts the risk of VTE. Chemotherapy and radiation increase the risk of VTE.[4,7]
The risk of VTE in cancer patients is increased by concomitant risk factors such as factor V Leiden mutation or prothrombin 20210A mutation, as well as by the presence of other comorbid features that influence the overall thrombotic complications in non-cancerous patients.[2,8]
Besides antineoplastic therapies, certain supportive care measures used in cancer treatment may also increase the risk of VTE, including red blood cell transfusions, as well as erythropoietin-stimulating agents for managing anemia for patients undergoing cancer treatment.[9]

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Pathophysiological mechanism of cancer induced thromboembolism

Several mechanisms may be involved in the pathogenesis of thromboembolic events in patients with cancer. These include (1) tumor cell procoagulants and/or cytokines, (2) tumor-associated inflammatory cell procoagulants and/or cytokines, and (3) mediators of platelet adhesion or aggregation generated by tumor cells and/or tumor-associated inflammatory cells. Stasis and endothelial damage may also be involved in the pathogenesis of thromboembolic events in patients with cancer.[10] Thromboembolism frequently worsens the course of malignancy and may be the first symptom of cancer.[10,11] The identification of multiple factors, including biomarkers, associated with the risk of cancer-associated VTE has prompted the development of risk scores for predicting VTE and its complications.[12]

Assessment of the thrombotic risk in cancer patients

The Khoranna score is based on five predictive models including cancer sites, platelet counts, hemoglobin level or the use of erythropoiesis-stimulating agents, leukocyte count and body mass index.[12] Risk predictor models involve the Ottawa score which identifies patients at the highest risk of recurrent VTE and who may benefit from prolonged anticoagulation treatment among those with cancer – associated VTE, and the Khoranna score for chemotherapy -associated VTE.[13]

Anticoagulation therapy

Patients with cancer frequently have both an increased thrombotic risk and an increased hemorrhage risk associated with certain cancer locations (e.g. GI, intracranial), thrombocytopaenia, and other coagulation defects (secondary to bone marrow invasion, cancer therapies, or cancer itself) and associated comorbidities (e.g. renal or hepatic dysfunction, GI toxicities). Several anticancer agents are further characterized by drug–drug interactions with anticoagulants. Thromboembolic risk, hemorrhage risk, drug–drug interactions and patient preferences (TBIP acronym) may render anticoagulation in cancer in a quite challenging way.[14]
Since 2019 when ITAC guidelines were published, three randomised clinical trials and 12 meta-analyses have assessed the efficacy and safety of LMWHs or direct oral anticoagulants for the treatment of cancer-associated thrombosis.[1,15] The initial treatment of established VTE (up to 10 days) included LMWHs, unfractionated heparin, or fondaparinux (followed by a vitamin K antagonist) An increased number of patients with cancer-associated thrombosis receiving LMWHs (n=1840) in six randomised clinical trials comparing direct oral anticoagulants with LMWH resulted in an upgrade from 1B to 1A for LMWHs as an initial treatment in the first 5–10 days.[16] Direct oral anticoagulants Rivaroxaban or edoxaban were recommended (grade 1B) in 2019 as the initial treatment options in patients with cancer-associated thrombosis who were not at high risk of gastrointestinal or genitourinary bleeding. Fondaparinux and unfractionated heparin remain acceptable alternative treatment options without new evidence.

Bleeding complications

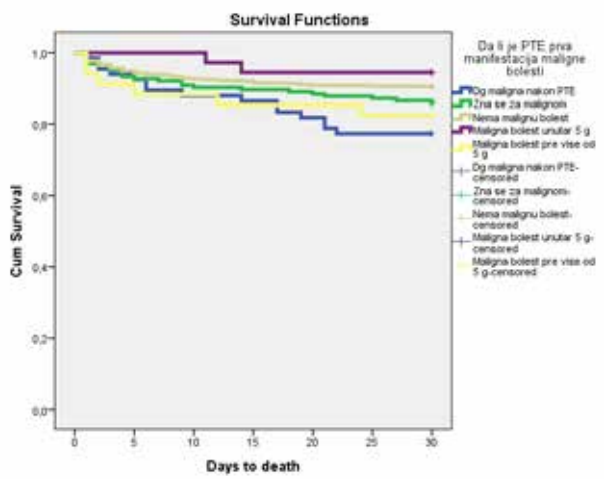
Bleeding complications are more common in patients with cancer than in patients without cancer. This may be directly related to the tumor itself, or indirectly related to chemotherapy- or RT-induced weakening of mucosal barriers.[17] GI and GU cancers in high-risk patients are associated with a significant excess bleeding risk compared with other solid tumors[18]. Thrombocytopaenia and platelet dysfunction due to hematological malignancies or bone marrow suppression may deteriorate bleeding. Other bleeding risk factors include advancing age, renal or hepatic impairment, metastatic disease, low body mass index, and treatment with ibrutinib, VEGFi, cetuximab, or bevacizumab.[17,18] Gastric protection with routine proton pump inhibitor use should be considered in all patients with cancer on DAPT or anticoagulation.[17,19]

REPER registry

In REPER registry that comprised 1814 patients, there were 163 (8.93%) patients with active cancer, 36 (1.98%) patients suffered from cancer within 5 years, 34 (1.87%) before 5 years and 66 (3.64%) patients had pulmonary embolism as a fist sign of cancer. Patients with pulmonary embolism as a first manifestation of cancer had a significantly highest risk of death during 30 days follow-up ($p<0.003$).

Case Processing Summary

Is PTE the first manifestation of malignancy	Total N	N of Events	Censored	
			N	Percent
Dg malignancy after PTE	66	15	51	77,3%
Known malignancy	163	23	140	85,9%
No malignancy	1515	146	1369	90,4%
Malignancy within 5 years	36	2	34	94,4%
Malignnancy more than 5 years	34	6	28	82,4%
Overall	1814	192	1622	89,4%



According to recently published 2022 ITAC guidelines, endorsed by the International Society on Thrombosis and Haemostasis, new evidence on the treatment and prophylaxis of cancer-associated thrombosis, including patients with cancer and with COVID-19 were summarized in the following tables.[1]

Treatment of incidental or symptomatic established venous thromboembolism (VTE) in patients with cancer

Table 1. Initial treatment of established VTE (up to 10 days of anticoagulation) in cancer patients[1]

LMWH once daily (eGFR ≥30 mL/min) (grade 1A). Enoxaparin (1 mg/kg), twice-daily in high risk of bleeding, moderate renal failure, the need for technical intervention surgery or changing regimen.
Rivaroxaban or apixaban (in the first 10 days), or edoxaban (started after at least 5 days of parenteral anticoagulation) for patients who do not have a high risk of gastrointestinal or genitourinary bleeding (eGFR ≥30 mL/min). (grade 1A)
UFH when LMWH or direct oral anticoagulants are contraindicated/not available (grade 2C)
Fondaparinux (grade 2D)
Thrombolysis can only be considered on a case-by-case basis (contraindications – brain metastasis)
Inferior vena cava filters when anticoagulant treatment is contraindicated or, in the case of pulmonary embolism, when recurrence occurs under optimal anticoagulation.

Table 2. Early (up to 6 months) and long-term (beyond 6 months) maintenance[1]

LMWHs are preferred over vitamin K antagonists
Direct oral anticoagulants (edoxaban, rivaroxaban, or apixaban) in the absence of strong drug–drug interactions or gastrointestinal absorption impairment (eGFR ≥30 mL/min) (grade 1A). Caution in patients with gastrointestinal tract malignancies, especially upper gastrointestinal tract malignancies,
LMWH or direct oral anticoagulants should be used for a minimum of 6 months (grade 1A).
Termination or continuation of anticoagulation should be based on individual evaluation of the benefit–risk ratio, tolerability, drug availability, patient preference, and cancer activity.

Table 3. Treatment of VTE recurrence in patients with cancer under anticoagulation[1]

Increase LMWH by 20–25% or switch to direct oral anticoagulants
For direct oral anticoagulants, switch to LMWH
For vitamin K antagonist, switch to LMWH or direct oral anticoagulants

Table 4. Treatment of established catheter-related thrombosis[1]

LMWHs for a minimum of 3 months and as long as the central venous catheter is in place
In patients with cancer and with catheter-related thrombosis, the central venous catheter can be kept in place if it is functional, well positioned, and not infected

Table 5. Prophylaxis of VTE in surgically-treated patients with cancer[1]

LMWH once daily (eGFR ≥30 mL/min) (grade 1A)
Low-dose UFH three times per day
There is insufficient evidence to support fondaparinux (grade 2C) or direct oral anticoagulants (grade 2B) as an alternative to LMWH for the prophylaxis of postoperative VTE in patients with cancer
Highest prophylactic dose of LMWH to prevent postoperative VTE
Extended prophylaxis (4 weeks) with LMWH after major abdominal or pelvic surgery (either laparotomy or laparoscopy) who do not have a high risk of bleeding (grade 1A
Mechanical methods are not recommended as monotherapy except when pharmacological methods are contraindicated (grade 2A)
Inferior vena cava filters are not recommended for routine prophylaxis (grade 1A)

Table 6. Prophylaxis of VTE in medically-treated patients with cancer[1]

LMWH or fondaparinux if eGFR ≥30 mL/min or UFH
LMWH (grade 1A) or DOAC (rivaroxaban or apixaban; grade 1B) in ambulatory patients with locally advanced or metastatic pancreatic cancer treated with systemic anticancer therapy and low risk of bleeding.
LMWH is not recommended for patients with locally advanced or metastatic lung cancer treated with systemic anticancer therapy, and low risk of bleeding
DOAC (rivaroxaban or apixaban) in ambulatory patients who are receiving systemic anticancer therapy and are at intermediateto-high-risk of VTE (Khorana score ≥2), and not actively bleeding or not high risk for bleeding (grade 1B).
In patients with myeloma treated with immunomodulatory drugs combined with steroids or other systemic anticancer therapies, VTE primary pharmacological prophylaxis is recommended (grade 1A); vitamin K antagonists at low or therapeutic doses and apixaban at prophylactic doses), LMWH at prophylactic doses, or low-dose aspirin (100 mg daily) (grade 2B).

Table 7. Prophylaxis of catheter-related thrombosis[1]

Use of anticoagulation for routine prophylaxis of catheter related thrombosis is not recommended (grade 1A).
Catheters should be inserted on the right side, in the jugular vein, and the distal extremity of the central catheter should be located at the junction of the superior vena cava and the right atrium (grade 1B).
In patients requiring central venous catheters, the use of implanted ports are suggested.

Table 8. Treatment of venous thromboembolism (VTE) in unique situations[1]

In patients with a brain tumour, LMWH or DOAC can be used for the treatment (grade 2A).
LMWH or UFH postoperatively for the prevention of VTE in patients with cancer undergoing neurosurgery
Primary pharmacological prophylaxis of VTE in medically treated patients with a brain tumour who are not undergoing neurosurgery is not recommended (grade 1B).
If eGFR <30 mL/min, UFH followed by early VKA (possible from day 1) or LMWH adjusted to anti-Xa concentration for the treatment of established VTE
If eGFR <30 mL/min an external compression device can be applied, pharmacological prophylaxis could be considered on a case-by-case basis; UFH can be used on a case-by-case basis
Full doses of anticoagulant can be used for the treatment of established VTE if the platelet count is >50 × 10^9 per L and there is no evidence of bleeding; for patients with a platelet count <50 × 10^9 per L, decisions on treatment and dose should be made on a case-by-case basis with the utmost caution
If platelet count >80 × 10^9 per L, pharmacological prophylaxis could be used; if the platelet count is <80 × 10^9 per L, pharmacological prophylaxis can only be considered on a case-by-case basis and careful monitoring is recommended
In the CASSINI64 and AVERT65 trials, patients with a platelet count as low as 50 × 10^9 per L were allowed to receive thromboprophylaxis
In patients with cancer who are pregnant, LMWH for treatment of established VTE and for VTE prophylaxis is suggested; avoidance of vitamin K antagonists and direct oral anticoagulants
In obese patients, consideration for a higher dose of LMWH should be given for cancer surgery
For the treatment of symptomatic catheter-related thrombosis in children with cancer, anticoagulant treatment is recommended for a minimum of 3 months and as long as the central venous catheter is in place
In children with acute lymphoblastic leukaemia undergoing induction chemotherapy, we recommend LMWH as thromboprophylaxis
In children requiring central venous catheters, we suggest the use of implanted ports over peripherally inserted central catheter lines

References

1. Farge D, Frere C, M Connors J, et al, the International Initiative on Thrombosis and Cancer (ITAC) advisory pane. 2022 international clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer, including patients with COVID-19. Lancet Oncol 2022;23(7):e334-e347.
2. Hamed NAM. Cancer associated thrombosis: still many unanswered questions. Biomed J Sci &Tech Res 2018;4(3):3977-3980.
3. van der Hulle T, den Exter PL, Kooiman J, et al. Meta-analysis of the efficacy and safety of new oral anticoagulants in patients with cancer-associated acute venous thromboembolism. J Thromb Haemost 2014;12:1116-1120.
4. Lyman GH, Carrier M, Ay C, et al. American Society of Hematology 2021 guidelines for management of venous thromboembolism: prevention and treatment in patients with cancer. The American Society of Hematology 2202. Blood Adv 2021;5(4):927-974.
5. Streiff MB, Holmstrom B, Angelini D, et al. Cancer-associated venous thromboembolic disease. Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2021;19(10):1181-1201.
6. Khorana AA, Francis CW, Culakova E, et al. Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy. J Thromb Haemost 2007;5:632–634.
7. Agnelli G, Bolis G, Capussotti L, et al. A clinical outcome-based prospective study on venous thromboembolism after cancer surgery: the @RISTOS project. Ann Surg 2006;243:89–95.
8. Ha N, Barnes GD. Optimal treatment approaches of cancer induced thrombosis. J Am Coll Cardiol 2017; expert analysis.
9. Bohlius J, Wilson J, Seidenfeld J, et al. Recombinant human erythropoietins and cancer patients: updated meta-analysis of 57 studies including 9353 patients. J Natl Cancer Inst 2006;98(10):708-714.
10. Bisceglia I, Maurea N. Thromboembolic disorders as a consequence of cancer. In: Lestuzzi C, Oliva S, Ferraù F, eds. Manual of Cardio-oncology. Springer International Publishing Switzerland, 2017:68-85.
11. Falanga A, Marchetti M, Russo L. The mechanisms of cancer-associated thrombosis. Thromb Res 2015;135 (Suppl 1):S8–11.
12. Khorana AA, Kuderer NM, Culakova E, et al. Development and validation of a predictive model for chemotherapy-associated thrombosis. Blood 2008;111(10):4902-4907
13. Delluc A, Miranda S, den Exter P, et al. Accuracy of the Ottawa score in risk stratification of recurrent venous thromboembolism in patients with cancer-associated venous thromboembolism: a systematic review and meta-analysis. Haematologica 2020;105(5):1436-1144.
14. Lyon A , López-Fernández T, Couch L, et al. 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS) Developed by the task force on cardio-oncology of the European Society of Cardiology (ESC). Eur Heart J 2022; https://doi.org/10.1093/eurheartj/ehac244
15. Farge D, Frere C, Connors JM, et al. 2019 international clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer. Lancet Oncol 2019; 20: e566–81.
16. Yan Y-D, Ding Z, Pan M-M, et al. Net clinical benefit of direct oral anticoagulants in patients with cancer and venous thromboembolism: a systematic review and trade-off analysis. Front Cardiovasc Med 2020;7:586020.
17. Steffel J, Collins R, Antz M, et al. 2021 European Heart Rhythm Association practical guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Europace 2021;23:1612–1676.
18. Angelini DE, Radivoyevitch T, McCrae KR, Khorana AA. Bleeding incidence and risk factors among cancer patients treated with anticoagulation. Am J Hematol 2019;94:780–785.
19. Roule V, Verdier L, Blanchart K, et al. Systematic review and meta-analysis of the prognostic impact of cancer among patients with acute coronary syndrome and/or percutaneous coronary intervention. BMC Cardiovasc Disord 2020;20:38.

Sažetak

Plućne embolije kod karcinoma: pregled i izazovi terapije

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Venski tromboembolizam (VTE) je jedan glavnih uzroka povećanog morbiditeta i mortaliteta pacijenata sa malignitetom. Veoma je važno proceniti rizik svakog pojedinačnog pacijenta u cilju adekvatnog lečenja, proceniti potrebu za primarnom i sekundarnom prevencijom VTE, i proceniti rizik od mortaliteta od akutnog plućnog embolizma. Postignut je značajan napredak u terapiji VTE kod bolesnika sa karcinomom. Oralni antikoagulansi nezavisni od vitamina K (NOAC) čine jednostavnijim terapiju VTE u poređenju sa nisko-molekularnim heparinima (LMWH) zahvaljujući njihovim karakteristikama, načinu primene, fiksnom doziranju i nižoj ceni terapije. Ipak, njihova primena zahteva poseban oprez, naročito kod bolesnika sa gastrointestinalnim malignitetima. Dostupni podaci o reperfuzionoj terapiju ističu značaj individualnog pristupa svakom pacijentu sa malignitetom i VTE.

Ključne reči: *karcinom, pulmonalni tromboembolizam, stratifikacija rizika, terapija*

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Review article

Chronic thromboembolic pulmonary disease

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Abstract Chronic thromboembolic pulmonary disease (CTEPD) with or without pulmonary hypertension (CTEPH) is rare, very often progressive complication of pulmonary embolism (PE). There was significant improvement in diagnostics and treatment of this disease in the recent years.
The aim of this review is to present current knowledge and guidelines for the management of CTEPH. We reviewed epidemiology, pathophysiology, diagnostics, risk stratification and various types of treatment options: medicament, balloon pulmonary angioplasty (BPA) and pulmonary endarterectomy (PEA). It is clear that multimodality treatment is the best approach for most of the patients with CTEPH and this became a part of 2022 European Society of Cardiology guidelines for the first time. The last 2019 ESC PE guidelines for the first time also recommend active follow-up of high-risk and symptomatic patients after acute PE for the early diagnosis of CTEPH. Both of these guidelines significantly improve the awareness for this rare disease and treatment of these patients.

Kew words chronic thromboembolic pulmonary hypertension, balloon pulmonary angioplasty, pulmonary endarterectomy

Epidemiology and pathophysiology

Chronic thromboembolic pulmonary disease with or without pulmonary hypertension is a rare complication of acute PE (CTED or CTEPH). It is classified as type IV PH, as PH caused by the obstruction in the pulmonary circulation. In the prospectively well-designed studies, the incidence of CTEPH is 1.6% after 6 months and 2,3% after 2 years of follow-up in the FOCUS study, and 1% after 6 months and 3.8% after 2 years in the Thromboembolic Pulmonary Hypertension Study Group.[1,2] It is unknown why the percentage of patients with CTEPH rise from 6 months to two years. Is it because of the recurrent venous thromboembolism during that period, or is it the evolution of the first process? It is interesting that approximately one third of the patients do not have an earlier history of acute pulmonary embolism and it is logical to assume that even low-risk PE can result in severe CTEPH.
The main pathophysiology of CTEPH is absence of thrombus dissolution and fibrotic changes of the thrombus which cause obstruction of the pulmonary artery tree and possible remodeling of the small arteries and paracrine reaction as a response to diminished pulmonary perfusion[3]. Hypercoagulable states and insufficient fibrinolysis are recognized as risk factors for CTEPH development. Hereditary deficiency of protein C and antithrombin, 4G PAI-1 homozygote state are the most important hereditary risk factors and antiphospholipid syndrome (primary or secondary) is the most important acquired thrombophilia which is related to CTEPH. Even large thrombus masses can dissolve in a few months after acute PE, and the presence of thrombophilia is probably more important than the burden of the thrombi. Chronic myeloproliferative and lymphoproliferative diseases are also associated with CTEPH development which might underline the role of leukocytes in the thrombus dissolution which is impaired in these diseases.

