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Case report

Coronary sinus atresia in a pediatric case: Review of literature

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ABSTRACT

Introduction: Coronary sinus (CS) is the venous drainage system of the heart. Absence of the CS or CS ostium atresia is rarely seen cardiac malformations. Congenital absence of CS usually is found together with other cardiac malformations.
Case: A one day old newborn was referred to our hospital for cyanosis. His saturation was 84% patient was referred to cardiology unit. In echocardiographic examination hypoplastic left heart syndrome was revealed. Prostoglandin infusion was started, catheterization was planned for ductal stent implantation. Catheterization revealed the presence of persistent left superior vena cava (LSVC). When radiocontrast was given to LSVC, it drained to the CS. However CS did not drain to right atrium at normal anatomy. Coronary sinus drained to the base of right atrium, where right superior vena cava opened, via a tunnel shaped vein (shown by arrow and schematically in Fig. 1).
Discussion: Absence of coronary sinus is an extremely rare condition, and in patients with other congenital cardiac malformations. Such malformations can be managed surgically or percutaneously. But either method may disrupt coronary venous drainage therefore it should be paid great attention to the anatomy before doing these procedures. Also it is important to inform the cardiac surgeons before the operation of associated cardiac lesions.
Conclusion: Coronary sinus atresia is a rare condition that should be kept in mind especially in complex heart defects; diagnosis is critical before starting surgical procedure.
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Introduction

Coronary sinus (CS) is the venous drainage system of the heart. Atresia of ostium or total absence of the coronary sinus is a rarely seen cardiac malformation. Congenital absence of CS usually is found together with other cardiac malformations; however, isolated congenital absence of CS is very rare.[1]

Case

A one day old newborn was referred to our hospital for cyanosis. He was born normal spontaneous vaginal way without any complication with good APGAR scores. His body weight was 3400 g. Tachypnea and subcostal retractions were seen in his initial physical examination. Therefore he was taken to intensive care to follow up his respiration. His saturation was 84% and nasal oxygen therapy was started. His chest x ray was normal. After 4–5 h despite the oxygen therapy; there was no change in saturation level. So they asked us for echocardiography and the patient was referred to our hospital. Echocardiographic examination revealed hypoplastic left heart syndrome. Prostaglandin infusion was started; catheterization was planned for ductal stent implantation. Catheterization revealed presence of persistent left superior vena cava (PLSVC). When radio contrast was given to PLSVC, it drained to the CS. However CS did not drain to the right atrium at normal anatomy. Coronary sinus drained to the base of the right atrium, where right superior vena cava opened, via a tunnel shaped vein (shown by arrow and schematically in Fig. 1).

Discussion

Great cardiac vein and Marshall vein unite to form coronary sinus which is located in the posterior atrioventricular groove that takes the venous drainage of the heart.[2]

Absence of coronary sinus is an extremely rare condition, and in patients with other congenital cardiac malformations, the differentiation of absence and atresia of CS may be difficult.[3] It is usually diagnosed in autopsy series. Atresia of coronary sinus may associate some malformations like PLSVC, atrial septal defect, and abnormal pulmonary venous return.[4,5,6]

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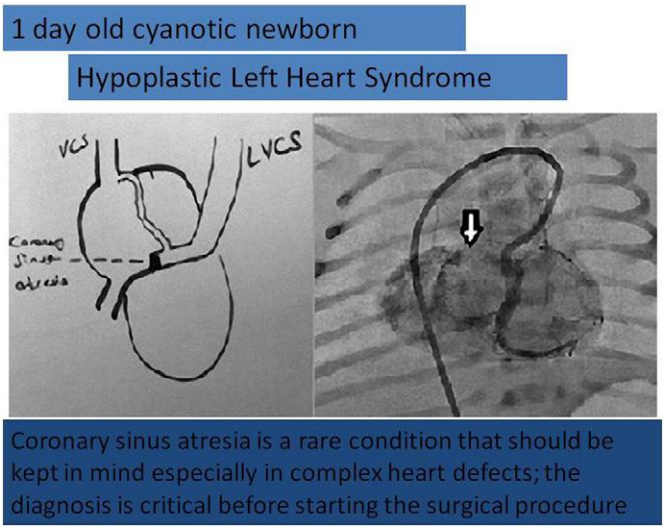


Fig. 1. Coronary sinus drained to the base of right atrium, where right superior vena cava opened, via a tunnel shaped vein (shown by arrow).

Thebesian veins were shown to drain directly into cardiac chambers or caval veins in patients with atresia of the CS ostium or congenital absence of the CS.[3]

Foale et al. reported a case of isolated congenital absence of the coronary sinus, with the left venous system draining into the left atrium via a narrowed great cardiac vein. The right venous system drained into the right atrium.[1] Roa et al. reported a case of complete absence of the coronary sinus, with multiple small fistulae draining into the left ventricle[7]; both cases had no PLSVC.

Yolcu et al. presented two cases of isolated congenital absence of CS without any associated cardiac malformations. Both were 40 years old adults, coincidentally during coronary angiography it was found that their venous system draining directly into the left ventricle through Thebesian veins.[8]

Such malformations can be managed surgical or percutaneous. It was told that PLSVC and coronary fistulae may be occluded by coil embolization. Chen et al. reported a case of coronary atresia with a PLSVC and coronary fistulae. Coronary flow drained simultaneously into the left superior vena cava and right pulmonary artery via an abnormally large coronary fistula. Coronary anatomy was shown with CT imaging. A large fistula was occluded by coil. The patient was free of symptoms after transcatheter coil embolization.[2]

Ohta et al. described the surgical treatment of coronary orifice atresia in an infant with a persistent left superior vena cava after total cavo-pulmonary connection for hypoplastic left heart syndrome. After total cavo-pulmonary connection operation, cardiac performance deteriorated. Catheterization revealed coronary sinus atresia with a persistent left superior vena cava. The coronary sinus was fenestrated to the left atrium by reoperation. The patient survived surgical treatment of coronary sinus ostial atresia unroofed to the left atrium, guiding the placement of the fenestration with a probe placed through the open cardiac end of left superior vena cava.[9]

Coronary venous drainage may be disrupted either by the surgical binding or percutaneous closure. Therefore it should be paid great attention to the anatomy before doing these procedures. It is important to inform the cardiac surgeons before the operation of associated cardiac lesions.[10] Because left SVC is usually ligated or occluded during cardiopulmonary bypass when there is a crossing vein between the left SVC and the right SVC. But it should be avoided if there is no coronary sinus orifice in the atrium.

