СРПСКИ АРХИВ
ЗА ЦЕЛОКУПНО ЛЕКАРСТВО
SERBIAN ARCHIVES
OF MEDICINE

Address: 1 Kraljice Natalije Street, Belgrade 11000, Serbia
☏ +381 11 4092 776, Fax: +381 11 3348 653
E-mail: office@srpskiarhiv.rs, Web address: www.srpskiarhiv.rs

Paper Accepted*

ISSN Online 2406-0895

Case Report / Приказ болесника

Marina Ostojić[1,♣], Jelena Simić[1], Rada Mišković[2,3], Olga Petrović[1,2], Ivana Nedeljković[1,2]

Kounis syndrome as a cause of acute coronary syndrome

Кунисов синдром као узрочник акутног коронарног синдрома

[1]University Clinical Center of Serbia, Cardiology Clinic, Belgrade, Serbia;
[2]University of Belgrade, Faculty of Medicine, Belgrade, Serbia;
[3]University Clinical Center of Serbia, Allergology and Immunology Clinic, Belgrade, Serbia

Received: July 6, 2023
Revised: February 5, 2024
Accepted: February 12, 2024
Online First: February 23, 2024
DOI: https://doi.org/10.2298/SARH230706018O

♣Correspondence to:
Marina OSTOJIĆ
Cardiology Clinic, University Clinical Center of Serbia, Koste Todorovića 8, 11000 Belgrade, Serbia
E-mail: **drmarinaostojic@gmail.com**

Kounis syndrome as a cause of acute coronary syndrome

Кунисов синдром као узрочник акутног коронарног синдрома

SUMMARY

Introduction Kounis syndrome (KS) represents an acute coronary syndrome (ACS) induced by a hypersensitivity reaction. First described by Kounis and Zavras in 1991, KS today represents an infrequently diagnosed clinical syndrome. Three different KS variants have been defined: type I vasospastic allergic angina, type II allergic myocardial infarction, and type III stent thrombosis.

Outlines of cases This study presents three cases of type II KS causing anaphylactic ACS. In the first case, a 66-year-old female presented with dyspnea, dizziness, and electrocardiography findings suggesting ACS after she was stung by a bee. In the second case, we present a 64-year-old female admitted to the Emergency Department with chest pain after an anaphylactic reaction due to an iodine contrast injection used for a thoracic computed tomography scan. In the third case, an 80-year-old female presented with chest pain, palpitation, and skin rash shortly after administration of the intravenous anesthetic Propofol during elective malignant colon tumor surgical intervention. All patients were treated at the Cardiology Clinic, University Clinical Center of Serbia.

Conclusion The primary mechanism of KS corresponds to the release of inflammatory mediators during a hypersensitivity reaction triggered by different sources. Although well known, constant reminders of this cause of ACS are needed.

Keywords: acute coronary syndrome; hypersensitivity reaction; anaphylaxis; Kounis syndrome

САЖЕТАК

Увод Кунисов синдром (КС) представља акутни коронарни синдром (АКС) изазван реакцијом преосетљивости. Описан по први пут 1991. год. од стране Куниса и Завраса, данас КС представља ретко дијагностикован клинички синдром. Описне су три различите варијанте КС: тип I, вазоспастична алергијска ангина, тип II, алергијски инфаркт миокарда и тип III, тромбоза коронарног стента.

Прикази болесникâ У нашој серији приказа болесника, приказана су три различите презентације типа ИИ КС које су довеле до анафилактичког АКС. У првом приказу, 66-годишња жена је добила симптоме у виду диспнеје, несвестице и бола у грудима, након уједа пчеле, уз електрокардиографске промене карактеристичне за АКС. У другом приказу, 64-годишња жена је добила болове у грудима након анафилактичке реакције током употребе јодног контрастног средства у склопу дијагностичке процедуре (компјутеризована томографија грудног коша). У трећем приказу, 80-годишња жена је добила болове у грудима, палпитације и осип по кожи руку и трупа након апликације интравенског анестетика пропофола током елективног хируршког лечења малигне болести дебелог црева. Све болеснице су лечене у Клиници за кардиологију, Универзитетског клиничког центра Србије.