Diagnosis and risk stratification

We have already mentioned that one third of CTEPH patients have no history of acute PE. Since that there are two different pathways in the diagnostics of CTEPH. The first one, after acute PE, purport the follow-up of patients after acute PE, where patients who have dyspnea or effort intolerance after PE should have echocardiography examination and brain natriuretic peptide blood measurement, and if there we found tricuspid regurgitation velocity greater than 2.8 m/s together with some other signs of right ventricle dysfunction, especially with the elevated BNP blood levels, this patient should be refer to the center specialized for the management of pulmonary hypertension[4]. Computed tomography (CT) of the lungs and pulmonary angiography (CTPA) are important for the differential diagnosis of PH. Proximal organized thrombi means that patient has CTEPH that can be treated with pulmonary endarterectomy (PEA). Enlarged, tortuous proximal PA with poor peripheral arborization is classical finding in PH of different etiology. Perfusion lung scintigraphy shows typical multiple perfusion defects in patients with CTEPH. Six minutes walking test and exercise testing serve for the risk stratification. After non-invasive examination,

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Table 1. Risk stratification in patients with PH. However, each parameter does not have the same value for the risk stratification. Clinical features are probably more accurate.

Parameters	Low <5%	Intermediate 5-20%	High >20%
Clinical signs of HF	No	No	Yes
Symptom progression	No	Slow	Rapid
Syncope	No	Occasional	Repeated
WHO-FC	I, II	III	IV
6-minute walking test	>440 m	165-440 m	<165 m
CPET	PeakO_2>15ml/min/kg	Peak$O_2$11-15ml/min/kg	PeakO_2<11ml/kg/min
BNP	<50pg/ml	50-800pg/ml	>800pg/ml
NT-proBNP	<300pg/ml	300-1100pg/ml	>1100 pg/ml
Echocardiography			
RA area	>18cm^2	18-26cm^2	>26cm^2
TAPSE/sPAP	>0.32mm/mmHg	0.19-0.32mm/mmHg	<19mm/mmHg
Pericardial effusion	No	Minimal	Moderate or high
MRI			
RVEF	>54%	37-54%	<37%
SVI	>40ml/m^2	26-40ml/m^2	<26mg/m^2
Hemodynamics			
RAP	<8mmHg	8-14mmHg	>14mmHg
CI	>2.5L/min	2.0-2.5L/min	<2.0L/min
SvO_2	>65%	60-65%	<60%

HF – heart failure, WHO-FC – world health organization functional capacity, CPET – cardiopulmonary exercise test, BNP – brain natriuretic peptide, NT-proBNP – N-terminal BNP, RA – right ventricle, TAPSE – tricuspid annulus plane systolic excursion, sPAP – systolic pulmonary artery pressure, MRI – magnetic resonance imaging, RVEF – right ventricle ejection fraction, SVI – systolic volume index, RAP – right atrium pressure, CI – cardiac index, SvO_2 – saturation of the venous blood.

right heart catheterization is necessary to prove the diagnosis of PH. Mean pulmonary arterial pressure greater than 20 mmHg, with pulmonary wedge pressure lower than 15 mmHg and pulmonary vascular resistance greater or equal to 3 Wood units are the criteria for precapillary PH[3]. Selective segmental pulmonary angiography is also necessary when balloon angioplasty is planned for the treatment of CTEPH.

The risk stratification is important for the treatment escalation of CTEPH patients and it is based on the risk of mortality in three risk stratums, where low risk patients have 1-year mortality risk less than 5%, intermediate risk patients have 1-year mortality risk of 5-20% and the highest risk group have 1-year mortality risk greater than 20%.(3) The most usable parameters for risk assessment are presented in table 1.

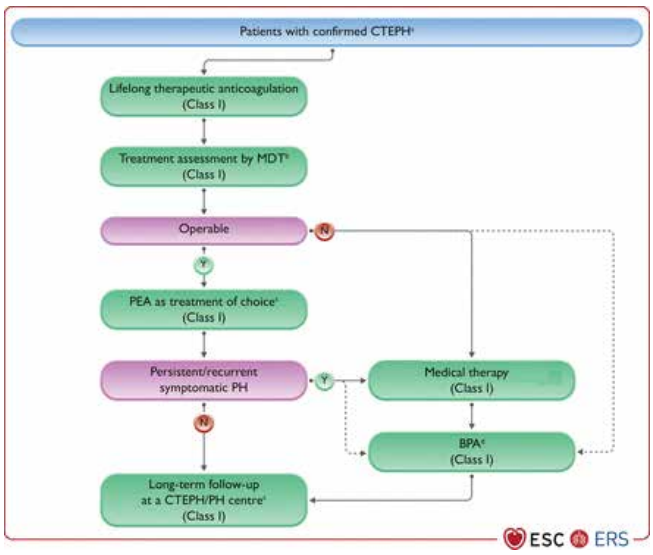

Figure 1. Management strategy in chronic thromboembolic pulmonary hypertension. Modified from ESC guideline 2023.[3]

Treatment

Treatment decision should be made by multidisciplinary team (MDT). If CTEPH patient is operable, PEA is class 1 recommendation according to the current guideline. If the patient is not operable, refuses operation or is susceptible to multi-modality approach, BPA and medical treatment should be considered. (3) (Figure 1). Today, medical therapy includes: riociguat (stimulator of soluble guanylate cyclase), treprostinil (prostacyclin vasodilator), macitentan and bosentan (endothelin receptor antagonists), sildenafil and tadalafil (5PDE inhibitors).

Balloon pulmonary angioplasty

Introduction (justification of catheter interventions in CTEPH and success of treatment)

Balloon-pulmonary-angioplasty (BPA) is one of the modalities of treatment of patients with CTEPH and is used in patients in whom pulmonary endarterectomy cannot be performed, or who refuse surgery. It can also be a part of a multi-modality approach where the patient has previously undergone surgery and/or drug treatment. The level of the pulmonary vascular tree that is most susceptible to this type of intervention is the segmental and subsegmental branches of the pulmonary arteries. In the last ten years, there has been an expansion in the

number of BPA procedures worldwide, and the latest recommendations for pulmonary hypertension from 2022 place BPA in class 1 recommendations for the treatment of CTEPH in patients in whom pulmonary endarterectomy is not possible.[3]

The efficacy of BPA has been demonstrated in CTEPH patients in terms of a 49%-66% reduction in peripheral vascular resistance (PVR), as well as an increase in six-minute walk distance (6MWD), right heart function, and quality of life.(ref) Efficacy is also directly proportional to the experience of the center dealing with BPA procedures, meaning that the number of performed procedures and hemodynamic improvements, together with the reduction of complications, follow a learning curve.[5] The results of recent research have shown that in CTEPH patients with PVR > 4 wood units, medical treatment before performing BPA reduces the frequency of complications.[6]

History of BPA in the world and in Serbia

The first case of BPA in CTEPH was published in 1988. The intervention was successfully performed by Dutch doctors (in Leiden) on a thirty-year-old patient.[7] In 2001, Feinstein et al published the first series of patients with CTEPH treated with BPA.[8] In 2003 and 2005, the first BPA interventions in two patients were performed in Serbia at the Military Medical Academy.[9] Years after, starting in 2012 Japanese, followed by the Poles and Norwegians in 2013, published their first series of cases. Today, these procedures are performed routinely in centers around the world. By May 2023, more than 100 BPA interventions have been performed at the Military Medical Academy.

Performing the procedure

The performance of BPA itself is a multi-phase procedure with a limited number of pulmonary arteries to be intervened in each procedure. This requires extensive preparation before each procedure that includes clear visualization and definition of lesion types, and then selection of lesions to be treated in one procedure. Diagnostic methods such as: MDCT-PA, V/Q scan and catheter-PA with precise hemodynamic parameters are used for this purpose. The patient should be presented to a multidisciplinary team that decides on the way to treat the patient and all the steps in order to prepare the patient as effectively as possible for the procedure itself. Careful selection of arteries and types of lesions to be treated, especially in the first few procedures, is very important in order to reduce the risk of complications and achieve the desired result. It is recommended that lighter lesions that have been shown to have a high degree of success (such as ring and web lesions) be performed during the first procedure. In the later stages, after the previous procedures have reduced the mean pressure in the pulmonary arteries (mPAP), more demanding lesions such as subtotal and total occlusions, possibly even tortuous lesions (only for very experienced centers, generally avoided) should be attempted. The strategy can be different, such as “segment by segment” treatment, or on the contrary, solving several different segments with lighter lesions per procedure, which is certainly decided by the interventional cardiologist team that performs the intervention. Previous reduction of mPAP, which is achieved by medical pretreatment and resolution of less complicated lesions, significantly reduces the probability of reperfusion edema of the lung segment, which occurs most often after the opening of total occlusion of a large segmental branch. The example of BPA procedure is depicted in Figure 1.

Standard introducer sheaths, catheters and workhorse wires, such as in standard PCI procedures are used for BPA as well. Namely, the most common approach is through the right or left femoral vein, with the use of a long introducer sheath of 6Fr or 7Fr, 0.035-inch wire (type and length may vary depending on the complexity of the procedure), then guide catheters, usually the JR, MP, AL (6Fr or 7Fr), but also other, standard workhorse 0.014-inch wire for passing the target lesion, or harder wires in case of total occlusions and balloons of variable diameter (2mm-8mm). During the intervention, constant monitoring of the patient is necessary, including: ECG, arterial pressure, O2 saturation. In most cases, BPA is completed by balloon inflation to achieve adequate reperfusion of a partially or completely occluded blood vessel of one or more lung segments. In some situations, however, stent implantation is allowed, in cases where the desired effect could not be achieved after balloon dilatation. In the case of stent implantation, it is not necessary to introduce antiplatelet therapy, but the patient continues with anticoagulant therapy, as in the case of only balloon dilatation.

The goal is to reduce mPAP as much as possible, ideally below 30 mmHg, and especially below 38 mmHg, be-

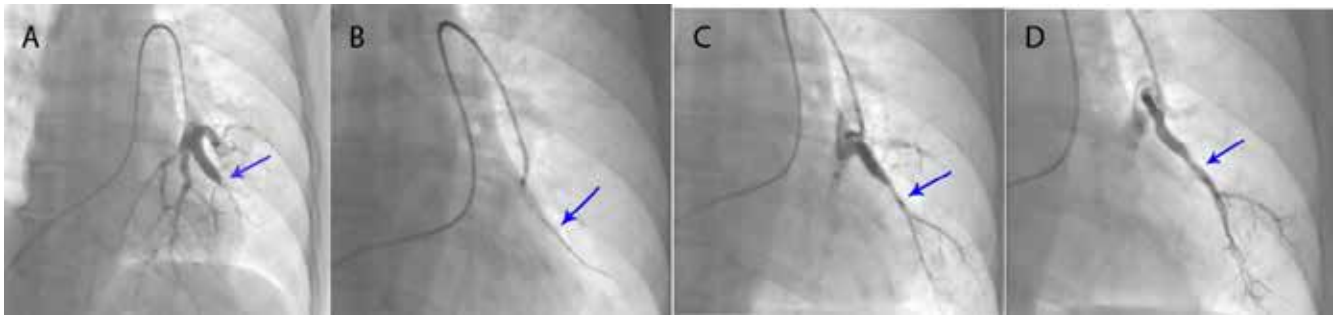

Figure 2. Total occlusion of the segmental left lower lobe artery (A); wire cross and balloon dilatation (B), opened segmental artery after BPA (C); final look after using bigger balloons (D). *The procedures were done in the Cath lab of the Military Medical Academy.*

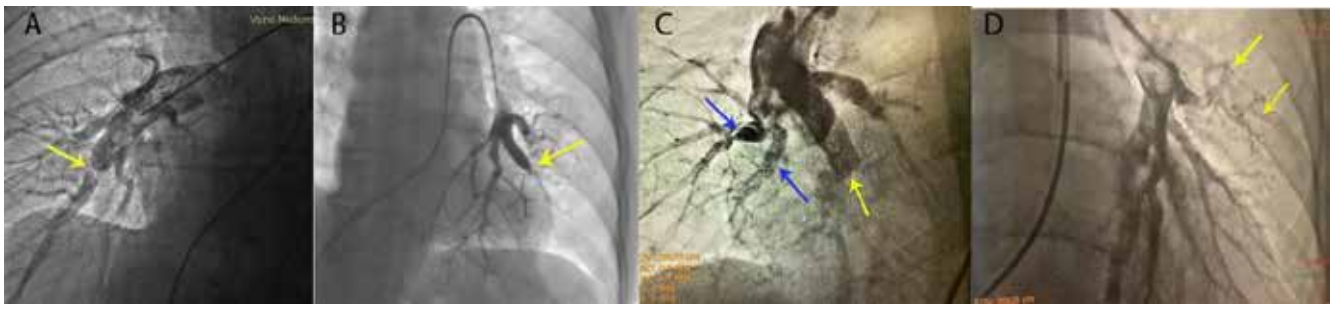

Figure 3. Types of lesions in CTEPH. Ring lesion (panel A);subtotal oclusion (panel B);Total oclusion (yellow arrow) and web and slit lesions (blue arrows) (panel C); tortuous lesion (panel D)

cause it has been shown that patients with mPAP ≥ 38mmhg have a significant reduction in life expectancy. Namely, multivariable analysis has shown that CTEPH patients with mPAP ≥ 38mmHg have long term mortality hazard ratio of 3.8, whereas it is 1.5 and 0.6 for thpse with mPAP below 38 mmHg and 30 mmHg, respectively.[10] The average number of procedures per patient that achieves optimal improvement of hemodynamic parameters is 4-6. They can be performed in time intervals from a few days to even a few months and depend on the general condition of the patient, the success of the previous procedures and the time needed to evaluate the effect of the drug/procedure.

Complications (types of complications and treatment)

Balloon pulmonary angioplasty, although very effective, carries some risk, and the frequency varies depending on the experience of the operator and the complexity of the lesions. This association of types and complexity of lesions determined on the basis of selective pulmonary angiography and success/complications performed in the same act was described in a paper published by Kawakami et al. in 2016.[11] Namely, Kawakami et al. defined 5 basic types of lesions at the level segmental and subsegmental branches. These lesions are mostly located before subsegmental branches such as the ring lesions, web and slit lesions, subtotal and total occlusions. The only lesion that is located on the subsegmental level is tortuous lesion (Figure 3 A-D). The tortuous type of lesion is definitely the most dangerous when it comes to complications during the BPA procedure (>40%), such as dissection or perforation and subsequent bleeding. These lesions are not only technically difficult for balloon dilatation, but it is a type of lesion that affects the distal parts of the subsegmental arteries, which can be very small in diameter (up to 0.5 mm) and are therefore more prone to injury. In contrast, the success rate of intervention in ring and web lesions is the highest reaching 90%-100%. Success in subtotal and total occlusions was 52.2% - 63.6%.

The most common complications are wire perforations, dissections or perforations due to balloon inflation. The consequence of these complications can be bleeding, which is most often manifested through hemoptysis. Another type of very common complication is edema of a segment or the entire lobe of the lung, which occurs as a result of reperfusion damage caused after the opening of a larger segmental branch that was previously totally occluded, and in conditions of elevated sPAP, usually > 40 mmhg. (Figure 3) Although these complications can end fatally, with adequate and timely treatment, they usually pass without major consequences. Perforations/ruptures with consequent bleeding can also heal spontaneously, by interrupting the procedure and giving oxygen through a mask. And yet, in most cases, intervention is necessary in the form of prolonged inflation of the balloon (about 5 min) with

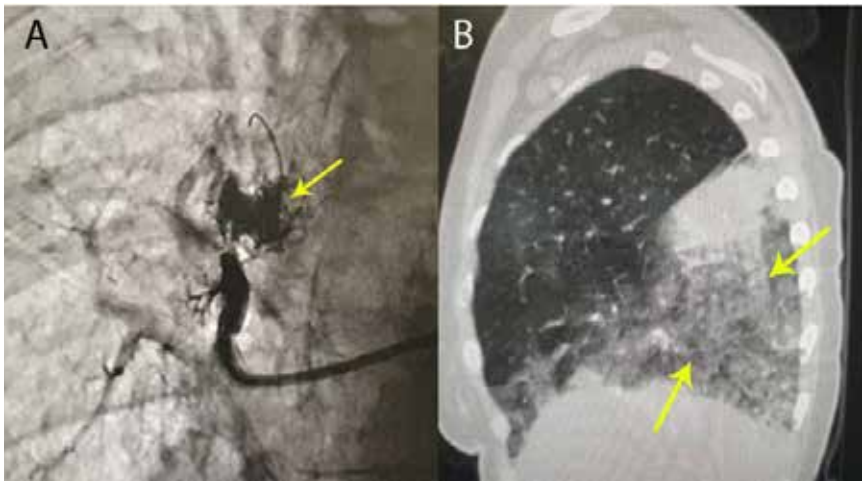

Figure 4. Examples of complications during the BPA procedures: Perforation od subsegmental branch and consequental bleeding with hemoptysis (A); reperfusion oedema of the left posterobasal segment of the lang (B).

complete occlusion of the bleeding blood vessel, administration of protamine sulfate to neutralize the effect of heparin and/or embolization of the blood vessel using a bioabsorbing gel or metal coil, or by implanting a covered stent.[12-14] In the case of localized reperfusion edema, the most important treatment measure is oxygen supplementation (most often in the form of substitution through a mask, administration of pressurized oxygen through a full-face mask or short-term intubation) along with other supportive measures. All patients with such complications must be treated and monitored in an intensive care unit

References

1. Valerio L, Mavromanoli AC, Barco S, et al. Chronic thromboembolic pulmonary hypertension and impairment after pulmonary embolism: the FOCUS study. Eur Heart J 2022;43:3387–3398.
2. Pengo V, Lensing AWA, Prins MH, et al. Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. N Engl J Med 2004;350:2257-2264.
3. Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J 2022;43:3618-3731.
4. Konstantinides S, Meyer G, Becattini C, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart Journal 2020;41:543-603.
5. Brenot P, Jaïs X, Taniguchi Y, et al. French experience of balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension. Eur Respir J 2019;53:1802095 [https://doi.org/10.1183/13993003.02095-2018].
6. Jaïs X, Brenot P, Bouvaist H, et al. Balloon pulmonary angioplasty versus riociguat for the treatment of inoperable chronic thromboembolic pulmonary hypertension (RACE): a multicentre, phase 3, open-label, randomised controlled trial and ancillary follow-up study. Lancet Respir Med 2022. doi:10.1016/S2213-2600(22)00214-4.
7. Voorburg JA, Cats VM, Buis B, Bruschke AV. Balloon angioplasty in the treatment of pulmonary hypertension caused by pulmonary embolism. Chest 1988; 94:1249–1253.
8. Feinstein JA, Goldhaber SZ, Lock JE, Ferndandes SM, Landzberg MJ. Balloon pulmonary angioplasty for treatment of chronic thromboembolic pulmonary hypertension. Circulation 2001; 103:10–13.
9. Obradovic S, Rusovic S, Gligic B. Plućna tromboembolija kroz prikaze slučajeva. Belgrade, MST Gajić, November 2011.
10. Cannon JE, Su L, Kiely DG, Page K, et al. Dynamic risk stratification of patient long-term outcome after pulmonary endarterectomy. Results from the United Kingdom national cohort. Circulation 2016;133:1761–1771.
11. Kawakami T, Ogawa A, Miyaji K, et al. Novel angiographic classification of each vascular lesion in chronic thromboembolic pulmonary hypertension based on selective angiogram and results of balloon pulmonary angioplasty. Circulation: Cardiovascular Interventions 2016;9:e003318.
12. Ejiri K, Ogawa A, Matsubara H. Bail-out technique for pulmonary artery rupture with a covered stent in balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension. JACC Cardiovasc Interv 2015; 8:752–753.
13. Inami T, Kataoka M, Shimura N, et al. Incidence, avoidance, and management of pulmonary artery injuries in percutaneous transluminal pulmonary angioplasty. Int J Cardiol 2015; 201: 35–37.
14. Hosokawa K, Abe K, Oi K, et al. Balloon pulmonary angioplasty-related complications and therapeutic strategy in patients with chronic thromboembolic pulmonary hypertension. Int J Cardiol 2015; 197: 224–226.