Conclusion

Coronary sinus atresia is a rare condition that should be kept in mind especially in complex heart defects; the diagnosis is critical before starting the surgical procedure.

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Case report

Hemolytic anemia due to hydrochlorothiazide: A case report

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ABSTRACT

Drug-associated hemolytic anemia is very rare. Hydrochlorothiazides are commonly used as diuretic or antihypertensive agents. In this report, we present an 80-year-old male patient who developed hemolytic anemia 20 days after using a combination of angiotensin receptor blocker and hydrochlorothiazide for the treatment of hypertension.

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Introduction

Autoimmune hemolytic anemia due to drugs is an immunologic condition characterized by the destruction of red blood cells induced by the antibodies that bind to the surface antigens of red blood cell membranes.[1] Hydrochlorothiazides are commonly used diuretic or antihypertensive agents. While immune hemolytic anemia due to hydrochlorothiazide is rare, severe hemolytic anemia cases have been reported. In this study, we aimed to present a patient who had been taking hydrochlorothiazide for the treatment of hypertension and was thought to develop autoimmune hemolytic anemia due to the drug.

Case report

Eighty-year-old male patient admitted to the emergency unit for paleness, icterus of sclera, shortness of breath, weakness, fatigue, and chest pain that started 20 days ago and increased gradually. According to his medical history, he underwent aorto-coronary bypass surgery 15 years ago and had a stent implanted 3 years ago. ECG showed ST depression in derivations V1–V6. Troponin showed a normal level of 0.01 μg/L. The patient was diagnosed with acute coronary syndrome and taken to the coronary intensive care unit where anti-ischemic therapy was started. His hemoglobin (Hb) and hematocrit (Hct) values were 7.5 g/dL (normal range: 13.2–17.4 g/dL) and 21% (normal range: 39–51%), respectively. Of the erythrocyte indices, mean corpuscular volume (MCV) was 100 fL (normal range: 76–96 fL), mean corpuscular hemoglobin (MCH) was 23.6 pg/cells (normal range: 27–33 pg/cells), and mean corpuscular hemoglobin concentration (MCHC) was 27.1 g/dL (normal range: 30–35.5 g/dL). Fragmented normochromic red blood cells and anisocytosis were seen in the peripheral blood smear. Reticulocyte rate was found as 3%. In addition, thrombocyte count was 211×10^3/μL (normal range: $150–450 \times 10^3$/μL). Biochemical parameters were as follows: blood urea nitrogen 90 mg/dL (normal range: 10–50 mg/dL), serum creatinine 1.1 mg/dL (normal range: 0.6–1.2 mg/dL), and serum sodium 136 mmol/L (normal range: 135–145 mmol/L) and potassium 4.8 mmol/L (normal range: 3.5–5.1 mmol/L). Of coagulation tests, prothrombin time (PT) was 13 s (normal range: 11–14 s), the reference range for international normalized ratio (INR) was 1.15 (normal range: 0.8–1.2), and activated partial thromboplastin time (aPTT) was 27.6 s (normal range: 21–36 s).

One unit of red blood cell suspension was given. Hb and Htc levels were increased to 9.6 g/dL and 24.6%, respectively; and then to 10.7 g/dl and 26.8%, respectively, following the administration of a second suspension of red blood cells. Vitamin B12 level was normal, folic acid level was low and ferritin level was high which were 242 pg/mL (normal range: 191–663 pg/mL), 4.5 ng/mL (normal range: 4.6–18.7 ng/mL) and 1080 ng/mL (normal range: 30–400 ng/mL), respectively. Control complete blood count values at day 2 were 8.5 g/dL for Hb and 22.1% for Hct. Consultation was requested from internal medicine department. Occult blood test in the stool was negative. Endoscopy was performed to exclude gastrointestinal bleeding. Thus, active gastrointestinal hemorrhage was excluded. Abdominal ultrasound revealed no intra-abdominal hematoma, mass, or hepatomegaly or splenomegaly. Indirect Coombs test was negative, but direct Coombs was positive as IgG + 2. Lactate dehydrogenase (LDH) was increased to 741 U/L (normal

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range: 240–480 U/L). Haptoglobin was <0.3 g/L (normal range: 0.3–2 g/L). Yes, total bilirubin and direct bilirubin levels were high which were 2.6 mg/dL (normal range: 0–1.2 mg/dL) and 1.1 mg/dL (normal range: 0–0.3 mg/dL), respectively. Urine analysis revealed proteinuria, and (+) bilirubin and (+++) hemoglobin. ANA serum dilution was negative. It was understood from his medical records that hemoglobin and Hct levels were 13.1 g/dL and 38.7%, respectively, 20 days ago. When his medical history was reviewed, it was seen that he was started on daily irbesartan 150 mg plus hydrochlorothiazide 12.5 mg for high blood pressure. The patient was then transferred to internal medicine clinic with the current findings for hemolytic anemia due to thiazide. Then, hydrochlorothiazide was stopped. After that, trandolapril was started for treatment of hypertension. The patient was put on follow-up program with periodic complete blood count analysis. At the end of the next following 2 weeks, a negative Coombs test result and a hemoglobin value of 10.5 g/dL were obtained. During follow-up, the hemoglobin values were 13.1 g/dL and 13.3 g/dL, 1 month later and 3 months later, respectively.

Discussion

Drug-associated hemolytic anemia is seen approximately in one out of a million individual. It may be lethal, possibly with no diagnosis established.[2] It was found out in 2007 that up to 125 different drugs may cause hemolysis.[3] Forty years ago, back when methyldopa and antibiotics like high doses of intravenous penicillin had been used commonly, most of the reported cases of hemolytic anemia were due to the use of these agents. Today, however, cases of hemolytic anemia are rather associated with cephalosporins since methyldopa is almost no more used and second- and third-generation cephalosporins are the leading antibiotics.[4,5]

Hemolytic anemia associated with drugs occurs through one of three basic mechanisms[6–9]: (i) drug absorption mechanism, where antibodies against the drug react with the adsorbed drug on the surface of red blood cell membrane. The antibody–antigen complex that is formed on the surface of red blood cell membrane is removed from the circulation by reticulo-endothelial system, thus resulting in extravascular hemolysis; (ii) immune complex mechanism, in which drug–antibody complex binds to the red blood cell membrane activating the complement cascade; this process leads to acute intravascular hemolysis; and (iii) auto-antibody type, in which antibodies against the drug bind to red blood cell membrane through cross reaction resulting in extravascular hemolysis (Table 2). (See Table 1.)