Закључак Основа механизма КС јесте ослобађање медијатора запаљења током хиперсензитивне реакције изазване различитим узрочницима. Иако је овај синдром прихваћен као узрочник АКС, неопходно је константно подсећање да треба мислити и на овај механизам настанка исхемије миокарда.

Кључне речи: акутни коронарни синдром; хиперсензитивна реакција; анафилакса; Кунисов синдром

INTRODUCTION

Kounis syndrome (KS) is defined as simultaneously arising acute coronary syndrome (ACS), myocardial infarction, or stent thrombosis in allergic hypersensitivity, anaphylactic, or anaphylactoid reaction settings. The first descriptions of allergic reactions associated with cardiovascular symptoms and signs appeared more than seven decades ago [1]. However, Kounis and Zavras 1991 first described “allergic myocardial infarction” caused by mast cell activation following allergic reactions [2]. The lifetime prevalence of allergy and anaphylaxis is increasing, with an estimated lifetime risk of 0.02-2.0%, with more KS reports in the

literature. Most data are sparse and based on isolated clinical cases and series, while exact pathophysiological mechanisms remain unclear [3–7].

Many inflammatory cells are activated during the allergic reaction, releasing their subsequent preformed mediators in circulation, leading to an inflammatory vicious cycle [8]. The entire arterial system seems vulnerable, and besides the coronary arteries, there have been reports of mesenteric and cerebral arteries affection [6-8].

Since its first description, three different variants of KS have been defined: type I vasospastic allergic angina (without coronary disease), type II allergic myocardial infarction (with prior coronary disease), and type III stent thrombosis (after percutaneous intervention) [3]. It was reported in every age group, race, and diverse geographic location. The treatment strategy for this syndrome may be particularly challenging due to simultaneous cardiac dysfunction and allergic reactions.

We present three cases of anaphylactic ACS treated in the University Clinical Center of Serbia from 2019 to 2021.

Case No. 1

A 66-year-old female presented to the Emergency Department (ED) after being stung by a bee while sitting in her yard. Shortly after the bite, she developed dyspnea, palpitation, and dizziness. Her medical history includes hypertension, type II diabetes mellitus, hyperlipidemia, and sideropenic anemia.

Emergency medical services found her in hemodynamic compromise. She was administered intravenous Epinephrine, Methylprednisolone, and Chloropyramine, which led to clinical improvement, and sent to ED for further evaluation. Serum tryptase level 3 hours after the event was 19.8 ng/mL (normal value < 11 ng/ml).

The initial electrocardiogram (ECG) demonstrated ST - elevations in the aVR, and V1 leads with ST - depression in D1, D2, aVL, aVF, and V4-V6 leads with right bundle branch block pattern (Figure 1). The patient was admitted to the Coronary Care Unit (CCU), where she was hemodynamically stable with a slightly lower level of arterial pressure (100/60 mmHg). Her high-sensitive troponin T (hsTn T) was elevated at 289 ng/L (normal value < 14 ng/L). The patient was treated with corticosteroids, antihistamines, and protocol for ACS with dual antiplatelet therapy, Acetylsalicylic acid 100 mg and Clopidogrel 75 mg, with a beta-blocking agent (Bisoprolol 2.5 mg). During the first days of treatment, she did not experience

chest pain or heart failure. Transthoracic echocardiography showed mild aortic stenosis with hypokinesis of inferobasal septum and inferior wall, altered left ventricular systolic function (ejection fraction (EF) 45%), and mild ischemic mitral insufficiency.

Coronary angiography showed triple vessel disease with left main stenosis 50-70%, proximal left anterior descending artery (LAD) stenosis 50-70% and medial LAD stenosis 50-70%, ostial circumflex artery (Cx) stenosis 50-70%, medial right coronary artery (RCA) stenosis 50-70% with distal occlusion (Figure 2). After initial cardiology treatment and recovery, she was transferred to the Clinic for Cardio surgery, where she underwent myocardial revascularization.