Sažetak

Hronična tromboembolijska plućna bolest

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Hronična tomboembolijska plućna bolest (HTEPB) sa ili bez plućne hipertenzije (HTEPH) je retka, često progresivna komplikacija plućnog embolizma (PE). Beleži se značajan napredak u dijagnostici I tretmanu ovih bolesnika u poslednjim godinama.

Cilj ovog revijalnog rada je da prikažu savremeno znanje i preporuke za tretman HTEPH. Prikazana je epidemiologija, patofiziologija, dijagnostika, klasifikacija rizika, I različite metode za lečenje: lekovima, balon plućnim angioplastikama (BPA), I plućna end-arterektomija (PEA). Jasno je da je multimodalni pristup lečenja najbolji za većinu bolesnika sa HTEPH I ovakav stav je iznesen I u poslednjim preporukama za PH koje je objavilo Evropsko Udruženje Kardiologa 2022 godine. U poslednjim preporukama za tretman PE, takođe je preporučeno da se obrati pažnja na mogući razvitak HTEPH kod bolesnika koji imaju povišen rizik za razvoj ove komplikacije i/ili imaju tegobe koje bi mogle da ukažu na razvoj ove komplikacije u mesecima nakon akutne PE. Obe preporuke podižu svesnost o postanju ove retke komplikacije I poboljšavaju tretman ovih bolesnika.

Ključne reči: *hronična tromboembolijska plućna hipertenzija, balon angioplastika plućnih arterija, plućna endarterektomija*

Srce i krvni sudovi 2023; 42(2): 37-39

Case report

Right ventricular myxoma

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Abstract Right ventricular myxoma are primary rare benign cardiac tumors with each new case contributing to the new evidence in a management and treatment of the disease. We present an 80 year-old male patient with symptoms of fatigue on exertion and previous history of essential hypertension. Right ventricular myxoma was diagnosed on echocardiography and it was confirmed by futher diagnostic procedures. The most serious complication is arrhythmia and sudden cardiac death. A patient was referred for the urgent cardiosurgical intervention and successful extirpation of tumor was performed.

Kew words primary cardiac tumor, right ventricular myxoma, echocardiography

Background

Myxoma are round or oval-shaped, pedunculated, mobile, intra-cavity tumors[1]. They are rarely found in the ventricle, especially the right ventricle. The frequency of cardiac myxoma is 7 cases per 10,000 within the population and they account for 25-40% of all cardiac tumors in adults[1,3]. Primary cardiac neoplasms are relatively uncommon, with an overall incidence of 0.0017 to 0.19%[2]. Myxoma, benign primary tumor, account for 25-40% of all cardiac tumors in adults[2]. In regard to localization, 75-85% of myxomas originate within the left atrium, 15-20% in the right atrium[2,4], and only 2.5-4% within the ventricular chambers[2,4,5]. Right ventricular myxomas are particularly uncommon, with only 30 cases reported since 2010[6]. From a pathohistology perspective, myxoma consist stellate cells on a background of myxoid stroma and may be homogenous or present with central areas of hemorrhage, necrosis, calcification, and thrombosis[7].

Symptoms of right ventricular myxoma vary based on size and location within the cavity, but are often uncharacteristic which may lead to delayed diagnosis and unfavorable outcomes[7,8]. Clinical manifestations typically present with a triad of obstructive, embolic, and constitutional symptoms[4]. Patients with right ventricular outflow tract obstruction may present with symptoms of obstruction, or those similar to that in right sided congestive heart failure such as ascites, lower leg edema, and Superior Vena Cava Syndrome[4,7,8]. Patients may also exhibit dyspnea secondary to pulmonary embolization or constitutional symptoms such as fever, weight loss, and infection[4].

Echocardiography, computed tomography, and cardiac magnetic resonance imaging are the diagnostic modalities of choice, as well as preoperative imaging modalities crucial in surgical resection which is currently the treatment of choice[9]. Gold-standard diagnosis is mostly done post-resection with pathohistology analysis.

Case presentation

An 80 year old man with a history of essential arterial hypertension presented to the emergency department with complaints of fatigue upon exertion that became more pronounced in the previous 6 months. On examination, the patient was alert, well-oriented in all directions, afebrile, and eupneic. Significant physical examination findings included slight pretibial edema without varicosities and a discrete systolic murmur heard over the heart apex. All other parameters were normal. The patient underwent electrocardiography which showed sinus rhythm with a frequency of 70/min and in V1 and V2 slight negative T waves. Blood pressure was 140/80 mmHg. Laboratory results revealed sideropenic anemia and hypercholesterolemia. The transthoracic echocardiography showed an ovoid hypermobile solid tissue mass located at the right ventricular base, with a bipolar diameter of approximately 40mm, obstructing the right ventricular outflow tract (Figure 1, 2) It was determined that the mass was a right ventricular myxoma. During echocardiography, the severe tricuspid regurgitation and pulmonary hypertension was diagnosed with peak systolic pressure in the right ventricle of 88mmHg. The ejection fraction of the left ventricle was 60%. Cardiac surgery procedure and extirpation of myxoma was performed. Post-operative procedure and further follow-ups revealed no complications and patient stability. The right ventricle systolic pressure decreased to 45mmHg with now moderate tricuspid regurgitation.

Discussion

Cardiac tumors are rare and are mostly secondary while myxoma is the commonest primary cardiac tumor[10]. It is

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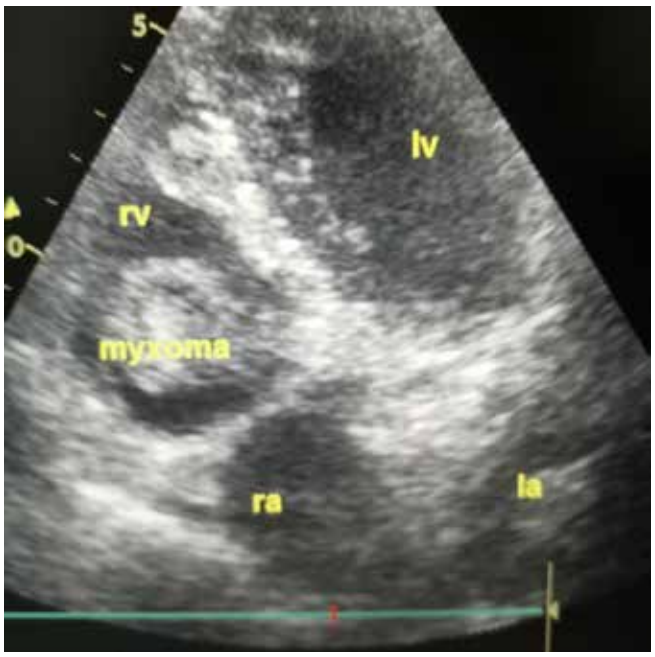

Figure 1. TTE 4-chamber view

observed more often in females than in males, with the mean age of presentation being 53 years[11]. Right ventricular myxoma is of unknown etiology, but genetics may play a role in disease development. Symptoms are varied and depend on multiple factors including location, size, mobility, and fragility[12]. Symptoms present with right ventricular outflow tachycardia obstruction such as shortness of breath and fatigue upon minimal exertion[13] as was observed in our case. These symptoms were secondary to pulmonary hypertension, a significant consequence of RV myxoma in our patient.. Although the tumor itself is benign, complications such as embolisation[15], pulmonary hypertension or sudden death may occur most significantly due to mechanical obstruction caused by the myxoma[15]. In 30-40% of all cases, embolism occurs[16] due to constant agitation of the tumor and may result in detaching of parts of the tumor or the whole tumor[17]. Specific characteristic of myxoma is its ability to mimic systemic autoimmune diseases due to secretion of interleukin 6 and 8 [18]. IL-6 is a pleiotropic cytokine that increases B cell differentiation and leads to increased synthesis of polyclonal immunoglobulins[18]. One of the rarest forms of cardiac malignancy, right ventricular myxoma, manifests with RVOT obstruction leading to syncope and it is essential that the diagnosis is made early, patient is sent to surgery and even though remission is rare, continuous follow up is needed[19]. In our case this 80 year old patient was not sent to echocardiography testing earlier in his lifetime and focus was on treatment of pulmonary hypertension. It is essential that clinicians recognize and identify right ventricular myxoma, define its cause and treatment through echocardiography as soon as possible. It also needs to be taken into consideration for differential diagnosis of B-cell lymphoma. B-cell lymphoma and right ventricular myxoma may give the same symptoms, such as right ventricular inflow obstruction and low cardiac output. Misdiagnosis can be made on echocardiography as well since both appear as a ventricular mass on the image. Treatment of the right ventricular myxoma needs

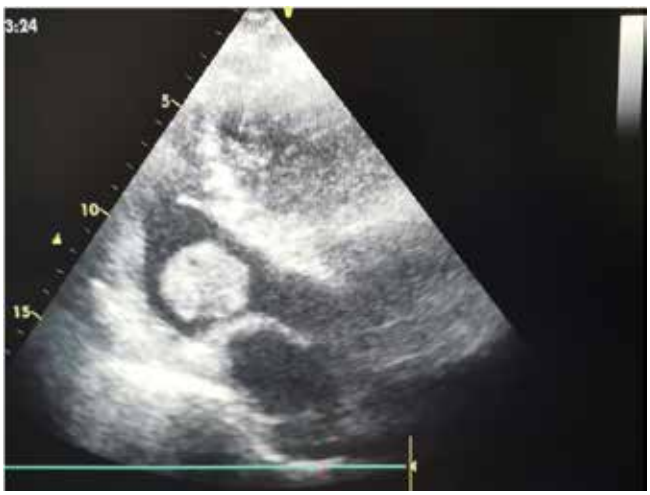

Figure 2. TTE

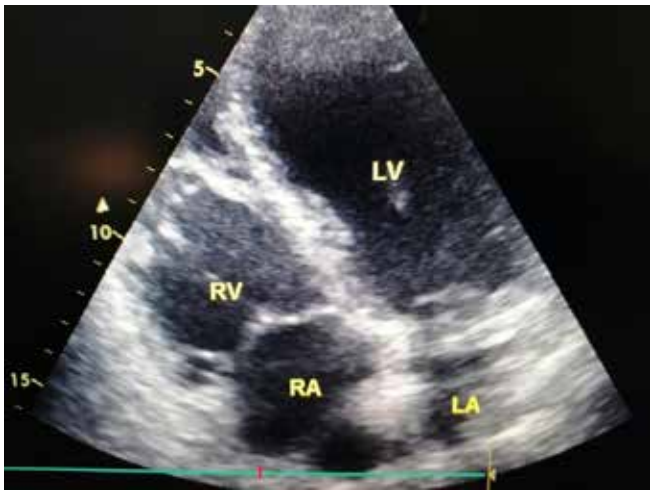

Figure 3. Post-operative TTE

to be urgent and tumor mass should be surgically removed. However, radiofrequency ablation may also be used for patients in poor clinical conditions where cardiac operation can be risky or it can be used as a supplementary technique for the treatment of obstructive cardiac tumors, when only partial resection is possible[20].

Conclusion

Cardiac myxomas filling the entire RV cavity, resulting in right ventricle inflow and outflow tract obstruction is very uncommon. Diagnosis can be achieved with echocardiography, and the patient should be referred for surgical intervention. These tumors should be excised on an urgent basis to avoid risk of embolization or even sudden death.

Patient Consent Form: Patient was informed about publication
Conflicts of interest: None declared
Financial support and sponsorship: None

References

1. Mahavar RK, Arora D, Singh A, Mishra M. Recurrent cardiac myxoma: A case report. Ann Card Anaesth. 2021 Oct-Dec;24(4):490-492.
2. Elbardissi AW, Dearani JA, Daly RC, et al. Survival after resection of primary cardiac tumors: a 48-year experience. Circulation 2008;118(14 Suppl):S7-S15.

3. Katiyar G, Vernekar JA, Lawande A, Caculo V. Cardiac MRI in right ventricular outflow tract myxoma: Case report with review of literature. J Cardiol Cases 2020;22(3):128-131.
4. Yuan SM, Yan SL, Wu N. Unusual aspects of cardiac myxoma. Anatol J Cardiol 2017;17(3):241-247.
5. Kuon E, Kreplin M, Weiss W, Dahm JB. The challenge presented by right atrial myxoma. Herz 2004;29(7):702-709.
6. Lacey BW, Lin A. Radiologic evaluation of right ventricular outflow tract myxomas. Tex Heart Inst J 2013;40(1):68-70.
7. Agrawal Y, Dada R, Dada J, Degregorio M. Primary mural infective endocarditis with associated central line infection. BMJ Case Rep. 2018;11(1):e227504.
8. Tok M, Oc M, Ucar HI, et al. Giant right atrial myxoma mimicking hepatic cirrhosis: a case report. Heart Surg Forum 2007;10(2): E107-E109.
9. Karagöz A, Keskin B, Karaduman A, Tanyeri S, Adademir T. Multidisciplinary approach to right ventricular myxoma. Braz J Cardiovasc Surg 2021;36(2):257-260.
10. Singh V, Singh SK, Devenraj V, Kumar S. Giant right ventricular myxoma obstructing both inflow and outflow tract. Indian J Thorac Cardiovasc Surg 2019;35(3):499-501.
11. Burke A, Tavora F. The 2015 WHO classification of tumors of the heart and pericardium. J Thorac Oncol 2016;11:441–452.
12. Saadeh AM, Hijazi EM, Saadeh NA. Right atrioventricular myxoma presenting with recurrent syncopal attacks. Am J Case Rep 2021;22:e927874.
13. Obrenovic-Kircanski B, Mikic A, Parapid B, et al. A 30-year-single-center experience in atrial myxomas: from presentation to treatment and prognosis. Thorac Cardiovasc Surg 2013;61:530–536.
14. Patil NP, Dutta N, Satyarthy S, Geelani MA, Kumar Satsangi D, Banerjee A. Cardiac myxomas: experience over one decade. J Cardiac Surg 2011;26:355–359.
15. Thadathilankal-Jess J, Snyman H, Janson J, Pecoraro A. Atrialized right ventricular myxoma in a patient with Ebstein's anomaly. Echo Research and Practice 2018. 5. ERP-17. 10.1530/ERP-17-0065.
16. St John Sutton MG, Mercier LA, Giuliani ER, Lie JT. Atrial myxomas: a review of clinical experience in 40 patients. Mayo Clinic Proceedings 1980;55(6):371–376.
17. Goh RYH, Mehrotra S, Buchholz S, Mehrotra D, Morton A. Rare association between giant right ventricular myxoma and right coronary artery tumour blush with complicating pulmonary tumour embolism. Case Rep Cardiol 2019;2019:5873606.
18. Singhal P, Luk A, Rao V, Butany J. Molecular basis of cardiac myxomas. Int J Mol Sci 2014;15(1):1315–1337.
19. David W, Rehman N, Singh R, David S. Inverted yoga and near syncope: an unusual diagnosis of right ventricular myxoma. Case Rep Cardiol 2018;2018:9231256.
20. Zheng MJ, Yang J, He GB, Zhou XD, Liu LW. Percutaneous radiofrequency ablation of obstructive right ventricular giant myxoma. Ann Thor Surg 2017;.105. 10.1016/j.athoracsur.2017.11.041.

Sažetak

Miksom desnog ventrikula

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Miksomi desnog ventrikula su veoma rijetki primarni tumori srca i time svaki novi slučaj doprinosi novom dokazu u dijagnozi i liječenju ovog oboljenja.. U ovom radu prikazali smo 80 godina starog muškarca sa simptomima zamora u naporu te od ranije anamnestički prisutnoj esencijalnoj hipertenziji. Miksom desnog ventrikula dijagnosticiran je ehokardiografijom i potvrđen odgovarajućim dijagnostičkim procedurama. Najčesća ozbiljna komplikacija je aritmija srca i iznenadna srćana smrt. Pacijent je upućen na urgentnu kardiohiruršku operaciju i urađena je uspješna ekstirpacija tumora.

Ključne riječi: *primarni kardialni tumor, miksom desnog ventrikula, ehokardiografija*

Srce i krvni sudovi 2023; 42(2): 40-45

Original article

Prognostic significance of heart rate recovery in patients with diabetes mellitus and silent ischemia

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Abstract

Introduction: Heart rate recovery (HRR) after stress testing is an indicator of normal vagal activity which is in relation to the risk of premature death. Therefore, the prognostic value of this parameter for adverse events needs to be investigated, especially in patients with diabetes whose heart innervation is often disturbed.

Methods: The research included 112 patients. The patient follow-up was performed via telephone interview. Patients were divided into groups with and without silent ischemia. Four major adverse events (MACE) were investigated: myocardial revascularization, heart failure with hospitalization, heart attack and all-cause death. Median follow up time was 5 years.

Results: Patients with silent ischemia had significantly lower HRR compared to patients without it (22.8 ± 10.4 vs. 29.4 ± 13.8 beats per minute, p=0.031). The risk of MACE was significantly higher in patients with silent ischemia compared to patients without it (54.2% vs. 25%, p=0.006), with patients with silent ischemia having 2.88 times higher incidence of MACE during long-term follow-up (HR 2.882; 95% CI 1.449-5.174; p=0.03). The group of patients with slow HRR had almost 2 times higher incidence of MACE during long-term follow-up in comparison to the group of patients with normal HRR (HR 1.918; 95%CI: 0.939-3.916; p=0.074).

Conclusion: Patients with diabetes and silent ischemia had significantly higher risk of MACE compared to patients without silent ischemia during long-term follow-up. To determine the importance of HRR in adverse event prediction in patients with silent ischemia, further research is needed with a larger number of patients.