Anemia associated with hydrochlorothiazide is an example of immune complex-type immune hemolytic anemias. Intravascular hemolysis develops as a result of activation of complement system by the binding of the drug to the red blood cell membrane and may be severe and fatal. Anemia, fragmented red blood cells on peripheral smear, hyperbilirubinemia, increased levels of LDH, reticulocytosis, positive Coombs test, hemoglobinuria and findings related with organ failures may be observed depending on the severity of hemolysis.[5] In our case, an immune event was considered since anemia, weakness and shortness of breath were gradually increased after hydrochlorothiazide was started with the absence of an anemia 20 days ago, accompanied by the fall in hemoglobin values following the administration of red blood cell suspensions and a positive Coombs test. Presence of fragmented red blood cells, hyperbilirubinemia, hemoglobinuria and decreased levels of haptoglobin (<0.3, normal range over the age of 50: 0.47–2.1 g/L) were among findings that demonstrated an intravascular hemolysis in our case.

In practice, Coombs test is used to investigate and diagnose these types of hemolysis. This test is a laboratory method used to identify the presence of incomplete antibodies attached to the red blood cells or circulating freely and is also known as antiglobulin test.[10] Positive direct Coombs test may indicate a hemolysis that develops through an immune complex-type reaction. In our case, polyspecific direct Coombs test IgG was positive and indirect Coombs test was negative.

In 1976, Vila et al.[11] had observed, for the first time, the episodes in a 67-year-old patient whom they treated with a combination of methyldopa and hydrochlorothiazide for hypertension during 4 years and associated the mild to moderate hemolytic anemia with the thiazide fraction of the medication. In 1980, Garratty et al.[12] observed a severe immune hemolytic anemia and renal failure in a 24-year-old black patient who ingested 15–20 tablets of methyldopa plus hydrochlorothiazide to commit suicide. They associated the hemolytic anemia with the antibodies associated with hydrochlorothiazide through immune complex mechanism. In these two cases of intravascular hemolysis, antibodies were developed against hydrochlorothiazide but not against methyldopa. In 1986, Shirey et al.[13] considered hemolytic anemia due to a drug when direct antiglobulin tested positive in a 53-year-old black female. They found similar antibodies against diuretics by characterizing hydrochlorothiazide antibody in serologic studies and offered an alternate diuretic therapy for patients.

Mortality is reported to be 40% when hemolytic anemia associated with drugs is assessed where hemolytic anemia due to ceftriaxones is associated with higher mortality among them.[5] Beck et al.[14] observed a case of hemolytic anemia in a 53-year-old black male patient 18 months after starting hydrochlorothiazide and methyldopa. It was the first case that ended up with death after hemolytic anemia due to hydrochlorothiazide. The patient had a positive direct and indirect Coombs test, a low level of haptoglobin of 0.5 g/dL and a high LDH in whom cause of death could not be established in autopsy but was considered as fatal immune hemolytic anemia associated with the use of hydrochlorothiazide.

Anemia may sometimes immediately be demonstrated by serious clinical findings while the diagnosis may be delayed as long as

Table 1
Laboratory values of the patient.

Day	Hb (g/dL)	Hct %	RBCs 10^6/μL	Total bil. (mg/dL)	Direct bil. (mg/dL)	LDH (U/L)
20 d ago	3.1	38	4.00	0.35	0.35	294
Day 1	7.5	21	2.07	1.54	0.70	322
Day 2	9.6	26.8	2.41			
Day 3	10.7	26.8	2.69			255
Day 4	8.5	22.1	2.18	2.99	1.14	347
Day 5	9.5	24.2	2.40	2.46	741	
3 m later	13.3	40.5	3.87	0.55	0.21	382

Hb: hemoglobin; Htc: hematocrit; RBCs: red blood cells; Bil: bilirubin; LDH: lactate dehydrogenase; d: days; m: months.

Table 2
Mechanism of drugs that cause immune hemolytic anemia.

Mechanism	Drug absorption (Hapten)	Immune complex	Auto-antibody
DAT	Positive anti-IgG	Positive anti-C3	Positive anti-IgG
Location of hemolysis	Extravascular	Intravascular	Extravascular
Drug	Penicillin	Quinidine	Alpha-methyldopa
	Ampicillin	Phanecetin	Mefenamic acid
	Methicillin	Hydrochlorothiazide	L-Dopa
	Carbenicillin	Rifampin	Procainamide
	Cephalothin	Sulfonamide	Ibuprofen
	Cephalordin	Isoniazid	Diclofenac
		Insulin	Interferon Alpha
		Tetracycline	
		Melphalan	
		Acetaminophen	
		Hydralazine	
		Probenecid	
		Chlorpromazine	
		Streptomycin	
		Fluorouracil	
		Sulindac	

DAT: direct antiglobulin test.

1–2 weeks after the intake of the drug in cases without a serious hemolysis, and anemia may be associated with other causes without any established diagnosis.[15] In our patient, a moderate anemia accompanied by a mild increase in LDH levels and positive Coombs test were found 20 days after the intake of the drug since the hemolysis was not severe.

Cessation of the drug in mild cases and steroids plus supportive care in more severe cases are recommended.[16,17] In our patient, the moderate anemia was recovered without any treatment after stopping hydrochlorothiazide.

The diagnosis of hemolytic anemia associated with drugs was established in our patient based on medical history and clinical signs and symptoms. Presence of fragmented red blood cells and hemoglobinuria suggested an intravascular hemolysis.

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Case report

Intermittent intravenous administration of Iloprost in patients with idiopathic pulmonary arterial hypertension

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ABSTRACT

Background and objectives: Because there is no cure for idiopathic pulmonary artery hypertension (IPAH), improving survival and stabilizing disease are key aims in any treatment strategy for patients with IPAH. Intravenous (IV) administration of prostacyclin positively affects the symptoms and hemodynamic of patients with IPAH.

This study sought to assess the efficacy of cyclic Iloprost administration in Iranian patients with IPAH.