Case No. 2

A 64-year-old female presented to the ED with chest pain after an anaphylactic reaction due to an iodine contrast injection used for a thoracic multislice computed tomography. She was regularly followed up after breast cancer, treated surgically and with chemotherapy nine years ago. Her personal history included hypothyroidism. Her medication included Capecitabine and Acetylsalicylic acid. She was a smoker and had a family history of cardiovascular disease.

Immediately after the intravenous application of the Iopromide contrast injection, she experienced dizziness, skin rash, and chest pain. The operating radiologist and Emergency medical services administered Adrenaline, Methylprednisolone, and Chloropyramine without improving symptoms. She was transferred to ED with ongoing dizziness, generalized urticaria, chest pain, and hypotension 90/60 mmHg.

An ECG showed sinus rhythm and signs of myocardial injury with a negative T wave in an anterior and inferior wall with ST-segment elevation of 1 mm in aVF with typical angina chest pain (Figure 3). Due to clinical deterioration with hypotension and electrical findings of ACS, she was admitted to the CCU.

Laboratory tests showed the following: serum hs Tn T 381 ng/L (normal value < 14 ng/L); creatine kinase 137 U/L; serum glucose 29 mmol/L and no abnormalities in electrolytes, renal function, and routine blood tests. At the time of hospitalization, analysis of blood tryptase was not available. Methylprednisolone, Chloropyramine, and dual antiplatelet treatment (Acetylsalicylic acid 100 mg, Clopidogrel 75 mg with Enoxaparinum 2x0.6 ml s.c.) were given. During the next hospital day, our patient's symptoms gradually improved with the maintenance of ECG changes.

Transthoracic echocardiography showed hypokinesis of the medial and apical septum and anterior wall with reduced left ventricular systolic function (EF 40%) and minor ischemic mitral insufficiency. Coronary angiography was postponed due to a hypersensitivity reaction to iodine contrast, withdrawal of symptoms, and stabilization of vital signs. During the further hospital stay, the patient did not have chest pain nor signs and symptoms of heart failure, with normalization of troponin level. She was discharged stable after seven days.

After four weeks, at the Allergy and Immunology Clinic, drug provocation tests with alternative iodine contrast (Ioversol) were performed and were negative. The patient was allowed to use the tested iodine contrast with a corresponding premedication. Following an allergological examination, elective coronary angiography was scheduled. Due to the COVID-19 pandemic, an invasive examination was postponed due to the patient's stable status. A year after the event, selective coronary angiography was scheduled. An angiogram showed a two-vessel disease with stenosis of proximal LAD 80-90% and medial RCA 70-90%. The percutaneous coronary intervention of proximal LAD and medial RCA with implantation of two drug-eluting stents was performed.

Case No. 3

An 80-year-old female with known hypertension, type II diabetes mellitus, hyperlipidemia, and chronic obstructive pulmonary disease presented to ED with chest pain, palpitation, and skin rash, which developed shortly after administration of intravenous anesthetic Propofol during the elective surgical intervention of malignant colon tumor. Shortly after administration of the drug, the patient was hypotensive (90/60 mmHg). The anesthesiologist administered her Methylprednisolone and Chloropyramine. The ECG demonstrated a new left bundle branch pattern (Figure 4). The intervention was canceled, and the patient was transferred to ED and further to the CCU with normal arterial pressure without ACS symptoms. Her hs Tn T was elevated at 96 ng/l, and the patient received dual antiplatelet therapy with low molecular heparin, antihistaminic, and corticosteroids. At the time of hospitalization, analysis of blood tryptase was not available. On the second day of hospitalization, her ECG returned to the prior normal recording (Figure 5).

Transthoracic echocardiography showed a standard dimension of the left ventricle without regional wall motion abnormalities and with borderline systolic function (EF 50%) and minor mitral insufficiency. The patient had no previous history of allergy reactions. Furthermore, until this operation, she had no interventions with total anesthesia.