Kew words stress-echocardiography test, diabetes mellitus, miocardial ishemia

Introduction

Coronary artery disease represents the leading cause of death in patients with type 2 diabetes mellitus.[1] The prognosis of diabetes is worsened by cardiovascular complications, which are more frequent and with more severe manifestations in these patients than ones without diabetes.[1,2] especially in the developing countries. Diabetes is a major cardiovascular risk factor; it often leads to severe cardiovascular complications, and coronary artery disease (CAD Myocardial ischemia is defined as a disturbed ratio of oxygen demand and supply during resting and/or during exertion, which manifests as haemodynamic (kinetic changes), metabolic (lactic production), electrical (repolarisation) and clinical (chest pain) consequences. Silent ischemia is defined as an absence of clinical symptoms during ischemia[2] especially in the developing countries. Diabetes is a major cardiovascular risk factor; it often leads to severe cardiovascular complications, and coronary artery disease (CAD It has been shown to occur in approximately 20% of asymptomatic patients with type 2 diabetes and early diagnosis is a crucial step in treatment.[3]

One of the explanations as to why a certain group of patients with a confirmed myocardial ischemia exibits symptoms while the other doesn't is that patients with diabetes, due to peripheral neuropathy and autonomous dysregulation, show an elevated threshold for pain stimuli. In addition, there is evidence that the pain receptors in the myocardium themselves are being qualitatively and quantitatively changed.[4]

Increase in heart rate during physical activity is a phenomenon coordinated by simultaneous activation of sympathetic and decrease in parasympathetic function.[5] Heart rate recovery (HRR) immediately after exercise is a process driven by the tone of the vagal nerve and its activation during resting. Adequate vagal tone is associated with a lower risk of premature death of all causes.[6] Therefore HRR, as a function of the vagal activity, can be used in risk stratificaton for premature cardiac death, as well as death from other causes.

The aim of our paper was to investigate the prognostic importance of HRR after physical or pharmacological stress testing in patients with diabetes, as well as the importance of silent ischemia occurring during and/or after stress testing for the occurrence of adverse cardiovascular events.

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Methods

Patients who had undergone a stress test in the Cardiology Department in the Clinical Center of Serbia in a period from January to May 2015 were identified retroactively through data acquired from the Polyclinic stress-echocardiography database. All of the subjects were diabetic. The diagnosis of diabetes was confirmed either by reviewing the documentation or on the basis of taking medication for the treatment of diabetes. Patient follow-up lasted 5 years. Four main events followed in the research were: myocardial revascularization (either percutaneous or surgical), heart failure hospitalization, heart attack and a fatal outcome from all-cause. Therefore, events were grouped into "major cardiac adverse events" (MACE) which encompassed first three events and "all adverse events" which encompassed all four. Information about these events was acquired through direct contact with patients via telephone interview. For those patients who experienced adverse events documentation was requested.

Stress electrocardiography and echocardiography

The test was performed according to the standard Bruce protocol or the modified Bruce protocol on a treadmill, as was previously defined.[7] A widely used treadmill testing tool, is a weighted index combining exercise time or capacity, maximum ST-segment deviation and exercise-induced angina. No previous studies have investigated whether the Duke treadmill score and its individual components based on bicycle exercise testing predict cardiovascular death. Design: Two populations with a standard bicycle testing were used: 3936 patients referred for exercise testing (2371 men, age 56 ± 13 years Moreover, we included patients who had undergone the dobutamine testing in doses 10, 20 and 40 mcg/kg/min.[8] The pharmacological stress test was performed until the submaximal heart rate was achieved, or otherwise until the last dose of 40 mcg/kg/min ran out.

Diagnostic end-points of stress echocardiography are: maximal dose (in pharmacological testinig) or maximal workload (in exercise testing); achievement of target heart rate; severe chest pain; obvious echocardographic positivity (with akinesia of ≥ 3 left ventricular segments); obvious electrocardiographic positivity (with > 2mV ST segment shift). Submaximal nondiagnostic endpoints of stress echo testing are intolerable symptoms or limiting asymptomatic side effects (hypertension, hypotension, supraventricular arrhythmias and complex ventricular arrhythmias).[9]

Patients were advised to stop taking beta blockers 24 hours prior to testing, considering they can affect the heart rate during testing, as well as ECG and ECHO findings.[10] by correlating heart rate recovery with known parameters of myocardial ischemia. Methods and Results. Included in the study were 304 consecutive patients (73% men

The level of physical effort was estimated by MET (metabolic equivalent) where 1 MET represents the amount of energy needed to burn 3,5ml of oxygen per kilogram per minute while resting.

The Duke score was calculated according to the formula: Duration of test – (5x maximal ST change in millimeters) – (4x angina index). The angina index has a value of 0 (no chest pain caused by exercise), 1 (pain that doesn't affect the ability to exercise) and 2 (pain that affects the ability to exercise).[7] a widely used treadmill testing tool, is a weighted index combining exercise time or capacity, maximum ST-segment deviation and exercise-induced angina. No previous studies have investigated whether the Duke treadmill score and its individual components based on bicycle exercise testing predict cardiovascular death. Design: Two populations with a standard bicycle testing were used: 3936 patients referred for exercise testing (2371 men, age 56 ± 13 years

Before starting the test, as well as after every phase of testing, the heart rate, systolic and diastolic pressure were measured, and the ECG and ECHO findings were read. One minute after the test was concluded heart rate was measured. HRR was calculated as the difference between the biggest value measured during testing and the value measured after the first minute of resting. The normal value of HRR is minimum 18 beats per minute.[11] The stress test was considered positive if there were ischemic changes registered on the ECG (ST depression or elevation ≥ 1mm in two consecutive leads, newly formed T wave changes) and/or worsening of segmental kinetics on the ECHO immediately after stopping the treadmill or during the pharmacological stress test. A positive test for ischemia without patients experiencing any clinical symptoms was considered silent ischemia.

Statistical analysis

Software SPSS for Windows v21.0 (SPSS Inc. Chicago, IL, SAD) was used for the statistical analysis of the collected data. Numerical (continuous) variables were presented as the arithmetic mean ± standard deviation, while the nominal (categorical) variables were presented as absolute frequencies with a percentage share. The Student t test was used for testing numerical variables, while the chi-square test of independence or the Fisher exact test were used for testing categoric variables. A Kaplan-Meier curve with log rank test was used for analyzing the difference in frequency of events between the two tested groups of patients during the follow-up period. The risk rate between the two tested groups of patients was estimated by Cox-regression analysis. Statistical significance was set at $p<0,05$.

Results

A total of 112 patients with positive exercise testing for myocardial ischemia were included in the analysis. Mean age of patients was 63 ± 9 years and 59 (52,7%) of them were male. Forty patients (35,7%) had a history of heart attacks, while 53 (47,3%) patients had a previous myocardial revascularisaton. During stress testing 24 (21,4%) patients had ischemic changes without ac-

companying symptoms (silent ischemia), while 88 (78,6%) patients had a clincally manifest myocardial ischemia during the test. Other demographic and clinical data of interest can be found in Table 1.

Mean value of HRR for the entire examined population was 27,7 ± 12,1 beats per minute. Patients with silent ischemia had a significantly lower HRR in comparison to patients without silent ischemia (22,8 ± 10,4 vs. 29,4 ± 13,8 beats per minute, p=0,031). BMI and Duke score were significantly lower in the group of patients with silent ischemia compared to the group without it (25,7 ± 3,5 vs. 27,9 ± 3,8 kg/m^2, p=0,013; 3,1 ± 4,1 vs. 6,2 ± 2,8 kg/m^2, p=0,003). Other demographic and clinical characteristics of patients with and without silent ischemia can be found in Table 2.

Major adverse cardiac events and all adverse events were significantly more frequent in patients with silent ischemia comapred to patients without silent ischemia (41,7% vs. 21,6%, p=0,047; 54,2% vs. 25,0%, p=0,006). The group of patients with silent ischemia had a 2,88 times higher risk for all adverse events in the long-term follow-up period compared to the group of patients without silent ischemia (HR 2,88; 95%CI: 1,449-5,174; p=0,03). (Figure 1)

Twenty-four patients had slow HRR (values of 18 beats per minute and lower), 8 (33,3%) with silent ischemia and 16 (18,2%) without silent ischemia. However, statistically significant difference in occurence of slow HRR in patients with silent ischemia compared to the patients without silent ischemia was not observed (p=0,109).

When the examined population was devided according to slow and normal HRR, a group of 24 (21,4%) patients with slow HRR and 88 (78,6%) patients with normal HRR was formed. In the group of patients with normal HRR a more frequent usage of diuretics, nitrates and statins was observed compared to the group of patients with slow HRR (66,7% vs. 27,3%, p<0,001; 54,2% vs. 27,3%, p=0,013; 75,0% vs. 51,1%, p=0,037). In addition, this group achieved the submaximal heart rate during the stress test much more frequently compared to the patients with slow HRR (50,0% vs. 76,7%, p=0,011). No significant difference in all adverse events was shown between these two groups (p=0,082). Demographic and clinical characteristics of patients with slow and normal HRR can be found in Table 3. The group of patients with slow HRR had an almost 2 times higher risk of all adverse events in the long-term follow-up period compared to the group of patients with normal HRR (HR 1,918; 95%CI: 0,939-3,916; p=0,074). (Figure 2)

Table 1. General demographic and clinical characteristics of the patients

Variable	N=112
Male gender	59 (52,7%)
Age (years)	63 ± 9
BMI (kg/m^2)	27,2 ± 3,7
Positive family history	58 (51,8%)
Smoker	51 (45,5%)
Hypertension	97 (86,6%)
Diabetes (oral andidiabetics)	54 (42%)
Diabetes (insulin dependant)	16 (14,3%)
Hyperlipoproteinemia	76 (67,9%)
Previous myocardial infarction	40 (35,7%)
Previous revascularization (percutaneous or surgery)	53 (47,3%)
Antiaggregation therapy	76 (6,9%)
β blockers	81 (72,3%)
ACE inhibitors/aldosteron receptor antagonists	67 (59,8%)
Calcium channel blockers	39 (34,8%)
Diuretics	40 (35,7%)
Nitrates	37 (33%)
Statins	63 (56,3%)
Resting heart rate (beats per minute)	77,3 ± 15,2
Systolic blood pressure (mmHg)	124,3 ± 14,3
Diastolic blood pressure (mmHg)	75,3 ± 7,3
Submaximal heart rate (beats per minute)	132,7 ± 7,9
Maximal heart rate during testing (beats per minute)	135,3 ± 1,1
Achieved submaximal heart rate	78 (70,9%)
Maximal systolic blood pressure during testing (mmHg)	158,5 ± 22,9
Maximal diastolic pressure during testing (mmHg)	84,2 ± 6,6
Test duration (min)	6,4 ± 2,2
Duke score	5,6 ± 3,3
MET	7,5 ± 2,3
Heart rate recovery (beats per minute)	27,7 ± 12,1
Slow heart rate recovery	24 (21,4%)
Adverse events	29 (25,9%)

BMI – body mass index; MET – metabolic equivalent of task

Discussion

Our research showed that patients with silent ischemia have a significantly higher number of adverse events in comparison to patients without silent ischemia during stress testing, which is in accordance with some of the previously published studies.(12)"ISSN":"15583597","abstract":"Myocardial ischemia can occur without overt symptoms. In fact, asymptomatic (or silent We also demonstrated that a statistically significant difference in HRR exists between patients with and without silent ischemia. On the other hand, in patients with inadequate HRR no statistically significant difference in the occurence of MACE was observed between patients with silent ischemia and those without it. This can be explained by the fact that minimal values used for slow HRR vary in literature (13)compare it to other test responses, evaluate its diagnostic value and clarify some of the methodologic issues surrounding its use. BAGKGROUND: Studies have highlighted the value of a new prognostic feature of the treadmill test - rate of recovery of HR after exercise. These studies have had differing as well as controversial results and did not consider diagnostic test characteristics. METHODS: All patients were referred for evaluation of chest pain at two university-affiliated Veterans Affairs Medical Centers who underwent treadmill tests and coronary angiography between 1987 and 1999 were determined to be dead or alive

Table 2. Demographic and clinical characteristics of patients with silent ischemia and patients without silent ischemia

Variable	Patients with silent ischemia (N=24, 21,4%)	Patients without silent ischemia (N=88, 78,6%)	p value
Male gender	16 (66,7%)	43 (48,9%)	0,122
Age (years)	64 ± 10	63 ± 9	0,768
BMI (kg/m^2)	25,7 ± 3,5	27,9 ± 3,8	0,013
Positive family history	12 (50%)	46 (52,3%)	0,843
Smoker	11 (45,8%)	40 (45,5%)	0,974
Hypertension	22 (91,7%)	75 (85,2%)	0,412
Diabetes (oral andidiabetics)	8 (33,3%)	46 (52,3%)	0,100
Diabetes (insulin dependant)	2 (8,3%)	14 (15,9%)	0,347
Hyperlipoproteinemia	18 (75%)	58 (65,9%)	0,398
Previous myocardial infarction	10 (47,1%)	30 (34,1%)	0,492
Previous revascularization (percutaneous or surgery)	11 (45,8%)	42 (47,7%)	0,869
Antiaggregation therapy	15 (62,5%)	61 (69,3%)	0,526
β blockers	16 (66,7%)	65 (73,9%)	0,485
ACE inhibitors/aldosteron receptor antagonists	13 (54,2%)	54 (61,4%)	0,524
Calcium channel blockers	7 (29,2%)	32 (36,4%)	0,512
Diuretics	8 (33,3%)	32 (36,4%)	0,784
Nitrates	9 (37,5%)	28 (31,8%)	0,600
Statins	10 (41,7%)	53 (60,2%)	0,104
Resting heart rate (beats per minute)	74,7 ± 13,0	78,1 ± 15,5	0,330
Systolic blood pressure (mmHg)	128,8 ± 17,8	123,6 ± 13,4	0,126
Diastolic blood pressure (mmHg)	76,7 ± 8,2	75,1 ± 7,1	0,365
Submaximal heart rate (beats per minute)	132,2 ± 8,2	132,9 ± 7,6	0,701
Maximal heart rate during testing (beats per minute)	133,9 ± 15,3	135,2 ± 17,5	0,731
Achieved submaximal heart rate	16 (66,7%)	62 (72,1%)	0,605
Maximal systolic blood pressure during testing (mmHg)	156,3 ± 18,1	158,4 ± 24,4	0,693
Maximal diastolic pressure during testing (mmHg)	85,6 ± 5,8	83,8 ± 6,9	0,248
Test duration (min)	6,4 ± 2,9	6,5 ± 2,2	0,911
Duke score	3,1 ± 4,1	6,2 ± 2,8	0,003
MET	7,7 ± 3,0	7,6 ± 2,2	0,127
Heart rate recovery (beats per minute)	22,8 ± 10,4	29,4 ± 13,8	0,031
Slow heart rate recovery	8 (33,3%)	16 (18,2%)	0,109
All adverse events	13 (54,2%)	22 (25%)	0,006
Major cardiac adverse events	10 (41,7%)	19 (21,6%)	0,047

BMI – body mass index; MET – metabolic equivalent of task

after a mean seven years of follow-up. All-cause mortality was the end point for follow-up, and coronary angiography was the diagnostic gold standard. RESULTS: There were 2,193 male patients who had treadmill tests and coronary angiography. Heart rate recovery at 2 min after exercise outperformed other time points in prediction of death; a decrease of <22 beats/min had a hazard ratio of 2.6 (2.4 to 2.8 95% confidence interval and amongst the diagnostic institutions in which the tests are conducted. This is why certain publications propose that the cut off value for normal HRR should be reduced and more precise reference values should be found for all patients.(5,10,14,15)we hypothesized that a delayed fall in the heart rate after exercise might be an important prognostic marker. METHODS For six years we followed 2428 consecutive adults (mean [+/-SD] age, 57+/-12 years; 63 percent men

Chronic hyperglycemia is associated with damage and dysfuncion of different systems of organs, of which complications are most commonly seen in the nervous and cardiovascular system.(16) Diabetic patients sometimes have autonomic dysregulation, caused by neuropathy and damaged nerve endings. This change is seen foremostly on blood vessels, disabling adequate wall muscle tonus, as well as on the heart muscle where it reduces and sometimes disables physiological response to changes in preassure, volume and increased need during exercise.[17] A change in heart rate during exercise is used as a marker of preservation of the myocardial autonomic innervation, more precisely the decrease of heart rate in the first minute of resting after physical activity or pharmacological effort. Potential prognostic value of HRR as a marker for cardiac and all-cause mortality has been described in literature.[14] In our paper there was a tendency for the prognostic value of HRR to be statistically significant, therefore it can be hypothesized that the difference would have been significant had there been a larger number of patients included.

The next important parameter that showed a statistically significant difference between groups was the Duke score. Its prognosic value in events related to cardiological complications has been described in literature in detail and is considered today as an indispensable scoring system during stress testing.[18–20] including ST-segment depression, chest pain, and exercise duration. However, its usefulness for providing diagnostic estimates has yet to be determined. Methods and Results - A logistic regression model was used to predict significant (≥75% stenosis Our research showed that patients with silent ischemia during stress testing had a significantly lower Duke score values, which is related to a higher rate of cardiovascular mortality.[21] This correlates with our findings regarding to the occurence of MACE, which were significantly more common in patients with silent ischemia.

Conclusion

Patients with silent myocardial ischemia had a significantly higher risk of major adverse cardiac events in the long-term follow-up period compared to patients without silent ischemia. There was a statistically insignificant difference in the value of HRR between patients with and without silent ischemia. Studies with a larger number of patients are needed in order to determine the significance of HRR after stress testing in predicting adverse events in patients with diabetes and silent ischemia.