Materials and methods: This longitudinal study was conducted on 20 patients with IPAH. Upon hospitalization, the patients received intermittent IV administration of Iloprost 6 hours a day for 5 days; this cycle was repeated every 6 weeks, total duration of treatment was 12 months. New York Heart Association/World Health Organization (NYHA/WHO) functional classification (FC), 6-minute walk test (6MWT), mean pulmonary arterial pressure (PAPm), right ventricular pressure (RVP), and serum level of N-terminal pro b-type natriuretic peptide (NT-proBNP) were assessed at baseline, during and after completion of treatment course. The data were analyzed using SPSS version 13.

Results: The FC, PAPm, and RVP significantly decreased after the treatment ($P < 0.001$). No change occurred in the level of oxygen saturation during the 6MWT but the distance walked significantly increased after the intervention compared to baseline. Level of NT-proBNP significantly decreased in patients after treatment ($P = 0.009$).

Conclusion: Intermittent IV administration of Iloprost decreases the FC, PAPm, RVP, and serum level of NT-proBNP and increases the distance walked in the 6MWT by patients.

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Introduction

Pulmonary hypertension (PH) refers to an increase in mean pulmonary arterial pressure (PAPm) ≥ 25 mmHg as assessed by right heart catheterization (RHC).[1] This condition can be idiopathic, congenital, or acquired, related to diseases and conditions such as connective tissue diseases, congenital heart disease, portal hypertension, AIDS, and some toxins and medications such as appetite suppressing drugs; PAH does not have a good prognosis.[2–4] Idiopathic pulmonary artery hypertension is a rare disorder with an unknown etiology, in which occlusion of small pulmonary arteries increases the PAPm and results in secondary right ventricular insufficiency.[5] The prevalence of PAH in the United States varies from 4.5 to 12.3 per 100,000 population.[1] In Europe, its prevalence has been reported to be 15–60 patients per one million individuals.[6–7] In the UK, the prevalence of PAH is 97 per one million.[1] The prevalence of PAH is 15 per one million, and the prevalence of IPAH is 5.9 per one million population in France.[8] Approximately 50% of PAH patients in all registries suffer from IPAH, heritable PAH, or drug-induced PAH.[1] Thus, it can be estimated that among the 77-million population of Iran, 150 subjects develop PAH annually.[1] Considering the survival rate of 1–2 years (without treatment), approximately 400–450 patients in Iran suffer from IPAH. The statistics of patients registered in the referral centers are close to this value taking into account some related factors. Before the development of new medications, the mean survival rate of patients with PAH was less than 3 years.[2]

Medications such as oxygen, calcium channel blockers, warfarin, digoxin, and diuretics have long been used for these patients as part of conventional therapy. These medications are selected based on the current treatment protocols for chronic cardiac and respiratory diseases and based on the pathophysiological mechanism proposed for the left heart congestive failure, hypoxia in patients with obstructive pulmonary diseases, and systemic hypertension and are referred to as symptomatic treatment.[5] Calcium channel blockers (CCB) must be prescribed only for patients with a positive response to vasodilator test; these patients

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require precise follow-up and may need some specific treatments.[6,9] Medications recently recommended for these patients include endothelin receptor antagonists (ERAs), soluble guanylate cyclase stimulators such as riociguat, phosphodiesterase type 5 inhibitors (PDE-5I) such as sildenafil, and prostanoids such as epoprostenol and Iloprost.[10–11]

In patients with positive vasodilator test, who are categorized as low-risk group based on clinical examinations, CCB is the first choice of treatment. If CCB do not improve the patient's condition, specific treatment with oral ERAs such as bosentan or PDE-5Is such as sildenafil may be started. For low-risk patients with a negative vasodilator test, treatment with one of the specific medications is started.[1] For high-risk patients with a negative test, continuous treatment with IV prostacyclin can be effective; in such cases, epoprostenol, treprostinil, or Iloprost is the first choice of treatment.[12]

Prostacyclin (PGI2) is a strong vasodilator, which prevents the proliferation of endothelial smooth muscle cells; however, the synthesis of prostacyclin decreases in IPAH.[11] Evidence shows that administration of IV prostacyclin along with conventional treatments for more than 12 weeks can positively affect exercise capacity, FC, and hemodynamic of cardiovascular patients.[13] Prostacyclin is an important homeostasis regulator and is a strong short-acting prostanoid produced in the vascular endothelium. Iloprost-β-cyclodextrin clathrate, also known as Iloprost, is a synthetic, chemically strong, and stable prostacyclin.[14–15] Iloprost is an analog of epoprostenol, also known as prostacyclin (PGI2), which mimics the pharmaceutical properties of epoprostenol. It prevents platelet aggregation in vessels, causes vascular dilation, and enhances the blood flow through the vessels; thus, it also prevents polycythemia.[14,16] This drug can be administered via three routes of oral, inhalation, and injection.[11]

This drug is most commonly administered intravenously.[16] Intravenous administration of Iloprost requires hospitalization since patients should be monitored for the side effects of the drug during administration such as tachycardia, hypotension,[17] headache, and flushing.[16] Iloprost and epoprostenol are chemically similar with the exception that Iloprost is more stable, readily available, and easier for use at home.[18] Iloprost decreases the resistance of peripheral vessels and the mean arterial pressure while it increases the cardiac index and heart rate. Also, it increases the renal blood flow[19] but has a natriuretic effect and increases the excretion of sodium in urine; however, this is independent of the related hemodynamic changes.[16]The clearance of this drug is 15–20 mL/kg/min and has a half-life of 5–20 min. Most of it (70%) is excreted through the kidneys and 12–17% is excreted via other routes.[15] To obtain an effective plasma level, it must be continuously infused in an amount of 1–2 ng/kg/min.[19] By introduction of new medications such as epoprostenol and Iloprost, 1-year and 3-year survival rates of patients increased by 68–88%.[20]