Coronary angiography was performed. One vessel disease with proximal LAD stenosis of 50% and medial sub-occlusion of LAD 90-99% was fined. After multidisciplinary team consultation, she was transferred to the Clinic for Cardio surgery and underwent myocardial revascularization with the left internal mammary artery on LAD. Previously, allergologic testing for sensitivity to other anesthetics was made. After a short recovery period, she underwent a successful operation on a colon tumor.

We confirm that we have read the journal's position on issues involving ethical publication and affirm that this work is consistent with those guidelines. Written consent to publish all shown material was obtained from patient.

DISCUSSION

KS is induced by the activation of mast cells and platelets, interacting with inflammatory cells, such as macrophages and T-lymphocytes, leading to a discharge of inflammatory mediators, like histamine, platelet-activating factor, arachidonic acid products, and various cytokines and chemokines during the allergic activation course [8].

Our cases support KS as a recognizable phenomenon by showing three forms of type II KS with myocardial infarction after exposition to different allergens. Iodine contrast, bee sting, and intravenous anesthetic lead to the development of allergic myocardial infarction. Our patients had different ECG changes, all with elevated hs Tn T at the initial presentation.

Furthermore, in Case 1, the patient had no chest pain or typical skin rash known to be an allergic reaction following a bee sting. Without knowing of insect bites, KS would not have been considered. In Case 2, multiple exposures to iodine contrast led to the development of KS with consequence obstacles in further cardiovascular diagnosis and treatment. Also, in Case 3, there were only transient ECG changes and a few symptoms.

This unique disease should be thought of when allergic symptoms, electrocardiographic changes, and elevated cardiac enzymes accompany acute onset chest pain. All patients referred to ED with chest pain and ST -elevation on ECG should be interrogated for allergic events. Also, every patient with an allergic reaction in the ED should have an ECG recording.

Dealing with both cardiac and allergic symptoms simultaneously makes treating KS challenging. Treatment with corticosteroids and antihistamines alleviates symptoms in patients with type I KS. For hypersensitivity-induced vasospasm, drugs of choice are vasodilators, such as calcium channel blockers [9]. Along with type II and type III KS, all standard protocols for

ACS should be applied [10.11]. In contrast, the use of Morphine and other drugs are known to have histamine-liberating properties should be avoided due to the potential of aggravating histamine-induced vasospasm, while Epinephrine use must be done with caution due to its potentially vasospastic effect on coronary arteries [11].

Mast cells in allergic reactions interact with macrophages and T-lymphocytes. These cells produce and store secretory granules, released when specific antigens react with IgE antibodies attached to them, inducing degranulation (realizing histamine, leukotrienes, proteases, chymase, and many more mediators) [10]. This process occurs only in around 10% of atopic individuals. All these pre-formed and newly synthesized inflammatory mediators released locally and running into systemic circulation can cause either coronary artery spasm, which could progress to acute myocardial damage, or coronary plaque erosion or thrombosis, which establishes the main clinical manifestations of KS [11, 12, 13].

KS is doubtlessly a common disease. So far, many case reports support its presence, but knowledge about the pathophysiology still needs to be improved. More studies are required to enhance proper diagnostics and treatment strategies. Correct and prompt treatment is necessary to improve patient prognosis and outcome. In addition to cardiological evaluation and treatment, it is essential to conduct an adequate allergological examination to identify potential disease triggers. We emphasize the importance of ECG in allergic reactions and vice versa, consideration of allergic episodes in patients with ACS.

ACKNOWLEDGMENTS:

The Ministry of Science, Education and Technological Development of the Republic of Serbia (Project No. 41022) supported this case with technical support (equipment and materials).

Conflicts of interest: None declared.