References

1. Grundy SM, Benjamin IJ, Burke GL, et al. Diabetes and cardiovascular disease: A statement for healthcare professionals from the american heart association. Circulation 1999;100:1134-1146.
2. Barthelemy O, Le Feuvre C, Timsit J. Silent myocardial ischemia screening in patients with diabetes mellitus. Arq Bras Endocrinologi Metabol 2007;51:285–293.
3. Yamada T, Yoshitama T, Makino K, Lee T, Saeki F. Heart rate recovery after exercise is a predictor of silent myocardial ischemia in patients with type 2 diabetes. Diabetes Care 2011;34(3):724–726.
4. Maseri A, Crea F, Kaski J, Davies G. Mechanisms and significance of cardiac ischemic pain. Prog Cardiovasc Dis 1992;35(1):1–18.
5. Cole CR, Blackstone EH, Pashkow FJ, Snader CE, Lauer MS. Heart-rate recovery immediately after exercise as a predictor of mortality. N Engl J Med 1999;341(18):1351–1357.
6. Hadaya J, Ardell JL. Autonomic modulation for cardiovascular disease. Front Physiol 2020;11:e617459.
7. Salokari E, Laukkanen JA, Lehtimaki T, et al. The Duke treadmill score with bicycle ergometer: Exercise capacity is the most important predictor of cardiovascular mortality. Eur J Prev Cardiol 2019;26(2):199–207.
8. Sicari R, Cortigiani L. The clinical use of stress echocardiography in ischemic heart disease. Cardiovasc Ultrasound 2017;15(1): 7. doi: 10.1186/s12947-017-0099-2.
9. Picano E, Pasanisi E, Venneri L, Agrusta M, Mottola G, Sicari R. Stress echocardiography. Curr Pharm Des 2005;11(17):2137–2149.
10. Georgoulias P, Orfanakis A, Demakopoulos N, et al. Abnormal heart rate recovery immediately after treadmill testing: Correlation with clinical exercise testing, and myocardial perfusion parameters. J Nucl Cardiol 2003;10(5):498–505.
11. Maddox TM, Ross C, Ho PM, et al. The prognostic importance of abnormal heart rate recovery and chronotropic response among exercise treadmill test patients. Am Heart J 2008;156(4):736–744.
12. Conti CR, Bavry AA, Petersen JW. Silent ischemia: Clinical relevance, J Am Coll Cardiol 2012;435–441.
13. Shetler K, Marcus R, Froelicher VF, et al. Heart rate recovery: Validation and methodologic issues. J Am Coll Cardiol. 2001; 38(7):1980–1987.
14. Qiu S, Cai X, Sun Z, et al. Heart rate recovery and risk of cardiovascular events and all-cause mortality: A meta-analysis of prospective cohort studies. J Am Heart Assoc 2017;6: e005505. doi: 10.1161/JAHA.117.005505.
15. Watanabe J, Thamilarasan M, Blackstone EH, et al. Heart rate recovery immediately after treadmill exercise and left ventricular systolic dysfunction as predictors of mortality: The case of stress echocardiography. Circulation 2001;104(16):1911–1916.
16. American Diabetes Assosciation. Diagnosis and classification of diabetes mellitus. Diabetes Care 2013;Suppl 1:S67-74.
17. Agashe S, Petak S. Cardiac autonomic neuropathy in diabetes mellitus. Methodist DeBakey cardiovascular journal. NLM (Medline) 2018;14:251–256.
18. Shaw LJ, Peterson ED, Shaw LK, et al. Use of a prognostic treadmill score in identifying diagnostic coronary disease subgroups. Circulation 1998;98(16):1622–1630.
19. Mark DB, Hlatky MA, Harrell FE, et al. Exercise treadmill score for predicting prognosis in coronary artery disease. Ann Intern Med 1987;106(6):793–800.
20. Dzenkeviciute V, Sapoka V, Kasiulevicius V, et al. Value of Duke treadmill score in predicting coronary artery lesion and the need for revascularization. Kardiol Pol 2017;75(5):439–444.
21. Kwok JMF, Miller TD, Hodge DO, Gibbons RJ. Prognostic value of the Duke treadmill score in the elderly. J Am Coll Cardiol 2002; 39(9):1475–1481.

Sažetak

Prognostički značaj oporavka srčane frekvence kod bolesnika sa dijabetesom melitusom i „nemom" ishemijom

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Uvod: *Oporavak srčane frekvence (OSF) nakon testa opterećenja predstavlja jedan od pokazatelja normalne vagalne aktivnosti koja je povezana sa rizikom od prevremene smrti. Stoga, treba ispitati prognostičku vrednost ovog parametra za moguće neželjene događaje, pogotovo kod bolesnika sa dijabetesom kod kojih je inervacija srca često oštećena.*
Metod: *U istraživanje je uključeno 112 bolesnika. Bolesnici su podeljeni na one sa nemom ishemijom miokarda i one bez nje. Praćena su četiri glavna neželjena događaja (MACE): revaskularizacija miokarda, popuštanje srca sa hospitalizacijom, infarkt miokarda i smrtni ishod. Medijana praćenja bolesnika je iznosila pet godina.*
Rezultati: *Bolesnici sa nemom ishemijom su imali značajno manji OSF u odnosu na bolesnike bez nje (22,8 ± 10,4 vs. 29,4 ± 13,8 otkucaja u minuti, p=0,031). Rizik od pojave MACE-a bio je značajno veći u grupi sa nemom ishemijom u odnosu na one bez nje (54,2% vs. 25%, p=0,006). Grupa bolesnika sa nemom ishemijom je imala 2,88 puta veći rizik od pojave MACE-a u dugoročnom period praćenja, u odnosu na grupu bolesnika bez nje (HR 2,88; 95%CI: 1,449-5,174; p=0,03). Grupa bolesnika sa sporim OSF je imala skoro 2 puta veći rizik od pojave MACE-a u dugoročnom period praćenja, u odnosu na grupu bolesnika sa normalnim OSF (HR 1.918; 95%CI: 0.939-3.916; p=0.074).*
Zaključak: *Bolesnici sa dijabetesom i nemom ishemijom miokarda imali su značajno veći rizik od pojave MACE u dugoročnom periodu praćenja u odnosu na bolesnike bez neme ishemije. Za utvrđivanje značaja OSF u predikciji neželjenih događaja kod bolesnika sa nemom ishemijom potrebne su studije sa većim brojem bolesnika.*

Ključne reči: *stres-ehokardiografski test, dijabetes melitus, ishemija miokarda*

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Case report

The significance of long-term patients monitoring after anthracycline administration

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Abstract Anthracyclines are drugs used to treat various types of cancers, including breast cancer. They are still among the most effective anticancer drugs used today and their broad use has dramatically improved cancer survival statistics. Unfortunately, though mortality rates decrease with their use, life-altering cardiac sequelae from anthracyclines remain a problem, such as patients developing late-onset heart failure secondary to anthracycline-induced cardiotoxicity (AIC). We present a case of 63-year-old female who was admitted to the Cardiology Clinic due to the symptoms of heart failure. Fourteen years earlier she had a left-sided mastectomy due to breast cancer treated with radiotherapy and chemotherapy. The chemotherapy regime was FAC (5-fluorouracil, doxorubicin and cyclophosphamide). Echocardiogram showed enlarged left ventricle (58mm/51mm), with reduced ejection fraction (EF 20%). There was a large effusion in the left pleura. This finding was primarily related to the treatment of breast cancer with chemotherapy.

Kew words anthracycline-induced cardiotoxicity, breast cancer, heart failure

Introduction

Anthracyclines are drugs extracted from Streptomyces spp. and used to treat various types of cancers, including leukemia, lymphoma, breast cancer and many metastatic cancers[1]. Even though anthracyclines were discovered over 50 years ago, they are still among the most effective anticancer drugs used today[2]. The different types available for treatment are: Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, Valrubicin. The explanations of cytostatic and cytotoxic actions of anthracyclines point to a number of different mechanisms, including free radical formation, lipid peroxidation, direct membrane effects and enzyme interactions. The most widely accepted mechanism for the action of anthracyclines is their interaction with topoisomerase-II. The ternary complex thus formed prevents the re-ligation of the ds-DNA breaks. Subsequently, it promotes growth arrest and apoptotic cell death[1,3].

The broad use of anthracyclines for over 40 years has dramatically improved cancer survival statistics. Unfortunately, though mortality rates decrease with anthracyclines, life-altering cardiac sequelae from anthracyclines remain a problem, with a range of 5% to 23% of patients developing late-onset heart failure secondary to anthracycline-induced cardiotoxicity (AIC)[4,5].

Anthracycline-mediated cardiotoxicity is dose-dependent and cumulative, with the damage imposed to heart occurring upon the very first dose and then accumulating with each anthracycline cycle. Cardiotoxic effects of anthracyclines range in severity and are classified by time of onset as *acute*, occurring during or immediately after infusion; *early*, occurring within 1 year of exposure; and *late*, occurring 1 to 20 years after initial exposure[5,6].

Case presentation

We present a case of 63-year-old female who was admitted to the Cardiology Clinic due to the symptoms of heart failure. Patient complained of increased fatigue, which has been present for the past three months. She was initially treated at a regional hospital, when bilateral pleural effusions were found (larger on the left side) and dilated cardiomyopathy with ejection fraction (EF) 25% was found by echocardiography. Pleural biopsy puncture was performed and no significant changes were found. A CT (computerized tomography) of the thorax was performed, which showcased consolidation of pulmonary parenchyma and severe fibrotic changes in basal segments of the both lungs. Diuretics, beta-blocker and amiodarone were introduced into the therapy, but the day before admission to our Clinic, she complaint of shortness of breath, which is why she was rehospitalized. She had a positive family history for cardiovascular diseases (CVD).

Fourteen years earlier, she had a left-sided mastectomy due to breast cancer treated with radiotherapy and chemotherapy. The chemotherapy regime was FAC, which consisted of 5-fluorouracil, doxorubicin and cyclophosphamide. Two years after mastectomy, the reconstruction of the left breast was performed (regularly monitored, tumour markers were normal).

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Physical examination showed regular heart rate, with discrete systolic murmur over the apex, heart rate was 110 bpm, and arterial blood pressure was 100/70 mmHg. Auscultatory over the lungs left base weakened respiratory sound. Electrocardiogram (ECG) showed sinus rhythm with left bundle branch block (LBBB). Laboratory tests showed increased B-type natriuretic peptide (BNP) 613, C-reactive protein was 28.7, troponin 0.0049, D-dimer 3.69, iron 4.0, with preserved renal function.

X-ray heart and lungs showed: no active pathological changes were seen in the lung parenchyma. The right costophrenic sinus was shallower, while in the left the pleural effusion was present. The breast implant was observed on the left side. The cardiac silhouette was slightly enlarged. Echocardiogram (exam was hindered by the silicone implant in the left breast) showed enlarged left ventricle (EDD 58 mm, ESD 51 mm), with reduced ejection fraction (EF 20%) and without segmental kinetics changes. There was 2+ mitral regurgitation and 2+ tricuspid regurgitation, SPDK was 60 mmHg. This finding was primarily related to the treatment of breast cancer with chemotherapy. Color doppler sonography (CDS) of the right leg veins: without signs of thrombosis were the common femoral and superficialis veins, and popliteal vein. Soleal sinus was with organized thrombotic masses. Prolongation of anticoagulant therapy with elastic compression stockings was indicated for the next six months.

Due to the findings of persistent pleural effusion, deep vein thrombosis and history of malignant disease, an oncologist was consulted, who suggested that a chest CT should be performed, in order to rule out a relapse of the oncological disease. However, the patient was not motivated. A pulmonologist was also consulted, who did not indicate an urgent pleural puncture, but recommended a bronchoscopy, for which the patient was also not motivated. CT coronary angiography was performed which did not show angiographically significant narrowings.

During hospitalization, the patient had no anginal complaints, there was no change in objective findings, and serial ECGs did not register any new changes, as well as rhythm and conduction disorders. Auscultatory findings indicating that left pleural effusion persisted. She was discharged with beta-blocker, loop diuretic, potassium-sparing diuretic, direct-acting oral anticoagulant (DOAC) and proton pump inhibitor. Eventhough our patient was highly recommended to visit a cardiologist during initial cancer treatment and after, she wasn't motivated.

Discussion

Breast cancer is the most common cancer among women. In the last twenty years early diagnosis, neoadjuvant and adjuvant systemic treatment that targeted to specific molecular targets have significantly reduced the mortality from breast cancer[7,8]. However, the increase in survival has allowed us to observe the cardiotoxic effects of anticancer therapy and increased mortality from cardiovascular causes. Anthracyclines are among the most commonly used and effective drugs in breast cancer treatment. In the past 30 years, they have become an important component of adjunctive and palliative therapy for breast cancer[9].

As previously stated in the introduction AIC is a significat side-effect of medication. In a 2013 meta-analysis, clinical cardiac toxic effects were reported in 6% of patients treated with an anthracycline after a median follow-up of 9 years, and subclinical cardiac toxic effects were described in 18% of patients[10]. Manifestations of AIC can range from asymptomatic electrocardiogram (ECG) changes and left ventricular (LV) dysfunction to profound cardiomyopathy and end-stage heart failure (HF)[11]. Particularly in our patient, ECG showcased LBBB while echocardiography revealed left ventricular dysfunction. Increasing recognition of the significant morbidity and mortality associated with AIC has led to exploration of treatment modalities to prevent its development. In preclinical studies, significant acute cardiotoxicity occurs at the time of the initial administration of anthracyclines that starts a cascade leading to the eventual development of LV dysfunction and HF. The mechanism of anthracycline's early cardiotoxicity is known to be related to free radical injury, contributing to the formation of reactive oxygen species and leading to the apoptosis of cardiomyocyte and intracellular damage[12]. On the other hand, the mechanism of delayed cardiotoxicity in the long-term survivors is multifactorial including myocardial mitochondria related apoptosis which results in metabolic remodelling of heart[13]. However, delayed cardiotoxicity presents as overt clinical manifestations such as HF only in extreme cases, and only slowly progressing ventricular abnormalities are detected in many cases[13].

Despite efforts to detect early cardiac dysfunction in anthracycline-treated patients, many will experience symptomatic and asymptomatic HF. Cancer survivors who develop late AIC with New York Heart Association (NYHA) class III–IV heart failure have a poor prognosis, with a 1-year mortality of 40% and 2-year mortality of 60%[14].

Based on *The American Society of Clinical Oncology Clinical Practice Guideline* it is widely recommended that cardiovascular risk factors are assessed prior to the initiation of any anticancer therapy. That includes blood pressure, smoking habits, blood sugar, lipid levels, and electrolyte abnormalities[15,16,17,18]. In patients considered to be at high risk of adverse cardiac events (i.e., those with cardiovascular risk factors, previous or pre-existing cardiac disease, or abnormal baseline cardiac assessments or biomarkers, of older age, or who have received prior radiotherapy or anthracycline therapy), cardioprotective treatments should be considered, including ACE inhibitors, angiotensin receptor blockers, or beta-blockers, prior to initiation of anticancer therapy[15,18]. Regular cardiac monitoring should also be considered and discussed with patients deemed at high risk of adverse cardiac events. Recommended by *The European Society for Medical Oncology Clinical Practice Guidelines* echocardiography is the preferred method for cardiac evaluation (including LVEF) before, during, and after cancer therapy. Because of its availability, avoidance in radiation exposure and safety for patients with concomitant renal disease[19]. Pre-treatment cancer therapy-related cardiovascular toxicity (CTR-CVT)

risk assessment should be performed using a recognized risk stratification method where multiple risk factors are incorporated to determine patient-specific risk[20]. While further validation is needed, *Heart Failure Association-International Cardio-Oncology Society* (HFA-ICOS) risk assessment tools should be considered to determine pretreatment risk of CTR-CVT as they are easy to use and implement in oncology services[21].

Serum cardiac biomarkers, such as troponins and natriuretic peptides, are recommended in conjunction with routine diagnostic cardiac imaging, in the monitoring of patients with clinical signs and symptoms of cardiac effects[22].

Discontinuation of anthracycline chemotherapy is recommended in patients with cancer who develop severe symptomatic cancer therapy related cardiac dysfunction (CTRCD)[23]. Temporary interruption of anthracycline chemotherapy is recommended in patients who develop moderate symptomatic CTRCD, and in patients who develop moderate or severe asymptomatic CTRCD. Guideline-based HF therapy is recommended in patients who develop symptomatic CTRCD or asymptomatic moderate or severe CTRCD during anthracycline chemotherapy. The use of an ACE-I/ARB or angiotensin receptor–neprilysin inhibitor, a beta-blocker, a sodium–glucose co-transporter-2 inhibitor, and a mineralocorticoid receptor antagonist is recommended unless the drugs are contraindicated or not tolerated.

Considering the previous amnestic and physical examination that excluded other causes of heart failure, we can assume that our patient experienced anthracycline-induced cardiotoxicity. Taking into account previously mentioned guidelines and our case report, we see the importance of long-term follow-up of patients and the appropriate introduction of cardio-protective therapy.

Conclusion

Today we know that the usage of anthracyclines can have a significant cardiotoxic effects. Considering that, the administration of anthracycline in chemotherapy should be in agreement with the chosen cardiologist. Also, long-term monitoring of patients should be necessary, bearing in mind that it represents the most important form of prevention for AIC. Even thought the increased attention in this field, many questions have not yet been answered and new studies are needed.

References

1. Venkatesh P, Kasi A. Anthracyclines. [Updated 2023 Jan 30]. U: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan. Dostupno na: https://www.ncbi.nlm.nih.gov/books/NBK538187/
2. McGowan JV, Chung R, Maulik A, Piotrowska I, Walker JM, Yellon DM. Anthracycline Chemotherapy and Cardiotoxicity. Cardiovasc Drugs Ther. 2017;31(1):63-75.
3. Chen W, Liu I, Tomiyasu H, Lee J, Cheng C, Liao AT, Liu B, Liu C, Lin C. Imatinib enhances the anti-tumour effect of doxorubicin in canine B-cell lymphoma cell line. Vet J 2019;254:105398.
4. Steinherz LJ, Steinherz PG, Tan CT, et al. Cardiac toxicity 4 to 20 years after completing anthracycline therapy. JAMA 1991;266: 1672–1677.
5. Geisberg CA, Sawyer DB. Mechanisms of anthracycline cardiotoxicity and strategies to decrease cardiac damage. Curr Hypertens Rep 2010;12(6):404-410.
6. Lipshultz SE, Alvarez JA, Scully RE. Anthracycline associated cardiotoxicity in survivors of childhood cancer. Heart 2008;94:525–533.
7. Tao, Z., Shi, A., Lu, C. et al. Breast cancer: Epidemiology and etiology. Cell Biochem Biophys 2015;72: 333–338.
8. Nicolazzi MA, Carnicelli, A Fuorlo M, et al. Anthracycline and trastuzumab-induced cardiotoxicity in breast cancer. Eur Rev Med Pharmacol Sci 2018;22: 2175-2185.
9. Cai F, Luis MAF, Lin X, et al. Anthracycline-induced cardiotoxicity in the chemotherapy treatment of breast cancer: Preventive strategies and treatment. Mol Clin Oncol 2019;11(1):15-23.
10. Lotrionte M, Biondi-Zoccai G, Abbate A, et al.. Review and meta-analysis of incidence and clinical predictors of anthracycline cardiotoxicity. Am J Cardiol 2013;112(12):1980-1984.
11. Vuong JT, Stein-Merlob AF, et al. Novel therapeutics for anthracycline induced cardiotoxicity. Front Cardiovasc Med 2022; 9:863314. doi: 10.3389/fcvm.2022.863314.
12. Lipshultz SE, Adams MJ. Cardiotoxicity after childhood cancer: beginning with the end in mind. J Clin Oncol 2010;28:1276–1281.
13. Lipshultz SE, Scully RE, Lipsitz SR, et al. Assessment of dexrazoxane as a cardioprotectant in doxorubicin-treated children with high-risk acute lymphoblastic leukaemia: long-term follow-up of a prospective, randomised, multicentre trial. Lancet Oncol 2010;11(10): 950-961.
14. Felker GM, Thompson RE, Hare JM, et al. Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. N Engl J Med 2000;342(15):1077-1084.
15. Zamorano J, Lancellotti P, Rodriguez Muñoz D et al. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). Eur Heart J 2016;37:2768–2801.
16. Curigliano G, Cardinale D, Suter T, et al; Cardiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy: ESMO Clinical Practice Guidelines. Ann Oncol 2012;23 Suppl 7:vii155-66.
17. Tarantini L, Gulizia M, Di Lenarda A et al. ANMCO/AIOM/AICO Consensus Document on clinical and management pathways of cardio-oncology: Executive summary. Eur Heart J Suppl 2017; 19(suppl D):D370–D379.
18. Virani SA, Dent S, Brezden-Masley C et al. Canadian Cardiovascular Society guidelines for evaluation and management of cardiovascular complications of cancer therapy. Can J Cardiol 2016;32(7): 831–841.
19. Plana JC, Galderisi M, Barac A et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: A report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2014;15:1063–1093.
20. Rossello X, Dorresteijn JAN, Janssen A, et al. Risk prediction tools in cardiovascular disease prevention: a report from the ESC Prevention of CVD Programme led by the European Association of Preventive Cardiology (EAPC) in collaboration with the Acute Cardiovascular Care Association (ACCA) and the Association of Cardiovascular Nursing and Allied Professions (ACNAP). Eur J Cardiovasc Nurs 2019;18:534–544.
21. Lyon A, López-Fernández T, Couch L, et al. 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS): Developed by the task force on cardio-oncology of the European Society of Cardiology (ESC). Eur Heart J 2022;43;41;4229–4361.
22. Armenian SH, Lacchetti C, Barac A et al. Prevention and monitoring of cardiac dysfunction in survivors of adult cancers: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2017;35:893–911.
23. Curigliano G, Lenihan D, Fradley M, et al. Management of cardiac disease in cancer patients throughout oncological treatment: ESMO consensus recommendations. Ann Oncol 2020;31:171–190.