Iloprost is administered in IPAH patients in two forms of continuous[21] and intermittent or cyclic infusion.[12] Continuous infusion requires adequate vascular access obtained by insertion of a permanent catheter in the subclavian vein and the drug is delivered to the patient by CADD1 infusion pumps. The drug is administered with the initial infusion rate of 0.5 ng/kg/min, which is gradually increased as long as no unbearable side effects occur. After hospital discharge, patients are visited in an outpatient setting every 6–12 weeks. In case of satisfactory clinical outcomes (based on the opinions of the attending physician and patients), the drug dosage does not change. In case of no change or aggravation of disease, the drug dosage increases unless unbearable side effects occur. Each patient visit must include history taking, physical examination, and 6MWT along with functional assessment using FC.[22] In intermittent or cyclic infusion, Iloprost is administered for five consecutive days for 6 hours a day. This cycle is repeated every 6 weeks. The initial infusion rate is 0.5 ng/kg/min, which later increases to 2 ng/kg/min.[9,12]

Following the initiation of treatment, its outcome must be evaluated in patients. Several tools are available for outcome assessment in IPAH patients such as echocardiography, assessment of hemodynamic parameters,[23] 6MWT,[24] biochemical markers such as serum uric acid,[25–26] FC,[27] and NT-proBNP.[28] Echocardiography is a noninvasive method suitable for primary and outcome assessments of treatment in these patients. This modality provides valuable information about the hemodynamic status of the right heart such as PAPm, status of the right and left ventricles, and atriums.[29–31] The 6MWT is affordable, simple, reproducible, standard, and objective[24] and has been introduced as the gold standard for the assessment of the treatment outcome in PAH patients by the European Agency for Evaluation of Medicinal Products and the Food and Drug Administration.[32–33] The 6MWT is the most important criterion for assessment of treatment outcome and severity of disease in patients in the clinical setting and in clinical trials for research purposes.[34] The level of NT-proBNP increases in IPAH patients by a reduction in the right ventricular function.[35] Studies show that in patients with PAH, the level of NT-proBNP is correlated to the functional[28] and hemodynamic[36] status of patients and can be used as a predictor of the survival of patients.[35,37]

Considering the high cost of prostacyclin medications[18] particularly in Iran, patients often cannot afford continuous treatment with this medication. Thus, patients who require IV prostacyclin according to the guidelines can only receive this drug in a cyclic fashion by hospitalization for 5 days per month and repeat this cycle every 6 weeks. No previous study has assessed the outcome and efficacy of cyclic administration of Iloprost in IPAH patients and the available ones have only focused on connective tissue diseases. Therefore, this study sought to assess the outcome and efficacy of cyclic treatment with Iloprost in Iranian patients with IPAH.

Materials and methods

This longitudinal study was conducted during 2011–2013 on patients presenting to Masih Daneshvari Hospital due to mean pulmonary artery pressure (mPAH). Only 20 patients during the above-mentioned time period required treatment with IV Iloprost. The inclusion criteria were definite diagnosis of IPAH based on right ventricular catheterization and the expert opinions of the cardiologists and pulmonologists of Masih Daneshvari Hospital, the need for treatment with IV Iloprost, and willingness for participation in the study. Data were collected using a researcher-designed questionnaire. This questionnaire included demographic information (age, sex, height, and weight of patients and duration of disease), FC, 6MWT (distance walked and drop in O2 saturation), echocardiographic findings (PAPm and RVP), hemodynamics on right ventricular catheterization (PAPm and atrial pressure), and level of NT-proBNP at baseline, in the first 6 weeks, in the second 6 weeks, and in the third 6 weeks of the study. The demographic part of the questionnaire was filled out by interviewing patients and the sections regarding clinical and paraclinical tests were filled out by the research supervisor based on the opinions of cardiologists and pulmonologists of Masih Daneshvari Hospital. The validity and reliability of these clinical and paraclinical tests have been assessed in several studies and the 6MWT is also known as the gold standard for assessment of patients with IPAH.[32,34] These tests are routinely performed for assessment of the course of treatment in IPAH patients hospitalized in Masih Daneshvari Hospital. After explaining the objectives of the study to patients, written informed consent was obtained from them. Patients were informed that they were free to leave at any time and that not participating in this study would not affect their course of treatment. Also, patients were ensured about the confidentiality of their information. Each patient

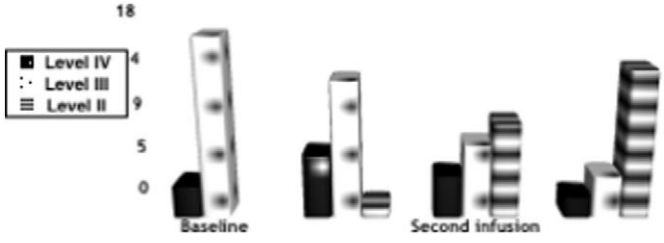


Diagram 1. Changes in the FC of patients following treatment.

Table 1
Demographic factor and base line characteristics.

n	Gender	Age	NYHA class	PAP cath	PAP echo	NT-proBNP	6MWT
1	F	27	III	75	75	760	538
2	F	37	III	80	80	854	423
3	F	30	III	85	90	208	375
4	F	38	IV	100	110	2250	183
5	F	37	III	95	95	1940	247
6	F	45	III	75	80	1264	305
7	F	28	IV	100	110	3280	195
8	F	27	III	90	95	1672	453
9	F	41	III	65	80	960	310
10	F	43	III	95	95	845	341
11	F	35	III	70	80	1250	275
12	F	37	IV	110	110	4783	175
13	F	28	III	65	85	1760	257
14	F	32	IV	110	120	7413	154
15	F	34	III	60	65	1452	196
16	F	31	IV	120	120	5340	60
17	F	34	III	95	90	986	327
18	F	24	III	65	80	705	231
19	F	40	III	85	85	604	510
20	F	32	III	75	80	965	192

presenting to Masih Daneshvari Hospital with PAH was routinely examined and treated. Prior to treatment, the questionnaire was filled out for patients requiring IV Iloprost who gave their written informed consent for participation in this study; IV Iloprost was then administered according to the protocol. The intermittent or cyclic protocol includes IV administration of Iloprost for five consecutive days for 6 hours daily. In this study, after hospitalization, the patients received IV Iloprost 6 hours a day for 5 days and then every 6 weeks after discharge. The initial infusion rate was 0.5 ng/kg/min at first, which was then increased to 2 ng/kg/min. The dose titrated up as long as no unbearable side effects occur within 2 h of Iloprost infusion. All of these patients also received 50 mg sildenafil daily and 125 mg bosentan twice daily during the study period. During the course of treatment, serum level of NT-proBNP was measured at each hospitalization. Echocardiography and FC were assessed. After the third injection, patients performed the 6MWT for assessment of functional capacity. The data were analyzed using SPSS version 13 and repeated-measures ANOVA, Friedman test, and the Pearson's correlation coefficient.