REFERENCES

1. Pfister CW, Plice SG. Acute myocardial infarction during a prolonged allergic reaction to penicillin. Am Heart J. 1950 Dec;40(6):945-7. doi: 10.1016/0002-8703(50)90191-8. PMID: 14789736.
2. Kounis NG, Zavras GM. Histamine-induced coronary artery spasm: the concept of allergic angina. Br J Clin Pract. 1991 Summer; 45 (2): 121- 8. PMID: 1793697.
3. Rajha E, Didi A, Dakik H, Mufarrij A. Acute ST Elevation Myocardial Infarction Due to Allergic Reaction, Kounis Syndrome. Am J Emerg Med. 2020 Feb;38(2):409.e5-409.e7. doi: 10.1016/j.ajem.2019.10.006. Epub 2019 Nov 16. PMID: 31785976.
4. Ollo-Morales P, Gutierrez-Niso M, De-la-Viuda-Camino E, Ruiz-de-Galarreta-Beristain M, Osaba-Ruiz-de-Alegria I, Martel-Martin C. Drug-Induced Kounis Syndrome: Latest Novelties. Curr Treat Options Allergy. 2023 May 30:1-18. Doi: 10.1007/s40521-023-00342-9. Epub ahead of print. PMID: 37361641; PMCID: PMC10227395.
5. Lin WJ, Zhang YQ, Fei Z, Liu DD, Zhou XH. Kounis syndrome caused by bee sting: a case report and literature review. Cardiovasc J Afr. 2023 Sep-Oct 23;34(4):256-259. doi: 10.5830/CVJA-2022-042. Epub 2022 Aug 29. PMID: 36044199.
6. Clemen B, Nwosu I, Chukwuka N, Cordeiro NL, Ibeson E, Gulati A, Ayzenberg S, Weindorf B. Recognizing Kounis Syndrome: A Report of Type 2 Kounis Syndrome and a Brief Review of Management. Cureus. 2021 Nov 18;13(11):e19712. doi: 10.7759/cureus.19712. PMID: 34934576; PMCID: PMC8684398.
7. Poggiali E, Benedetti I, Vertemati V, Rossi L, Monello A, Giovini M, Magnacavallo A, Vercelli A. Kounis syndrome: from an unexpected case in the Emergency Room to a review of the literature. Acta Biomed. 2022 Mar 14;93(1):e2022002. doi: 10.23750/abm.v93i1.11862. PMID: 35315408; PMCID: PMC8972874.
8. Kounis NG. Kounis syndrome: an update on epidemiology, pathogenesis, diagnosis and therapeutic management. Clin Chem Lab Med. 2016 Oct 1;54(10):1545-59. doi: 10.1515/cclm-2016-0010. PMID: 26966931.
9. Castro Jiménez A, Olivencia Peña L, García García R, Florido López F, Torres Sánchez E, Molina Navarro E. Therapeutic management in Kounis syndrome: allergen immunotherapy adjuvant to antithrombotic therapy. Emergencias. 2021 Jun;33(3):247-248. English, Spanish. PMID: 33978348.
10. Wilkerson RG. Drug Hypersensitivity Reactions. Immunol Allergy Clin North Am. 2023 Aug;43(3):473-489. doi: 10.1016/j.iac.2022.10.005. PMID: 37394254.
11. Cuevas-Bravo C, Juaréz-Guerrero A, Noguerado-Mellado B, Pérez-Ezquerra PR, Tornero-Molina P. Kounis syndrome: A case series. Ann Allergy Asthma Immunol. 2022 Aug;129(2):252-253. doi: 10.1016/j.anai.2022.05.021. Epub 2022 May 24. PMID: 35623584.
12. Jolobe OMP. Kounis syndrome and anaphylaxis. Am J Emerg Med. 2022 Jun;56:264. doi: 10.1016/j.ajem.2021.07.001. Epub 2021 Jul 7. PMID: 34247876.
13. Zisa G, Panero A, Re A, Mennuni MG, Patti G, Pirisi M. Kounis syndrome: an underestimated emergency. Eur Ann Allergy Clin Immunol. 2023 Nov;55(6):294-302. doi: 10.23822/EurAnnACI.1764-1489.260. Epub 2022 Jul 18. PMID: 35850501.