Sažetak

Značaj dugoročnog praćenja pacijenata nakon primene antraciklina

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Antraciklini predstavljaju grupu lekova koja se koristi za lečenje različitih vrsta karcinoma, uključujući karcinom dojke. Među najefikasnijim su lekovima koji se danas koriste i njihova široka upotreba dramatično je poboljšala statistiku preživljavanja od karcinoma. Nažalost, iako se stope mortaliteta obolelih od raka smanjuju njihovom upotrebom, određeni broj pacijenata koji su na terapiji antraciklinima razvija simptome i znake srčanog popuštanja usled kardiotoksičnosti prouzrokovane antraciklinima. Predstavljamo slučaj 63-godišnje žene koja je primljena u Kliniku za kardiologiju zbog simptoma i znakova srčanog popuštanja. Četrnaest godina ranije imala je levostranu mastektomiju zbog karcinoma dojke, nakon čega je lečena radioterapijom i hemioterapijom. Režim hemioterapije bio je FAC (5-fluorouracil, doksorubicin i ciklofosfamid). Učinjenim ehokardiografskim pregledom uočena je uvećana leva komora (58mm/51mm), sa smanjenom ejekcionom frakcijom (EF 20%). Uočen je veliki izliv u levoj pleuri. Ovaj nalaz prvenstveno je doveden u vezu sa lečenjem karcinoma dojke hemioterapijom.

***Ključne reči**: antraciklinima-prouzrokovana kardiotoksičnost, karcinom dojke, srčano popuštanje*

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Case report

Obstacles in the treatment of coronary artery disease in patients with cancer

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Abstract Cardiovascular disease (CVD) and cancer are the two leading causes of death worldwide, accounting for over 70% of all deaths. The prevalence of CVD and cancer is increasing, and the two conditions often coexist in the same patient. The management of patients with both CVD and cancer presents a significant challenge, as treatments for one condition may increase the risk of complications in the other. Despite advances in medical therapies and interventional procedures, CVD continues to be a significant public health challenge. The prevalence of CVD among cancer patients is even higher than the general population, and they have an increased risk of CVD-related morbidity and mortality. In this report, we present a case of 59-year-old man with a history of colon cancer who presented with ACS and treated with optimal medical therapy due to high bleeding risk. Our case highlights the importance of a multidisciplinary approach to the management of ACS in cancer patients, based on the latest gudielines and evidence-based practices.

Kew words acute coronary syndrome, cancer, dual antiplatelet therapy, bleeding

Introduction

Cardiovascular disease, especially ischemic heart disease and cancer are two of the leading causes of morbidity and mortality worldwide[1]. The incidence of cancer and cardiovascular disease continues to increase globally, and there is an increasing number of patients with both malignant and cardiovascular disease(2). Management of these patients poses a specific challenge for healthcare professionals, due to drug interactions, the effects of chemotherapy and radiation therapy on the cardiovascular system, and the high risk of both bleeding and thrombotic events[3,4,5,6]. Several studies have been conducted in recent years in order to enable better understanding of complex patophysiology of these patients and to identify potential strategies for effective treatment of this specific subgroup of patients[7].

Case presentation

Male patient, 59 years old, who was without known comorbidities until February 2019, had episodes of diarrhea for which he was examined by a gastroenterologist. Two months later patient had 4 to 6 diarrheal bloody stools per day, as well as one episode of rectorrhagia. This was the reason for reevaluation by gastroenterologist, a colonoscopy was performed and patient was diagnosed with colorectal cancer (adenocarcinoma) with secondary deposits in the liver. Colon surgery was performed next month, with formation of a colostomy. He was admitted to Institute for Oncology and Radiology of Serbia (IORS) two months after the surgery due to administration of the first cycle of adjuvant chemotherapy regimen according to the FOLFOX protocol (folic acid+5FU+oxaliplatin). After 30 minutes from the beginning of administration of the second dose of chemotherapy, patient complained of chest pain with propagation to his shoulders. Therapy administration was discontinued, ECG was performed, 1mm - ST depression and negative T waves in leads I, aVL, V5 and V6 were registered. Due to the suspicion of the development of acute coronary syndrome (ACS), dual antiplatelet therapy (DAPT) (acetylsalicylic acid 300mg, Clopidogrel 300mg) was prescribed along with PPI, the patient was referred to ER and because of elevated troponin plasma levels (hs TnT 170 ng/L, cut off 14ng/L) he was admitted to the Coronary ICU. An echocardiographic examination revealed normal left ventricle size (EDD/ESD 5.5/3.6 cm), without evidence of regional wall motion abnormalities, normal left ventricular function, EF 64%, without pericardial effusion. Selective coronary angiography revealed a 90-95% stenosis of the OM branch, without angiographically significant stenosis on other coronary arteries, and PCI of OM branch was indicated as soon as possible, depending on the clinical condition and the possibility of applying long - term DAPT. After the administration of next dose of dual antiplatelet therapy (acetylsalicylic acid 100mg, Clopidogrel 75mg), rectal and colostomy bleeding occurred, and a consultation

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with a gastroenterologist was performed, but, due to active rectal bleeding, permission for the use of dual antiplatelet and anticoagulant therapy was not obtained, and the patient was treated with optimal medical therapy in the further course of hospitalization. During hospitalization, the chest pain did not recur, nor did the gastrointestinal bleeding, the maximum value of hsTnT was 408, and after the normalization of the TnT value, the patient was transferred to IORS for further treatment of the malignant disease.

Discussion

The use of antithrombotic therapy in cancer patients with CVD is a topic of ongoing research. The European Society of Cardiology (ESC), the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO), and the International Cardio-Oncology Society (IC-OS) have jointly developed guidelines for the management of cardio-oncology patients[8]. The guidelines emphasize the importance of assessing the cardiovascular risk of cancer patients before initiating cancer treatment and regularly monitoring the cardiovascular status of cancer survivors. According to guidelines, it is advised to perform immediate PCI in patients with cancer presenting with STEMI or high-risk NSTE-ACS with life expectancy ≥6 months, while non-invasive approach is preferred in patients with poor cancer prognosis and/or very high bleeding risk. The guidelines recommend that the choice of antithrombotic therapy should be based on the type of cancer, the stage of cancer, the type of PCI, and the patient's bleeding risk. The guidelines also recommend that the duration of DAPT should be individualized based on the patient's bleeding and ischemic risks. One key theme that emerges from the literature is the elevated risk of both thrombotic and bleeding events in cancer patients undergoing PCI for AMI. Guo et al. found that cancer patients had a higher risk of both thrombotic and ischemic events following PCI, even after controlling for other risk factors such as age, gender, and comorbidities[6]. In addition, several studies have demonstrated that cancer patients undergoing PCI are at higher risk of readmission due to bleeding and ischemic events than non-cancer patients[9,10]. One study conducted by Bharadwaj et al. evaluated the outcomes of PCI in 6.5 million patients with a current or previous diagnosis of cancer in the United States. The study found that cancer patients who underwent PCI had a higher risk of in-hospital mortality, bleeding, and stroke when compared to non-cancer patients[3]. Similarly, Nakatsuma et al. found that cancer patients had significantly higher adjusted risk for all-cause death, non-cardiac death and major bleeding when compared to non-cancer patients[11].

In addition to the challenges of balancing the risks of ischemic and bleeding events, recent studies have also highlighted the importance of recognizing the common pathophysiology underlying cancer, atrial fibrillation, atherosclerosis, and thrombosis. A state-of-the-art review by Leiva et al. explores this common pathophysiology, noting that all of these conditions are characterized by an imbalance between pro-coagulant and anti-coagulant factors that can increase the risk of both thrombotic and bleeding events. Authors note that inflammation, hypercoagulability, and oxidative stress are all key drivers of both cancer and cardiovascular disease, and suggest that targeting these pathways may be a promising approach for managing competing risks in patients with both conditions and they suggest that better understanding of this shared pathophysiology could lead to improved prevention and treatment strategies for these conditions[2].

Several studies have explored the use of dual antiplatelet therapy (DAPT) in cancer patients undergoing PCI in ACS treatment, with focus on estimation of risk for both bleeding and thrombotic events. Tsigkas et al.(12) summarized the current evidence on DAPT use in patients with malignant disease. It is noted that shorter use of DAPT (1-3 months) reduces bleeding risk, but it is recommended that prolongation of DAPT use should be considered in patients with increased risk of thrombotic events. Tang et al. noted that among cancer patients treated with PCI in ACS, bleeding and all-cause mortality rates were lower when compared to non-PCI cancer patients with ACS[1]. Another study by Hayashi et al. investigated the cardiovascular and bleeding risks in patients with inactive cancer and AMI who received primary PCI using drug-eluting stent and DAPT. The study found that inactive cancer was associated with a higher risk of both major bleeding and cardiovascular events[13]. All of the above mentioned studies highlighted the need for individualised therapeutic approach. Similarly, a commentary by Mamas and study conducted by Potts et al. emphasizes the importance of individualized treatment strategies that take into account both ischemic and bleeding risk factors[5,14].

Several other recent studies have also highlighted the challenges of managing ACS in patients with cancer, including both short-term and long-term outcomes. For instance, a study by Matsumoto et al. found that presence of active cancer was associated with worse short-term and long-term outcomes in patients with ACS, including higher rates of major bleeding during index hospitalization and higher rates of both major bleeding and major adverse cardiovascular events after discharge when comapred to patients with a history of cancer and those without cancer[1]. A review by Lucà et al. highlights the importance of recognizing the increased risk of ACS in patients with cancer, as well as the challenges of managing both conditions simultaneously. The authors suggest that the management of such patients should be individualized based on the patient's bleeding and ischemic risks, the type of cancer, and its treatment, choosing invasive approach in case of STEMI and high-risk NSTEMI, while the non-invasive strategy should be reserved for low-risk NSTEMI patients and in cases of stable coronary artery disease (CAD)[7]. They also emphasize the importance of a multidisciplinary approach to the management of such patients. Similarly, Potts et al. suggest that treatment of cancer patients should be individualized and done in collaboration of cardiologists and oncologists[14]. Considering these evidences from

literature, and taking into account absence of significant ECG changes suggesting the development of STEMI or high-risk NSTEMI, reccurent symptoms of myocardial ischemia, signs or symptoms of heart failure and normalisaton of cardiospecific enzymes plasma levels, as well as presence of rectal and colostomy bleeding after loading dose and first day maintenance dose of DAPT, the medical team concluded that the risk of long-term DAPT use would be unacceptably high, and a decision was made to treat the patient with individually tailored optimal medical therapy (OMT).

Given the increased risk of adverse events in cancer patients undergoing PCI, it is important to consider strategies for reducing this risk. Some studies suggested an approach aimed to precisely identify patients who are at a higher risk of bleeding or thrombotic events and tailor their treatment accordingly[16,17]. In an editorial published in JACC: Cardiovascular Interventions, Ky and Fanaroff suggest that precision medicine can help to define bleeding and ischemic risk in cancer patients undergoing PCI by taking into account patient-specific factors such as cancer type, stage, and treatment history. Also, it is noted that current bleeding and ischemic risk scores may not adequately capture the unique risk profile of cancer patients, because they are based on results of trials in which those patients are not included[4].

In conclusion, the management of ACS in cancer patients is complex and requires a multidisciplinary approach. Clinicians should carefully evaluate the risks and benefits of different treatment options, taking into account the patient's individual characteristics, cancer type and stage, bleeding and thrombotic risk and the potential interactions between antiplatelet and anticoagulant therapy and chemotherapy. The latest guidelines provide comprehensive recommendations to guide clinicians in decision-making and treatment selection, but more research is needed to better understand the optimal management of ACS in cancer patients. By collaborating with oncologists and other specialists, clinicians can improve the outcomes of these challenging patients and provide better care.

References

1. Tang M, Wang Y, Cao X, et al. In-hospital and one-year outcomes in cancer patients receiving percutaneous coronary intervention for acute myocardial infarction: A real-world study. Front Cardiovasc Med 2023;9:1005473.
2. Leiva O, AbdelHameid D, Connors JM, et al. Common pathophysiology in cancer, atrial fibrillation, atherosclerosis, and thrombosis: JACC: CardioOncology State-of-the-Art Review. JACC CardioOncol 2021;3(5):619-634.
3. Bharadwaj A, Potts J, Mohamed MO, et al. Acute myocardial infarction treatments and outcomes in 6.5 million patients with a current or historical diagnosis of cancer in the USA. Eur Heart J 2020;41(23):2183-2193.
4. Ky B, Fanaroff AC. Adding precision to defining bleeding and ischemic risk with PCI in cancer patients. JACC Cardiovasc Interv 2021;14(10):1106-1108.
5. Mamas MA. Decision making in percutaneous coronary intervention in patients with cancer: balancing ischaemic and bleeding risk. Eur Heart J 2021;42(48):4982-4983.
6. Guo W, Fan X, Lewis BR, et al. Cancer patients have a higher risk of thrombotic and ischemic events after percutaneous coronary intervention. JACC Cardiovasc Interv 2021;14(10):1094-1105.
7. Lucà F, Parrini I, Abrignani MG, et al. Management of acute coronary syndrome in cancer patients: It's high time we dealt with it. J Clin Med 2022;11(7):1792.
8. Lyon AR, López-Fernández T, Couch L, et al; ESC Scientific Document Group (2022). 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). Eur Heart J 2022;43(41):4229–4361.
9. Marenzi G, Cosentino N, Cardinale D. Ischaemic and bleeding risk in cancer patients undergoing PCI: another brick in the wall. Eur Heart J 2021;42(10):1035-1037.
10. Kwok CS, Wong CW, Kontopantelis E, et al. Percutaneous coronary intervention in patients with cancer and readmissions within 90 days for acute myocardial infarction and bleeding in the USA. Eur Heart J 2021;42(10):1019-1034.
11. Nakatsuma K, Shiomi H, Morimoto T, et al. Influence of a history of cancer on long-term cardiovascular outcomes after coronary stent implantation (an Observation from Coronary Revascularization Demonstrating Outcome Study-Kyoto Registry Cohort-2). Eur Heart J. Quality of care & clinical outcomes 2018;4(3):200–207.
12. Tsigkas G, Vakka A, Apostolos A, et al. Dual antiplatelet therapy and cancer; balancing between ischemic and bleeding risk: A narrative review. J Cardiovasc Dev Dis 2023;10(4):135.
13. Hayashi H, Kataoka Y, Murai K, et al. Cardiovascular and bleeding risks of inactive cancer in patients with acute myocardial infarction who received primary percutaneous coronary intervention using drug-eluting stent and dual/triple antithrombotic therapy. Cardiovasc Diagn Ther 2022;12(6):803-814.
14. Potts JE, Iliescu CA, Lopez Mattei JC, et al. Percutaneous coronary intervention in cancer patients: a report of the prevalence and outcomes in the United States. Eur Heart J 2019;40(22):1790-1800.
15. Matsumoto T, Saito Y, Yamashita D, et al. Impact of active and historical cancer on short- and long-term outcomes in patients with acute myocardial infarction. Am J Cardiol 2021;159:59-64.
16. Giri J, Nathan AS. The pros and cons of percutaneous coronary intervention in patients with cancer. JACC CardioOncol 2019; 1(2):156-158.
17. Ueki Y, Vögeli B, Karagiannis A, et al. Ischemia and bleeding in cancer patients undergoing percutaneous coronary intervention. JACC CardioOncol 2019;1(2):145–155.

Sažetak

Teškoće u lečenju koronarne bolesti kod pacijenata sa karcinomom

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Kardiovaskularne bolesti (KVB) i maligniteti predstavljaju dva vodeća uzroka smrti širom sveta, a odgovorni su za oko 70% svih smrtnih ishoda. Prevalencija KVB i maligniteta je u porastu, a ova dva stanja su često istovremeno prisutna kod istog pacijenta. Lečenje pacijenata sa KVB i malignitetom predstavlja veliki izazov, jer terapijski pristup lečenju jednog oboljenja može povećati rizik od nastanka komplikacija pri lečenju drugog oboljenja. Uprkos razvoju medikamentne terapije i interventnih procedura, kardiovaskularne bolesti i danas prestavljaju značajan javnozdravstveni izazov. Prevalencija KVB među pacijentima sa malignitetima je veća nego u opštoj populaciji, a u ovoj grupi pacijenata je uočen i povećana stopa morbiditeta i mortaliteta od KVB. U ovom radu prikazan je je slučaj 59- godišnjeg muškarca sa karcinomom debelog creva kod koga je došlo do razvoja AKS lečenog individualno prilagođenom medikamentom terapijom zbog visokog rizika od krvarenja. Naš slučaj naglašava važnost multidisciplinarnog pristupa u lečenju AKS kod pacijenata sa malignetom, zasnovanog na najnovijim preporukama i dokazima iz velikih randomizovanih studija.

***Ključne reči**: akutni koronarni sindrom, karcinom, dvojna antiagregaciona terapija, krvarenje*

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Case report

Electrical storm in a patient with implantible cardioverter defibrillator

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Abstract Electrical storm is the occurrence of at least three episodes of malignant ventricular arrhythmia (sustained ventricular tachycardia/ventricular fibrillation) during 24 hours, most commonly in patients with an implanted cardioverter defibrillator. We present a 48-year-old patient with an implanted cardioverter defibillator in the secondary prevention of sudden cardiac death and the occurrence of an electrical storm in the form of polymorphic ventricular tachycardia with degeneration into ventricular fibrilation treated by the delivery of 10 intracardiac DC shocks in a several hours period. A multimodality approach to the patient was applied, which included the initial search for precipitating factors, electronic interrogation and changes in device programming, antiarrhythmic drug therapy and patient sedation. The applied measures are discussed in the context of the available literature. A multimodality approach to patients with electrical storm in specialized centers improves outcomes of such complex patients.