Results

All patients were females with a mean age of 34 ± 5.8 years. The mean height of patients was 160 ± 5 cm, the mean weight was 61 ± 14 kg, and the duration of disease was 3 ± 1 years.

The results of cardiac catheterization showed that the PAPm was 85.75 ± 17 mmHg and the right atrial pressure was 14 ± 3 mmHg before treatment. Before the IV administration of Iloprost, 75% of patients were FC III and 25% were FC IV. While after treatment with IV Iloprost, 70% of patients were FC II, 20% were FC III, and 10% were FC IV. Diagram 1 shows changes in the FC of patients compared to baseline. The Friedman test showed that the FC of patients significantly decreased compared to baseline ($P < 0.001$).

Diagram 1 shows echocardiographic changes in PAPm and RVP of patients. Repeated-measures ANOVA showed that PAPm and RVP of patients significantly decreased in post-treatment echocardiography.

The results also showed that the maximum and minimum distance walked was 538 and 60 m, respectively, in the 6MWT. Table 2 shows the mean and standard deviation of the distance walked in the 6MWT and the reduction in oxygen saturation rate during the test and at the end of study compared to baseline. As seen, no change was noted with regard to reduction in oxygen saturation during the test. However, walked distance at the end of study increased compared to baseline. (See Table 1.) (See Table 3.)

The highest and the lowest levels of NT-proBNP were 7413 pg/mL and 208 pg/mL, respectively, at baseline with a mean value of 1964 ± 1760 pg/mL. At the end of study, level of NT-proBNP increased in 5 patients (25%) and decreased in 15 patients (75%) compared to baseline. Diagram 2 shows the changes in NT-proBNP during the study. Repeated-measures ANOVA showed that the level of NT-proBNP in patients significantly decreased post-treatment ($P = 0.009$).

Discussion

Based on the results, intermittent IV administration of Iloprost effectively decreased FC, PAPm, RVP, and level of NT-proBNP and increased the distance walked in the 6MWT but blood oxygen saturation were not changed. Functional class is among the most important indicators of prognosis in patients with PAH. It has also been used in preliminary studies for assessment of the course of treatment in patients.[27] Higenbottam et al. showed that FC is among the most important predictors of PAH especially in class III and IV patients compared to class I and II subjects who receive Iloprost or epoprostenol for long periods of time.[18] Prior to the initiation of treatment with Iloprost, most patients had FC III and IV. But after intermittent treatment with Iloprost, many patients improved to FC. The PAPm is another predictor of disease status. The results of our study showed that the mean PAPm decreased in patients receiving intermittent IV infusion of Iloprost for long periods of time. Caravita et al. reported that long-term intermittent IV infusion of Iloprost in patients with connective tissue diseases decreased PAPm, inhibited PAH, and prevented the aggravation of disease.[9] Caramaschi et al. evaluated the efficacy of cyclic IV infusion of Iloprost to prevent PAH in patients with systemic sclerosis and reported that cyclic infusion of Iloprost for 15 months prevented PAH in these patients.[12] Bartman et al. showed that cyclic infusion of Iloprost prevented PAH in patients with systemic sclerosis.[38] Niewierowicz et al. in 1995[39] and Bartosik et al. in 1996 evaluated the efficacy of cyclic infusion of Iloprost for treatment of PAH in a number of patients with systemic sclerosis and reported the same results.[40] In all these studies, echocardiography was used to monitor the patients' status and PAPm. In contrast, Higenbottam et al., in their study, stated that the mean PAPm especially in patients receiving prostaglandin was not a suitable predictor of disease status or the course of treatment.[18]

Although the pulmonary vascular resistance[2,41] and the mean pressure of the right atrium are among the most important predictors of disease status and course of treatment in patients with PAH,[27,41] their measurement requires right heart catheterization. In the current study similar to some previous investigations,[9,12,38,40] right heart catheterization was performed for patients at baseline to confirm the diagnosis. To

Table 2
Changes in PAPm and RVP.

Time points	Variable	Baseline		First infusion		Second infusion		Third infusion		Repeated-measures ANOVA
		Mean	Sd	Mean	Sd	Mean	Sd	Mean	Sd	
Echocardiography	*PAPm*	91	25	90	22	85	21	81	22	$P < 0.001$
	RVP	88	26	88	20	84	20	80	22	$P = 0.050$
Catheterization	*PAPm*	85.75	17	–	–	–	–	–	–	

monitor the patients' status, echocardiography and assessment of PAPm were done. Echocardiography is a non-invasive method for primary assessment of the course and outcome of treatment and provides valuable information regarding the hemodynamics of the right heart.[29,31] It should be noted that each diagnostic procedure should be done based on the opinions of the experts and the patient's need. New guidelines on the control and treatment of PAH clearly state that repeat of cardiac catheterization is only allowed if the patient's condition has worsened or a modification has occurred in the type of treatment administered.[1] Since the condition of none of the patients in our study was worsened and there was no need to change the type of drug, repeat of right heart catheterization was not ethical.

In the 6MWT, no change was noted with regard to oxygen saturation rate during the test ($P = 0.244$). However, the distance walked in the 6MWT significantly increased post-treatment compared to baseline ($P < 0.001$). Caravita et al. showed significant increase in the distance walked in the 6MWT after IV infusion of Iloprost.[9]

Although the level of NT-proBNP decreased in only 75% of patients compared to baseline, statistical tests indicated a significant reduction in level of NT-proBNP in patients ($P = 0.009$). Evidence shows that in PAH, level of NT-proBNP is related to the functional status[28] and hemodynamics[36] of patients and it can be used as a predictor of survival of patients.[35,37] The results of studies in this regard indicate that in patients with PAH, the level of NT-proBNP has a strong inverse correlation with right ventricular insufficiency, and the plasma level of NT-proBNP is a predictor of mortality in these patients. The results of previous studies have also shown that patients with NT-proBNP ≥ 150 pg/mL have lower survival rates.[35] In the study by Caravita et al., a significant correlation was noted between PAPm and serum level of NT-proBNP; NT-proBNP and PAPm were also reported to have a significant reverse correlation with the distance walked in the 6MWT.[9]

Conclusion

The results of this study showed that intermittent IV administration of Iloprost in patients with PAH decreased the FC, PAPm, RVP, and level of NT-proBNP and increased the distance walked in the 6MWT. Since the palliative care has not been well addressed in the PAH literature, intermittent IV administration of Iloprost can be as the palliative care in IPAH with FC III and IV.