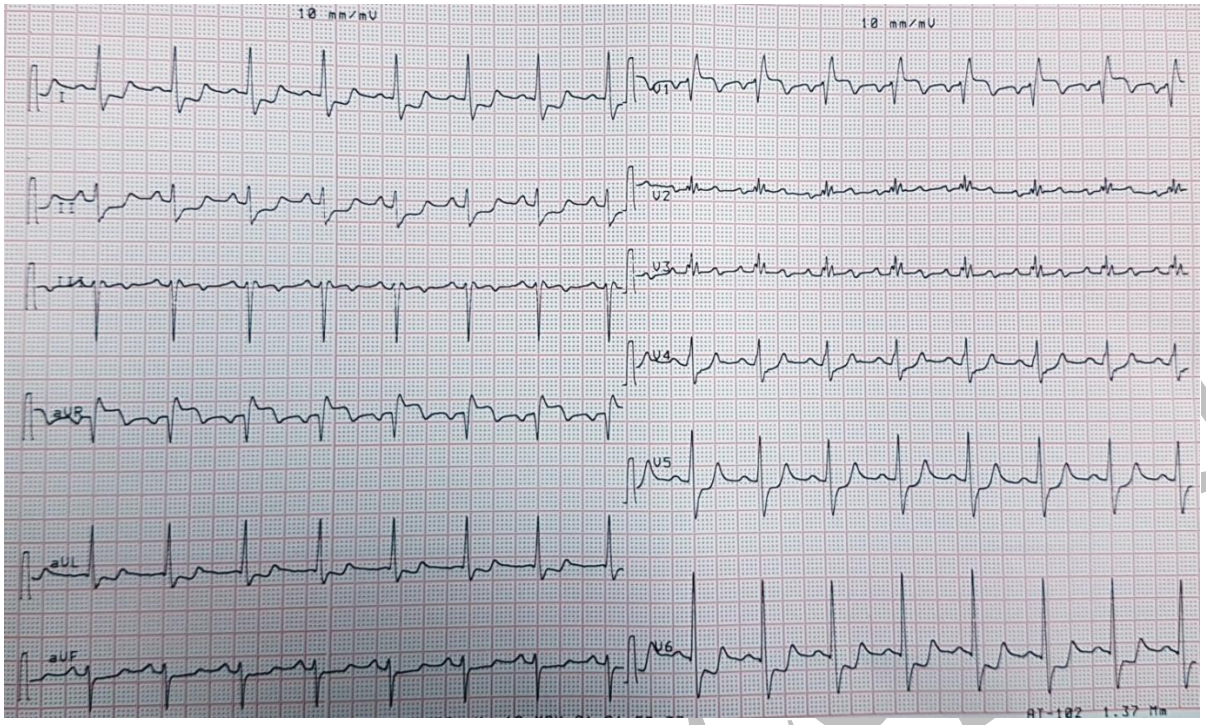

Figure 1. Electrocardiogram at the Emergency Department

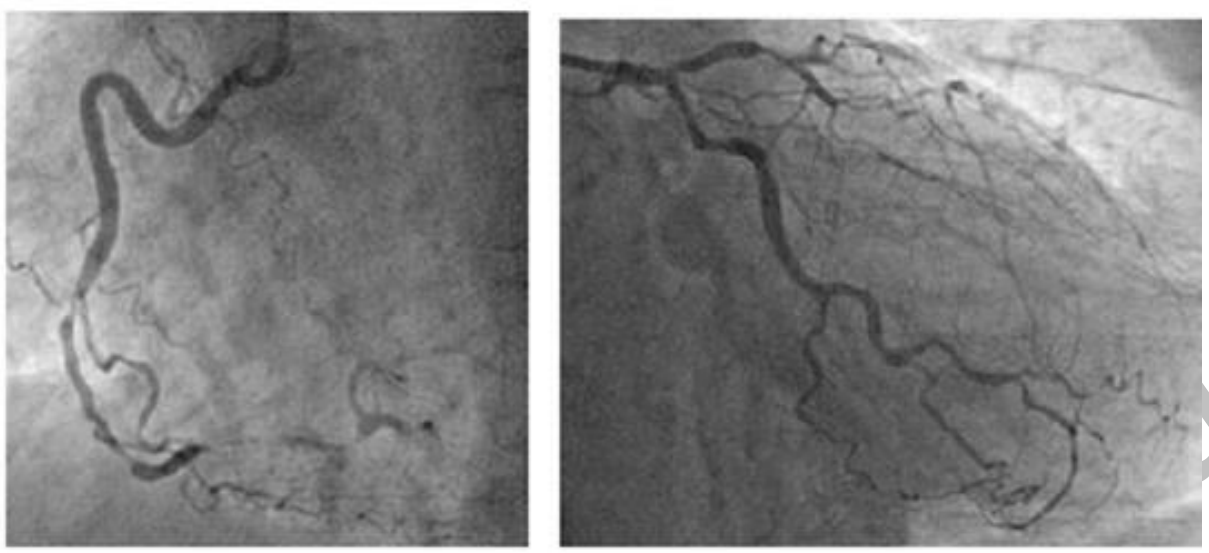

Figure 2. Coronary angiography: triple vessel disease