Kew words electrical storm, inplantable cardiac defibrilator, multimodality imaging

Introduction

An electrical storm represents consecutive attacks of malignant arrythmia (sustained ventricular tachycardia - VT or ventricular fibrillation - VF) within a short period of time. The most widely accepted is three episodes of ventricular arrhythmia within 24 hours[1], although recent analyzes indicate an increase in mortality with as much as two episodes within a three-month interval[2]. An electrical storm is a medical emergency and is presented by repeated ICD shocks or activation of antitachycardia pacing in patients with an implanted cardioverter defibrillator (ICD) or repeated syncope, cardiac arrest or symptoms and signs of low cardiac output in patients without an ICD. Acute treatment consists of patient stabilization, removal or treating of precipitating factors, ICD programming, pharmacological antiarrhythmic therapy, catheter ablation of the arrhythmogenic substrate, and modulation of the autonomic nervous system[1]. We present a patient with an electrical storm three and a half years after an ICD was implanted in the secondary prevention of sudden cardiac death. Acute care modalities and a review of the relevant literature are presented.

Case presentation

A 48-year-old, extremely obese male patient was admitted to the Department of internal medicine, Health Center Zaječar due to syncope in the sitting position accompanied by sweating. There was a rapid recovery of consciousness in a lying position. He was observed during the first 24 hours in the Coronary care Unit, without any heart rhythm disturbances noted. Then, in the Department of Cardiology, as an inpatient, 24-hour ECG monitoring was carried out, during which a cardiac arrest with VF occurred, which was successfully treated by an asynchronous DC shock of 270J. Several episodes of nonsustained ventricular tachycardia and two episodes of sustained polymorphic ventricular tachycardia were seen on the Holter ECG. VF was triggered by the R on T phenomenon. A coronary angiography was performed, considering that the patient had an acute myocardial infarction in 2002, and it showed intermediate lesions of the OM1 branch, two tight lesions followed by occlusion of the medial segment of the right coronary artery, with distal segment visualised through well-developed heterocollaterals from the left coronary system. Myocardial necrosis markers were negative, so the arrhythmia was not figured to be induced by acute coronary ischaemia and an ICD was implanted according to the secondary prevention of sudden cardiac death protocol. The patient was regularly followed as outpatient at the Pacemaker Center and there were no ICD activations (shocks and antitachycardia pacing) over the next three and a half years. With the performed echocardiography, the left ventricular ejection fraction was estimated to be 45%.

15.5.2021. after finishing work (afternoon shift as a medical technician) and a large meal, the patient felt

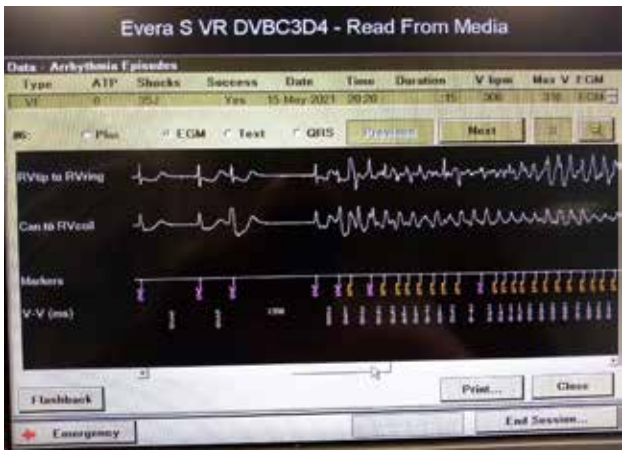

Figure 1

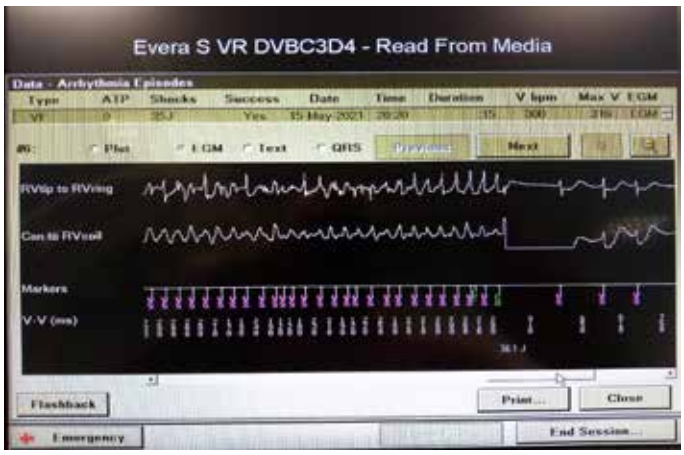

Figure 2

dizzy and experienced chest pain, which he thought was an intracardiac DC shock. The Emergency Medical Service was called, after which he was brought to the Internal Medicine Department. Interrogation of the ICD revealed 6 episodes of VF, which were caused by the degeneration of polymorphic VT initiated by the R to T phenomenon (pictures 1 and 2). In a short period, he had 4 more intracardiac DC shocks in the Coronary Care Unit. There was no hypokalemia that would promote arrhythmia - 4.7 mmol/L. Amiodarone i.v. (until then he was on a regular oral therapy with the drug) , lidocaine, metoprolol i.v. in repeated slow boluses of 5 mg and then bisoprolol 20 mg daily. The base rate of the ICD was raised to 80/min to promote ventricular pacing with sedation with midazolam i.v. Due to applied measures, the electrical storm stopped and the patient stabilized with signs of overt heart failure. Optimal medical therapy for heart faillure was instituted. Troponin was serially negative despite repeated DC shocks.

Recoronarography was performed, which showed stationary angiographic findings. Left ventricular ejection fraction was estimated at 42%. Subsequently, the patient returned to work with internal medicine outpatient visits and electronic ICD controls at the Pacemaker Center. In a two year follow up, there were no ventricular arrhythmia episodes detected. Obstructive sleep apnea was suspected as a significant comorbid condition contributing to arrhythmogenesis and referred to polysomnography, which has not yet been performed.

Discussion

It is not easy to estimate the incidence of electrical storm because it depends on the follow-up period in different studies, but in general in ICD patients ranges from 4-60%(3). Patients in whom an ICD is implanted for primary prevention usually have a lower incidence of electrical storms[4] compared to patients in whom secondary prevention of sudden cardiac death is carried out[5]. The frequency of occurrence is similar in patients with ischemic and non-ischemic cardiomyopathy (6). In the AVID study, 457 patients with an implanted ICD were observed, who were divided into three groups: the group with electrical storm; the group with non-clustered malignant ventricular arrhythmias that do not meet the criteria for electrical storm; group without any ventricular arrhythmias after implantation. Electrical storm is an independent risk factor for death, independent of left ventricular systolic function and other variables (OR 2.4), while non-clustered VT/VF is not (OR 1.0). The risk of death is highest in the first 3 months after an electrical storm and decreases over time[7]. In the study by Brigadeau *et al*[8] 307 patients with an implanted ICD were monitored. Independent predictive factors for the occurrence of electrical storm were chronic renal failure, ventricular tachycardia as an index arrhythmia and not taking hypolipemic drugs, while diabetics had a lower incidence of electrical storm (HR 0.49). The importance of electrical storm is best illustrated by a meta-analysis which showed that it increases mortality 2.5 times compared to patients with non-clustered ventricular arrhythmias and 3.3 times compared to patients without sustained ventricular arrhythmias[9].

One of the first line measures in the treatment of an electrical storm is the exclusion of inappropriate shocks. They may be the result of oversensing electrical potentials, atrial tachyarrhythmia or defibrillator lead fracture. If they are detected, ICD programming is carried out. Aggressive ICD programming with a lower heart rate threshold and shorter VF detection time and turning off antitachycardia pacing during ICD capacitor charging have been shown to be associated with the development of electrical storm[10]. Repeated intracardiac shocks alone increase morbidity and mortality[11]. In this context ICD shock burden should be reduced and antitachycardia pacing should be favored in order to terminate ventricular arrhythmia. This is achieved by increasing the heart rate, which represents the detection threshold, and by extending the arrhythmia detection time. Both interventions have been shown to reduce the number of shocks delivered, without increasing syncope, and also reduce mortality[12,13]. In some cases, the therapy delivered by the device is excluded, especially in a case of incessant VT that is well tolerated by the patient. If it is necessary and a subspecialist programming the defibrillator is not readily available, it can be turned off by placing a magnet over the device[14]. In the case of our patient, all delivered ICD shocks were appropriate, so an attempt was made to search for a precipitating factor. These are most commonly electrolyte disorders (hypokalemia, hypomagne-

semia), myocardial ischemia, worsening of heart failure, sepsis, discontinuation of antiarrhythmic drugs[1]. However, in most cases there is no identified reversible cause of an electrical storm. In the SHIELD study, a trigger was found in only 13% of cases[15].

In our patient, the potassium level on admission was normal, high-sensitivity troponin was negative even after multiple intracardiac shocks, which practically ruled out acute myocardial ischemia. Coronary angiography performed after the patient's stabilization during the same hospital episode indicated stationary angiographic findings on the epicardial coronary arteries. We were unable to routinely assess magnesium levels. The possible cause of the electrical storm in our patient could have been the heart failure worsening, as lung congestion signs were registered at the time of admission. Exacerbation of heart failure is one of the possible causes of electrical storm reported in the literature. In a prospective study by Guerra *et al*[16], 146 patients were followed, of whom 34 were initially hospitalized due to electrical storm, 82 due to heart failure worsening and 30 due to non-clustered VT/VF episodes. Patients from the first two groups had a similar and at the same time significantly higher mortality rate as well as a shorter time to rehospitalization compared to the third group. Among those initially hospitalized due to electrical storm, 25% were re-hospitalized due to electrical storm and 42% due to heart failure worsening. It was concluded that electrical storm in patients with heart failure and ICD can be considered a warning sign of impending pump failure and even overt heart failure, rather than as an independent event.

The ECG recording of arrhythmia during an electrical storm is significant because it indicates the possible etiology and thus the therapy of choice. Sustained monomorphic VT is the most common arrhythmia seen in an electrical storm and is caused by a re-entry mechanism on heterogeneous ventricular scar tissue as a consequence of ischemic and non-ischemic cardiomyopathy. On the other hand, polymorphic VT/VF storm is most often caused by myocardial ischemia, channelopathies or idiopathic VF in a structurally normal heart. A 12-channel ECG recording showing the morphology of ventricular premature beats that initiate an episode of polymorphic VT/VF is important for planning ablation of the arrhythmogenic substrate[17].

After confirming an electrical storm, a risk assessment is done. Patients with at least one of the following are treated as high-risk: hemodynamic instability, left ventricular ejection fraction below 30%, moderate to severe renal failure and the presence of chronic obstructive pulmonary disease. Such patients should be treated in intensive care units where sedation and mechanical ventilation are available[8]. Our patient did not meet the mentioned criteria, but due to the large number of delivered intracardial shocks in a short time frame and the development of congestive heart failure, he was treated in the Coronary Care Unit with constant electrocardiographic and hemodynamic monitoring.

Increased sympathetic tone plays an important role in the occurrence of an electrical storm[18]. Deep sedation with endotracheal intubation is recommended in high-risk patients in whom sustained arrhythmia with repeated intracardiac shocks is expected. These measures have positive psychological effects, reducing the patients discomfort. For sedation, benzodiazepines and short-acting opioid analgesics are recommended because they induce sedation and analgesia without negative inotropic effects. Anecdotally, the use of propofol as an effective means to terminate an electrical storm has been reported. It should be carefully used because of its cardiodepressant nature, and patients with an electrical storm usually have impaired left ventricular systolic function[17,19-21]. In our patient, we decided on the concept of so-called "conscious sedation" by giving repeated doses of modazolam of 2 mg i.v. so that relaxation and reduction of sympathetic tone in the patient was achieved without respiratory depression and the need for mechanical ventilation. The absence of a therapeutic effect would lead to us to escalate to deep sedation and mechanical ventilation, but this was not necessary in this particular case due to successful termination of electrical storm.

Antiarrhythmic drug therapy has historically been considered the mainstay of electrical storm treatment[17]. Although logical, this concept has its limitations. In a meta-analysis by Santagnelli *et al*[22], it was found that treatment with antiarrhythmic drugs reduces the probability of recurrent storm by 1.5 fold, but without decreasing mortality. When assessing pharmacological agents individually, only amiodarone was found to reduce the number of episodes of malignant ventricular arrhythmias and ICD shocks, while sotalolol, azimilide, and celivarone did not. On the other hand, unlike other antiarrhythmic drugs, amiodarone is associated with 3.36 fold higher mortality compared to a group of patients who received standard therapy, without specific antiarrhythmic drugs. The choice of antiarrhythmic drug depends on the cause of the electrical storm, the severity of the associated heart failure, and potential toxicity. In an electrical storm with VT, a vicious circle of events can occur when repeated intracardiac shocks induce new VT episodes and further shocks by increasing the sympathetic tone. Therefore, the suppression of increased sympathetic tone with the use of B blockers is an initial measure in the treatment of electrical storm[17]. In the MADIT II study, the use of B blockers in the treatment of ventricular arrhythmias reduced recurrent ventricular arrhythmias by 52%[23]. A recent study with a smaller sample size randomized patients with electrical storm to receive i.v. propranolol or metoprolol for the first 24 hours with mandatory coadministration of amiodarone i.v. in both groups. Patients who received propranolol had fewer recurrent ventricular arrhythmias in the first 24 hours (53% vs. 90%), fewer ICD shocks delivered, shorter time to termination of the arrhythmia, and shorter hospitalization time. The explanation for the effectiveness of non-selective B blockers in this context is the downegulation of β1 receptor seen in patients with heart failure. Instead of the usual β1:β2 receptor ratio of 70:30 to 80:20 in healthy cardiomyocytes, in heart failure this ratio is 60:40. In this study, propranolol

proved to be an effective and safe agent, especially considering that the subgroup receiving it had an average left ventricular EF of 25%[24]. This should be used in the context of its use in the acute phase of electrical storm, because propranolol itself is not indicated in the chronic therapy of heart failure[25]. Our patient was already on chronic oral therapy with amiodarone and 5 mg bisoprolol per day. In the acute phase, we re-administered amiodarone i.v. in the loading dose with simultaneous administration of lidocaine 120 mg i.v. bolus + 1200 mg/12h continuous infusion. In addition, we used 3 i.v. boluses of metoprolol 5mg every 5 minutes and then continued with 20mg bisoprolol per day. Although aggressive, this approach, with the use of midazolam and the programmed basic frequency of the ICD of 80/min, led to the cessation of further arrhythmias and stabilization of the patient. Overdrive pacing with a frequency faster than the patient's spontaneous heart rate acted by means of suppression of ventricular premature beats, because the record from the ICD programmer clearly indicated that these were episodes of polymorphic VT initiated by the R to T phenomenon, with further degeneration to VF and lead to the delivery of an intracardiac DC shock. The successful application of a similar therapeutic approach in individual cases was used by several groups of authors[26-28]. This strategy is also mentioned in the latest ESC guidelines for ventricular arrhythmias and the prevention of sudden cardiac death, in the algorithm after exhausting other therapeutic options in patients in whom bradycardia or post-extrasystolic pauses induce the occurrence of polymorphic VT/VF, without labeled class of recommendations and level of evidence[29].

One of the therapeutic measures in patients with electric storm is radiofrequency (RF) ablation of the arrhythmogenic substrate in specialized centers high volume centers. According to the latest ESC guidelines on this topic, it has a class IIa recommendation, level of evidence C for use in patients with repeated polymorphic VT/VF episodes resistant to antiarrhythmic therapy and revascularization[29]. After clinical stabilization we did not refer the patient to ablation , yet decided on clinical follow up. It has proven to be correct so far, because in the follow up period of two years, there were not any clinical episodes of VT/VF and also no episodes detected by electronic device interrogation. Considering the patient's habitus (body mass index of 38kg/m^2) and targeted anamnestic data on poor sleep quality and daytime sleepiness, it was suspected that obstructive sleep apnea in this particular patient may increase the arrhythmogenic potential. Such an association has been demonstrated in a number of smaller studies[30-31]. In a larger randomized study, it was shown that in patients with implanted CRT-D, sleep breathing disorders (obstructive and, even to a greater extent, central sleep apnea) are independently associated with shorter event-free survival, time to the first monitored ventricular arrhythmia and appropriate ICD therapies[32]. Our patient, for now, is not motivated for diagnosis and possibly treatment of sleep breathing disorders.

Conclusion

Electrical storm is the most dramatic clinical event in patients with an implanted cardioverter defibrillator that requires adequate diagnostics and multimodality approach in specialized centers with appropriate equipment and personnel. This approach improves the outcome of such complex patients.