Limitation

The effect of treatment can not only be explained by the Iloprost, because all of these patients also received sildenafil and bosentan during the study period and ethically we could not stop basic treatment of patients. Also patients were followed only with echocardiography because none of our patient's condition has worsened and no modification has occurred in the type of treatment administered.

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Table 3
Comparison of the results of 6MWT at baseline and at the end of study.

Time Variable	Baseline		End of study		Paired t-test
	Mean	Sd	Mean	Sd	
Distance walked in meters	287	124	351	114	p < 0/001
Reduction in oxygen saturation	7	8	6	4	P = 0/244

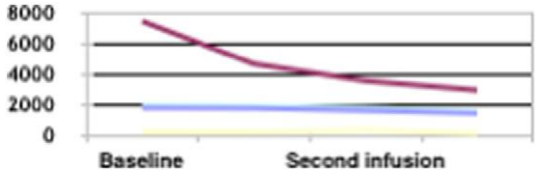


Diagram 2. Changes in the mean level of NT-proBNP following treatment.

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Case report

A rare case: Falsely positive ECG for ASMI in patient with ASD admitted with acute coronary syndrome

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ABSTRACT

Electrocardiogram (ECG) is widely used in the diagnosis of myocardial infarction (MI). It mostly gives important hints to detect the infarct-related artery (IRA). The changes in the morphology and in the position of the heart cause changes in ECG as well. Though ECG is used for the diagnosis of MI, it is not sufficient on its own in detecting the location of the underlying lesion. The pathologies changing the morphology of the heart, such as the atrial septal defect (ASD), increase the margin of error of ECG. We report a rare case; falsely positive ECG for anteroseptal MI in patient with ASD admitted with acute coronary syndrome. Coronary angiography revealed right coronary artery (RCA) lesion in the patient with acute MI who was found to have ST elevation in both precordial and inferior derivations. As a potential cause of mismatch between IRA and infarct location at ECG, echocardiography showed right ventricle dilatation related with cribriform ASD. It was percutaneously closed at 30 days after MI. Therefore, when observed a mismatch between IRA and infarct location at ECG, a detailed examination should be performed to determine potential causes of the mismatch.

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Introduction

ECG is widely used in the diagnosis of MI. It mostly gives important hints to detect the IRA.[1] ST elevation at anteroseptal derivation of ECG (precordial V1–4 leads) is frequently related with mid lesions of left anterior descending artery (LAD). Rarely, mid LAD occlusions cause to ST elevation at inferior derivation in addition to anteroseptal changes when LAD surrounded the apex.[2] The changes in the morphology and in the position of the heart cause changes in ECG as well. A coronary angiography revealed RCA lesion in our patient with acute MI who was found to have ST elevation in both precordial and inferior derivations. Subsequent echocardiography showed us the ASD enlarging the right ventricle which we closed 30 days after the MI. In current literature, it has been reported that non-dominant RCA occlusions may present ST elevation at V1–3 leads.[3] Also, ST-segment elevation in leads V1–4 has been reported during isolated right ventricle MI.[4]

We present an anteroseptal MI pattern related with RCA occlusion in patient with ASD as rare cause of mismatch between ECG and IRA.

Case

The 56-year-old male patient was admitted to the Emergency Department at the 2nd hour of the clamping chest pain. The first ECG revealed a 1 mm ST elevation in V1–4 and D3-AVF (Fig. 1). When the coronary angiography showed a recanalization and thrombosis in severe RCA lesion, stent implantation was performed. The postoperative ECG revealed ST resolution (Fig. 2). Fig. 3 shows the coronary angiography procedure performed. A control angiography was performed upon the presence of chest pain and similar changes in the ECG in the follow-up period. It was seen that the RCA was blocked. Medical intervention was made and TIMI-3 flow was enabled.

The echocardiography revealed 50% election fraction, enlarged right ventricle, 2° tricuspid insufficiency, 35 mmHg pulmonary artery pressure estimated by the tricuspid insufficiency jet, and negative and positive contrast transmission in Qp/Qs = 1.7 subcostal examination (Fig. 4). Transesophageal echocardiography revealed many cribriform type ASD of which the largest was 6 mm. The whole cribriform region was detected to be 20 mm wide. The patient with enlarged right ventricles and a ratio of Qp/Qs = 1.7 underwent the percutaneous ASD closure procedure 30 days after the MI (Fig. 5).

Discussion

Elevation in both inferior and anterior derivations is not common in the patients admitted with acute MI. This may be caused by the LAD lesions surrounding the apex in these patients.[2] In their study on 885

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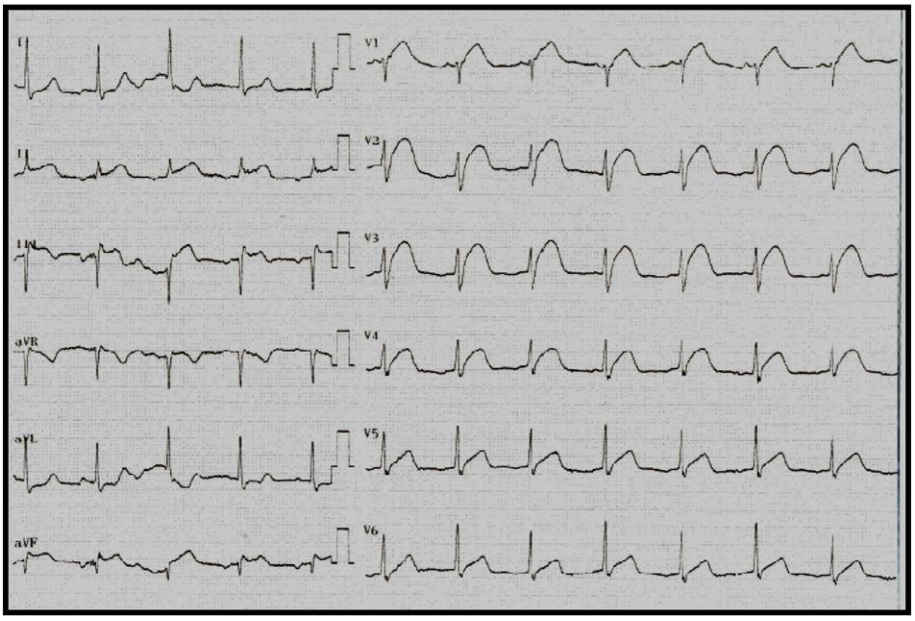