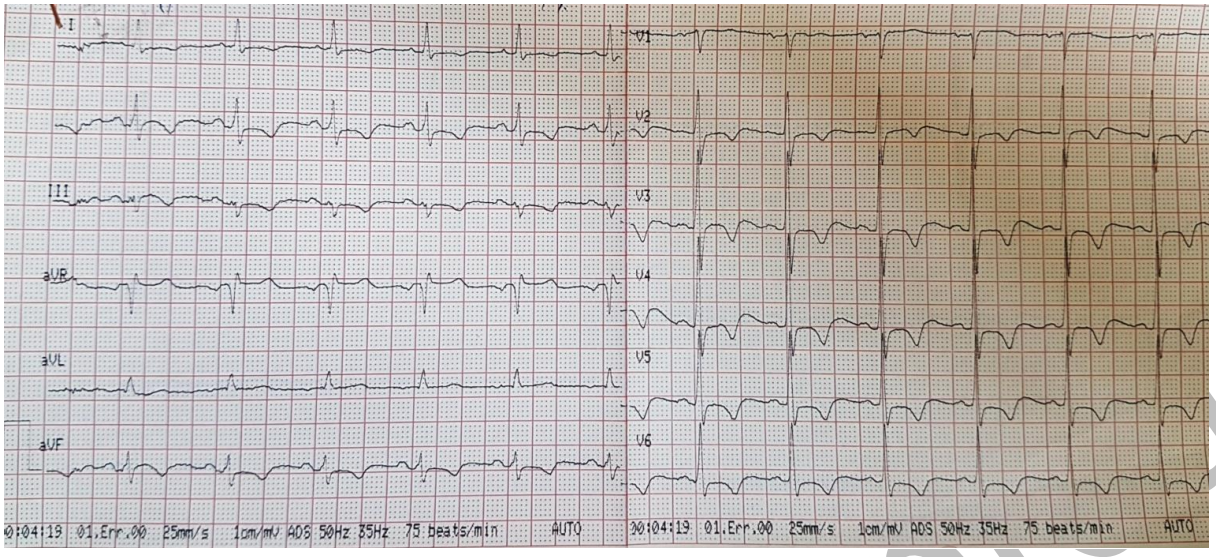

Figure 3. The patient's initial electrocardiogram showed negative T wave in the anterior and inferior wall with ST depression in aVR