References

1. Elsokkari I, Sapp J. Electrical storm: prognosis and management. Progr Cardiovasc Dis 2021;66:70-79.
2. Elsokkari I, Parkash R, Tang A, et al. Mortality risk increases with clustered ventricular arrhythmias in patients with implantable cardioverter-defibrillators. JACC: Clinical Electrophysiology 2020;6(3):327-337.
3. Proietti R, Sagone A. Electrical storm: incidence, prognosis and therapy. Indian Pacing Electrophysiol J 2011;11(2):34.
4. Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. NEJM 2002;346 (12):877-883.
5. Bänsch D, Böcker D, Brunn J, et al. Clusters of ventricular tachycardias signify impaired survival in patients with idiopathic dilated cardiomyopathy and implantable cardioverter defibrillators. J Am Coll Cardiol 2000;36(2):566-573.
6. Streitner F, Kuschyk J, Dietrich C, et al. Comparison of ventricular tachyarrhythmia characteristics in patients with idiopathic dilated or ischemic cardiomyopathy and defibrillators implanted for primary prevention. Clin Cardiol 2011;34(10):604-609.
7. Exner DV, Pinski SL, Wyse DG, et al. Electrical storm presages non sudden death: the antiarrhythmics versus implantable defibrillators (AVID) trial. Circulation 2001;103 (16):2066-2071.
8. Brigadeau F, Kouakam C, Klug D, et al. Clinical predictors and prognostic significance of electrical storm in patients with implantable cardioverter defibrillators. Eur Heart J 2006;27(6):700-707.
9. Guerra F, Shkoza M, Scappini L, et al. Role of electrical storm as a mortality and morbidity risk factor and its clinical predictors: a meta-analysis. Europace 2013;16(3):347-353.
10. Guerra F, Palmisano P, Dell'Era G, et al. Implantable cardioverter-defibrillator programming and electrical storm: results of the OBSERVational registry On long-term outcome of ICD patients (OBSERVO-ICD). Heart Rhythm 2016;13:1987–92.
11. Moss AJ, Schuger C, Beck CA et al. Reduction in inappropriate therapy and mortality through ICD programming. N Engl J Med 2012;367:2275–2283.
12. Auricchio A, Schloss EJ, Kurita T, et al. Low inappropriate shock rates in patients with single- and dual/triple-chamber implantable cardioverter-defibrillators using a novel suite of detection algorithms: painFree SST trial primary results. Heart Rhythm 2015; 12:926–036.
13. Wilkoff BL, Williamson BD, Stern RS, et al. Strategic programming of detection and therapy parameters in implantable cardioverter-defibrillators reduces shocks in primary prevention patients: results from the PREPARE (primary prevention parameters study. J Am Coll Cardiol 2008;52:541–550.
14. Zeppenfeld K, Tfelt-Hansen J, De Riva M, et al. ESC Scientific Document Group, 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: Developed by the task force for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death of the European Society of Cardiology (ESC) Endorsed by the Association for European Paediatric and Congenital Cardiology (AEPC). Eur Heart J 2022;43(40):3997–4126.
15. Hohnloser SH, Al-Khalidi HR, Pratt CM, et al. Electrical storm in patients with an implantable defibrillator: incidence, features, and preventive therapy: insights from a randomized trial. Eur Heart J 2006;27(24):3027-3032.
16. Guerra F, Flori M, Bonelli P, et al. Electrical storm and heart failure worsening in implantable cardiac defibrillator patients. Europace 2015;17(2):247–254.
17. Geraghty L, Santangeli P, Usha T, et al. Contemporary management of electrical storm. Heart Lung Circ 2018;1(11):1443-1506

18. Vaseghi M, Shivkumar K. The role of the autonomic nervous system in sudden cardiac death. Progress Cardiovasc Dis 2008; 50:404–419.
19. Mandel JE, Hutchinson MD, Marchlinski FE. Remifentanil-midazolam sedation provides hemodynamic stability and comfort during epicardial ablation of ventricular tachycardia. J Cardiovasc Electrophysiol 2011;22:464–466.
20. Mulpuru SK, Patel DV, Wilbur SL, et al. Electrical storm and termination with propofol therapy: a case report. Int J Cardiol 2008; 128:6–8.
21. Martins RP, Urien JM, Barbarot N, et al. Effectiveness of deep sedation for patients with intractable electrical storm refractory to antiarrhythmic drugs. Circulation 2020;142:1599–1601.
22. Santangeli P, Muser D, Maeda S, et al. Comparative effectiveness of antiarrhythmic drugs and catheter ablation for the prevention of recurrent ventricular tachycardia in patients with implantable cardioverter-defibrillators: a systematic review and meta analysis of randomized controlled trials. Heart Rhythm 2016;13:1552–1559.
23. Moss AJ, Zareba W, Jackson Hall W, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002;346:877–883.
24. Chatzidou S, Kontogiannis C, Tsilimigras D, et al. Propranolol versus metoprolol for treatment of electrical storm in patients with implantable cardioverter defibrillator. J Am Coll Cardiol 2018; 71:1897–906.
25. McDonagh T, 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.
26. Kurisu S, Inoue I, Kawagoe T, et al., Temporary overdriving pacing as an adjunct to antiarrhythmic drug therapy for electrical storm in acute myocardial infarction. Circulation J 2005;69(5):613–616.
27. Yoshida T, Naito Y, Nishimura K. Temporary ventricular overdrive pacing for electrical storm after coronary artery bypass grafting. Gen Thorac Cardiovasc Surg 2011;59(11):756–759.
28. Magdi M, Mubasher M, Alzaeem H, et al. Resistant ventricular arrhythmia and the role of overdrive pacing in the suppression of the electrical storm. Case Rep Cardiol 2019;6592927:4.
29. Serizawa N, Yumino D, Kajimoto K, et al. Impact of sleep-disordered breathing on life-threatening ventricular arrhythmia in heart failure patients with implantable cardioverter-defibrillator. Am J Cardiol 2008;102:1064-1068.
30. Fichter J, Bauer D, Arampatzis S, et al. Sleep-related breathing disorders are associated with ventricular arrhythmias in patients with an implantable cardioverter-defibrillator. Chest 2002;122:558 –561.
31. Mehra R, Benjamin EJ, Shahar E et al. Sleep Heart Health Study. Association of nocturnal arrhythmias with sleep-disordered breathing: The Sleep Heart Health Study. Am J Respir Crit Care Med 2006;173:910–916.
32. Bitter T, Westerheide N, Prinz, C, et al. Cheyne-Stokes respiration and obstructive sleep apnoea are independent risk factors for malignant ventricular arrhythmias requiring appropriate cardioverter-defibrillator therapies in patients with congestive heart failure. Eur Heart J 2020;32(1):61–74.

Sažetak

Električna oluja kod pacijenta sa inplantabilnim kardioverter defibilatorom

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Električna oluja predstavlja pojavu najmanje tri epizode maligne komorske aritmije (održiva ventrikularna tahikardija/ventrikularna fibrilacija) tokom 24h, najčešće kod bolesnika sa implantiranim kardioverter defibrilatorom. U radu se prikazuje bolesnik starosti 48 godina sa implantiranim ICD u sekundarnoj prevenciji naprasne srčane smrti i pojavom električne oluje po tipu polimorfne VT sa degeneracijom u VF prećenu isporučivanjem 10 intrakardijalnih DC šokova u periodu od nekoliko sati. Prikazan je multimodalitetni pristup bolesniku koji je uključivao inicijalnu potragu za precipitirajućim činiocima, elektronsku interogaciju i promene u programiranju uređaja, antiaritmijsku terapiju i sedaciju bolesnika. Primenjene mere diskutovane su u kontekstu dostupne literature. Multimodalitetni pristup bolesnicima sa električnom olujom u specijalizovanim centrima poboljšava prognozu ovako kompleksnih bolesnika.

Ključne reči: *električna pluja, inplantabilni srčani defibrilator, multimodalitetni imidžing*

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Case report

Tachycardia-induced cardiomyopathy: Recovery of systolic ejection fraction after sinus rhythm restoration

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Abstract This case report presents a 63-year-old patient who presented with symptoms of palpitations, skipped heartbeats, fatigue, and shortness of breath. The patient had been experiencing these symptoms for a year, with recent exacerbation. After the diagnostic workup, a diagnosis of tachycardia-induced cardiomyopathy (TIC) was established, where atrial fibrillation (AF) was the arrhythmia that induced the cardiomyopathy. Initial attempts to convert the patient's rhythm to sinus using Amiodarone were unsuccessful. Therefore, electrical cardioversion was performed, resulting in the successful restoration of sinus rhythm. The patient's ejection fraction (EF) was closely monitored post-cardioversion, and a remarkable improvement in systolic function was observed. The stability of sinus rhythm was maintained during the follow-up period, highlighting the importance of terminating the tachycardia that led to cardiomyopathy in the restoration of EF. This case report underscores the critical role of interventions aimed at managing and resolving tachycardia-induced cardiomyopathy, emphasizing the significance of restoring normal cardiac rhythm to achieve improved systolic ejection fraction. Early recognition and appropriate management of tachycardia-induced cardiomyopathy are essential in preventing long-term cardiac dysfunction and enhancing overall patient outcomes.

Kew words tachycardia-induced cardiomyopathy, atrial fibrillation, electrical cardioversion , ejection fraction

Introduction

Tachycardia-induced cardiomyopathy (TIC) is a condition characterized by impaired cardiac function resulting from prolonged periods of elevated heart rate. One potential consequence of TIC is a decrease in systolic ejection fraction (EF)[1,2]. While the primary focus is on restoring sinus rhythm, in some cases, pharmacological interventions may prove unsuccessful. In such instances, electrical cardioversion can be an effective option[3]. This article presents a case study where electrical cardioversion successfully converted atrial fibrillation (AF) to sinus rhythm, leading to the recovery of systolic ejection fraction in a patient with TIC.

Case preseentation

A 63-year-old patient presented to the Emergency Department with complaints of palpitations, skipping heartbeats, fatigue, and shortness of breath. The symptoms have been present for a year but have intensified over the past few days. Electrocardiography (ECG) during the examination revealed atrial fibrillation with a ventricular rate of approximately 105 beats per minute. An attempt was made to pharmacologically convert the patient to sinus rhythm using intravenous Amiodarone, but without success. The patient was started on Acenocoumarol and Amiodarone tablets and discharged for home treatment with instructions to return for a follow-up visit in a few days and to undergo an echocardiogram (ECHO) of the heart. After two weeks, an outpatient ECHO was performed, which showed an enlarged left ventricle with normal wall thickness, globally impaired kinetics, without clear kinetic abnormalities, and a significantly reduced ejection fraction (EF) of 20%. The left atrium was enlarged (4.4) with mitral regurgitation 2+. Atrial fibrillation with a ventricular rate of 95 beats per minute was still observed on the electrocardiogram. Subsequently, a Holter ECG was performed, which consistently showed atrial fibrillation with a ventricular rate ranging from 53 to 156 beats per minute and an average rate of 110 beats per minute. No other rhythm disturbances were recorded. During the course of treatment, the patient switched from an vitamin K dependent oral anticoagulant (Acenokumarol) to a non-vitamin K antagonist oral anticoagulant (NOAC) (Rivaroxaban). The patient was also started on an angiotensin receptor-neprilysin inhibitor (ARNI) and a sodium-glucose co-transporter-2 (SGLT-2) inhibitor, and a hospital admission was scheduled for further cardiological evaluation. One month later, the patient was admitted to the hospital. The echocardiographic findings showed no significant changes, with an EF of 20%. Atrial fibrillation

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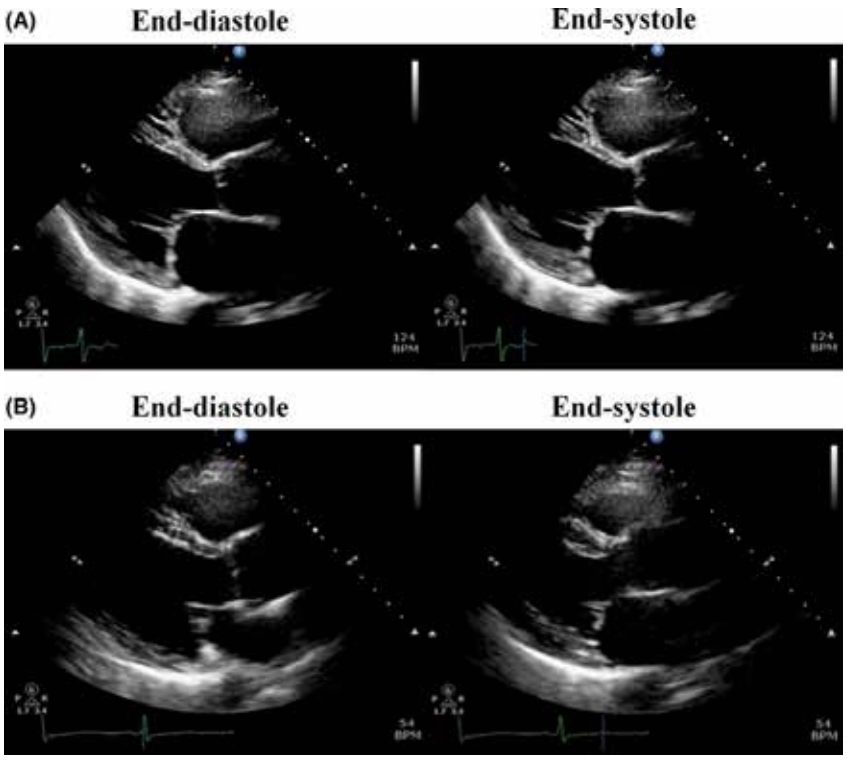

Figure A and B, A) Transthoracic echocardiography on admission showed a dilated left atrium and left ventricle. The left ventricular wall motion was severely and diffusely hypokinetic. The left ventricular ejection fraction calculated by the biplane Simpson's method was 20%. B) Transthoracic echocardiography after 6 months depicted systolic function improvement in both the left atrium and left ventricle. The left ventricular ejection fraction was 65%.

with a heart rate of 100 beats per minute was observed on the electrocardiogram. Coronary angiography was performed, revealing no angiographically significant stenosis. Due to the unsuccessful attempt to pharmacologically convert atrial fibrillation to sinus rhythm, it was decided to proceed with direct-current cardioversion. In an analgesic-sedated state, a synchronized DC shock of 200J was delivered, successfully converting atrial fibrillation to sinus rhythm. The patient was monitored in the intensive care unit and remained hemodynamically stable, maintaining sinus rhythm. The patient was discharged from the hospital on a NOAC (CHA_2DS_2-VASc-2), Amiodarone, and a comprehensive heart failure treatment regimen. Six months later, the patient returned for a follow-up visit. Subjectively he feels well and denies any sensation of palpitations or skipped heartbeats. Sinus rhythm was observed on the electrocardiogram. A repeat ECHO was performed, showing a significant improvement in left ventricular systolic function to 65%.

Tachycardia-induced cardiomyopathy (TIC) is a condition characterized by impaired cardiac function resulting from prolonged periods of elevated heart rate[1,2]. The sustained rapid heartbeat places excessive stress on the heart, leading to structural and functional abnormalities, including a decrease in systolic ejection fraction (EF). TIC may manifest months to years after the onset of the responsible tachycardia, but because TIC is a rate dependent cardiomyopathy, those patients with higher tachycardia rates develop TIC earlier[4]. However, with timely intervention and restoration of sinus rhythm, patients with TIC have the potential for significant recovery in their EF.

Tachycardia, defined as a heart rate greater than 100 beats per minute, can result from various causes, including atrial fibrillation, atrial flutter, ventricular tachycardia, or supraventricular tachycardia. Prolonged tachycardia episodes lead to a decrease in the heart's ability to pump blood efficiently, ultimately affecting cardiac function and structure.

TIC, the prolonged and rapid heart rate disrupts the coordination and efficiency of the heart's pumping action. The constant demand for increased cardiac output causes the ventricles to work harder and become less effective in contracting and emptying blood. As a result, the systolic ejection fraction decreases, indicating reduced cardiac performance[5]. The cornerstone of TIC management involves identifying and addressing the underlying cause of tachycardia. Various treatment options are available, including medication, catheter ablation, and electrical cardioversion. Although, due to the serious potential consequences of this syndrome, a definitive cure to the arrhythmia as can be obtained with a catheter ablation, should be pursued whenever possible[6]. The primary goal is to restore sinus rhythm, allowing the heart to regain its normal rhythm and optimize cardiac function.

Once sinus rhythm is successfully restored, patients with TIC often experience significant improvements in their systolic ejection fraction. As the heart rate stabilizes, the ventricles can contract more effectively and pump blood efficiently. The reduced workload on the heart allows for the recovery of myocardial function and structural remodeling. The recovery of systolic ejection fraction after sinus rhythm restoration in TIC patients can vary. In some cases, EF improvement may be ob-

served within weeks, while in others, it may take several months. The duration and severity of tachycardia, as well as individual patient factors such as age, overall health, and underlying cardiac conditions, can influence the rate and extent of EF recovery[7].

While sinus rhythm restoration plays a crucial role in EF recovery, it may not be the sole determinant. Additional factors, such as the presence of underlying structural heart disease, coexisting comorbidities, and the overall response to treatment, can impact the extent of EF improvement. Concurrent management of heart failure, including lifestyle modifications, medication therapy, and cardiac rehabilitation, may be necessary to optimize recovery[8].

In this case due to the failure of pharmacological conversion, the decision was made to proceed with electrical cardioversion. The patient underwent external synchronized direct-current (DC) shock, resulting in the successful restoration of sinus rhythm. Post-cardioversion, the patient's EF was closely monitored. Over time, there was a significant improvement in systolic ejection fraction, indicating enhanced cardiac function. The recovery of EF demonstrated the positive impact of electrical cardioversion on the patient's TIC.

Electrical cardioversion is a highly effective procedure for restoring sinus rhythm in patients with certain cardiac arrhythmias, particularly atrial fibrillation and atrial flutter. By delivering a synchronized electric shock to the heart, electrical cardioversion aims to reset the heart's electrical activity and promote coordinated contractions. While the procedure has a high success rate, careful patient selection, appropriate sedation, and close monitoring are essential to ensure safety and optimal outcomes[3].

After successful sinus rhythm restoration and improvement in systolic ejection fraction, ongoing monitoring and follow-up are essential. Regular echocardiography and clinical evaluations can help assess the recovery progress and guide further management decisions. Lifestyle modifications, adherence to medication, and continued surveillance for potential arrhythmias are critical for long-term maintenance of cardiac health.

Conclusion

Tachycardia-induced cardiomyopathy is a condition characterized by impaired cardiac function resulting from prolonged periods of elevated heart rate. However, with prompt identification and restoration of sinus rhythm, patients with TIC have the potential for significant recovery in their systolic ejection fraction. The normalization of heart rate allows for improved myocardial function.

References

1. Mohamed H. Tachycardia-induced cardiomyopathy (Tachycardiomyopathy). Libyan J Med 2007 Mar 1;2(1):26-29.
2. Umana E, Solares CA, Alpert MA. Tachycardia-induced cardiomyopathy. Am J Med 2003;114(1):51-55.
3. Lown B. Electrical reversion of cardiac arrhythmias. Br Heart J 1967;29(4):469–489.
4. Quiniou G, Chevalier JM, Barbou F, et al. Tachycardia-induced cardiomyopathy, unusual and reversible cause of left ventricular dysfunction: report of 9 cases. Ann Cardiol Angeiol (Paris) 2000;49(5):301-308.
5. Calò L, De Ruvo E, Sette A, et al. Tachycardia-induced cardiomyopathy: mechanisms of heart failure and clinical implications. J Cardiovasc Med (Hagerstown) 2007;8(3):138-143.
6. Wood MA, Brown-Mahoney C, Kay GN, et al. Clinical outcomes after ablation and pacing therapy for atrial fibrillation : a meta-analysis. Circulation 2000;101(10):1138-1144.
7. Fenelon G, Wijns W, Andries E, et al. Tachycardiomyopathy: mechanisms and clinical implications. Pacing Clin Electrophysiol 1996;19(1):95-106.
8. Iyer RV. Ventricular dysfunction: tachycardia induced cardiomyopathy. Indian Pacing Electrophysiol J 2008;8(Suppl. 1):S122-129.

Sažetak

Kardiomiopatija izazvana tahikardijom: oporavak sistolne ejekcione frakcije nakon obnavljanja sinusnog ritma

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U našem prikazu slučaja radi se o bolesniku starom 63 godine koji se javio na pregled zbog osećaja lupanja i preskakanja srca, zamaranja i nedostatka vazduha. Ovi simptomi su bili prisutni tokom godinu dana, a intenzivirali su se nekoliko dana pre pregleda. Nakon urađene dijagnostike postavljena je dijagnoza tahikardijom indukovane kardiomiopatije(TIC) gde je atrijalna fibrilacija (AF) bila aritmija koja je izazvala kardiomiopatiju. Prvi pokušaji konverzije u sinusni ritam primenom Amiodarona nisu bili uspešni, zato je izvršena elektrokonverzija, što je rezultiralo uspešnim uspostavljanjem sinusnog ritma. Ejekciona frakcija (EF) je pažljivo praćena nakon elektrokonverzije i zapaženo je značajno poboljšanje sistolne funkcije. Tokom perioda praćenja u daljem toku se održava sinusni ritam, što ukazuje na značaj terminisanja tahikardije koja je dovela do kardiomiopatije u obnovi EF. Ovaj prikaz naglašava ključnu ulogu intervencija usmerenih ka lečenju tahikardijom indukovane kardiomiopatije, ističući značaj uspostavljanja sinusnog ritma u poboljšanju ejekcione frakcije. Rano prepoznavanje i preduzimanje odgovarajućih terapijskih mera za lečenje tahikardijom indukovane kardiomiopatije su od suštinskog značaja u sprečavanju trajnog oštećenja srčanog mišića i postizanju najboljih mogućih ishoda za bolesnika.

Ključne reči: *tahikardijom indukovana kardiomiopatija, atrijalna fibrilacija, elektrokonverzija, ejekciona frakcija*

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