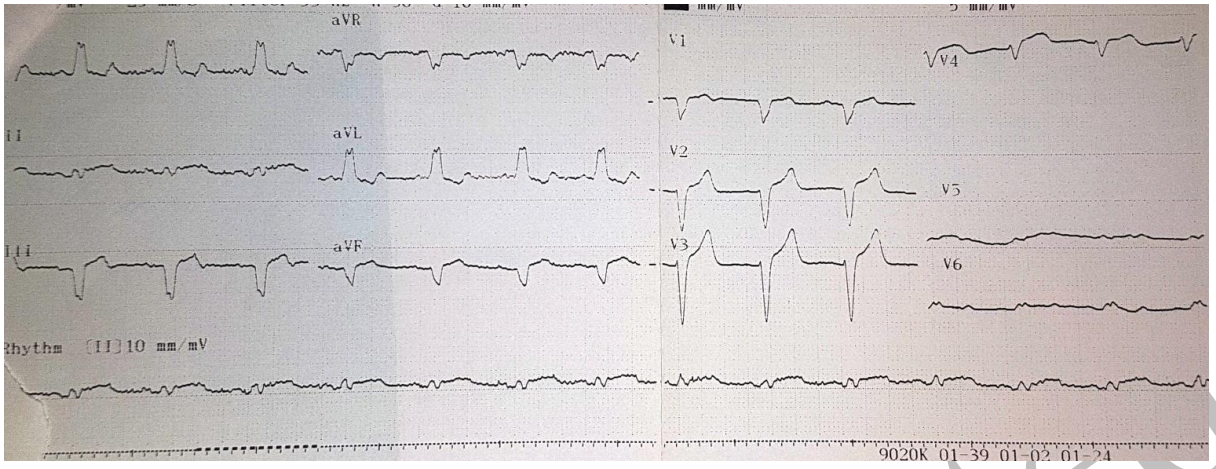

Figure 4. Electrocardiogram after administration of anesthetic shoving left bundle branch block pattern

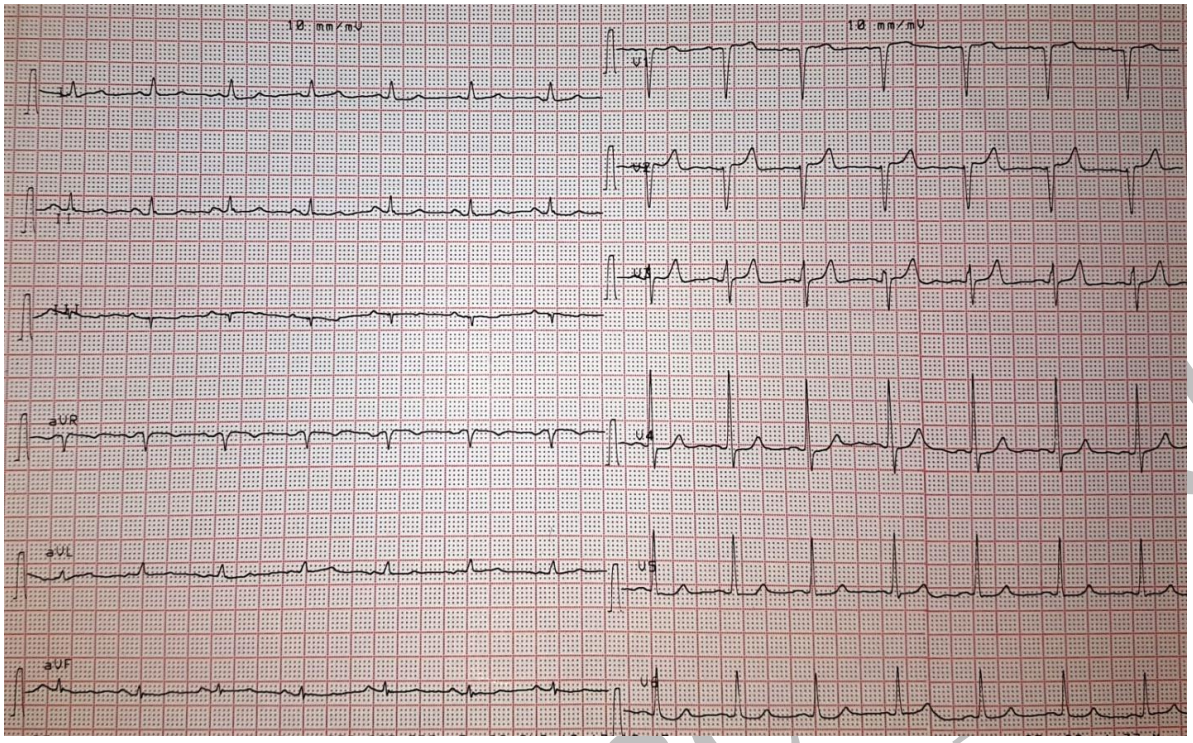

Figure 5. Electrocardiogram on second hospital day, same as preoperative findings