Fig. 1. Electrocardiogram during chest pain. ST in V1–4 and D2–3 aVF.

patients with ST elevation, Taglieri et al. detected ST elevation in anterior and inferior derivations in 8 (1%) patients.[5] In the study by Yip et al., simultaneously ST elevations in precordial and inferior derivations were found in 37 (4%) of 924 acute MI patients. LAD lesions surrounding the apex were detected in 8 (21%) of these 37 patients. This was associated with the high number of coronary artery lesions in other patients.[6] On the other hands, it has been reported that non-dominant RCA occlusions may present ST elevation at V1–3 leads.[3] Also, Kinch and Ryan reported to ST-segment elevation in leads V1–4 during isolated right ventricle MI.[4] Patients suffering from MI with ASD have been reported in the literature.[7] Right-to-left shunt may be seen in the patients with ASD following right ventricular infarction.[8–10] We detected RCA lesion in the patient with ST elevation in anterior and inferior derivations. Anatomical properties of RCA are compatible with right dominance at the coronary supply. The subsequent echocardiography revealed that the right ventricle was enlarged secondarily to cribriform ASD. We postulated that the right ventricle enlarged secondarily to ASD in the patient caused rotation of the heart which, in turn, led to ST elevation in precordial derivations.

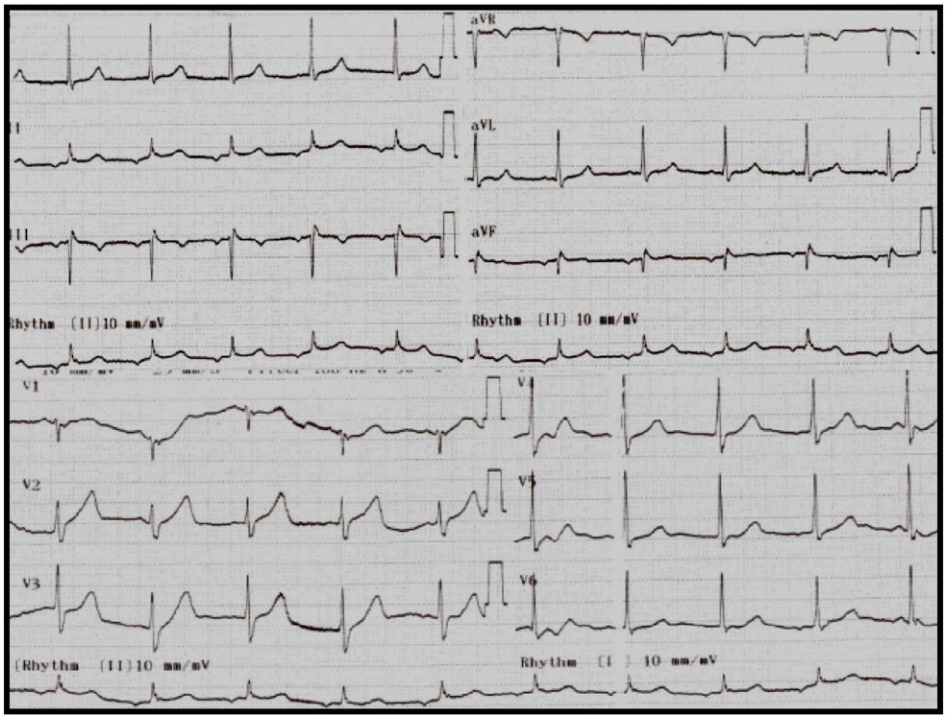


Fig. 2. Electrocardiogram following the stent implantation in the patient's right coronary lesion. ST resolution can be seen in inferior and anterior derivations.

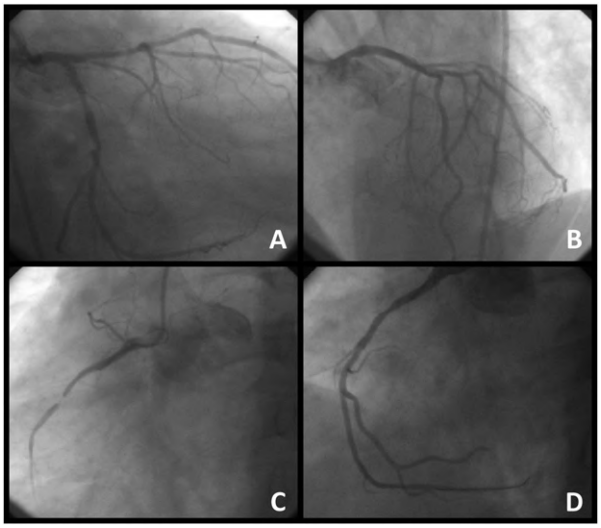


Fig. 3. Coronary angiographic images: A: Right anterior oblique-caudal angle; B: Right anterior oblique-cranial angle; C: Underlying lesion in RCA; D: Angiographic image after stent implantation in RCA.

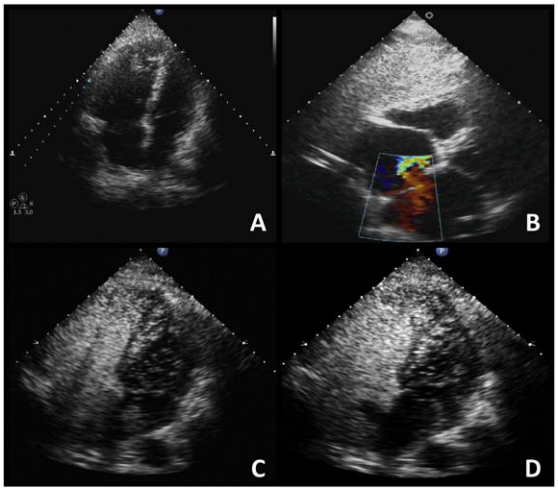


Fig. 4. Echocardiographic images: A: Enlarged right ventricles in parasternal long axis image; B: Color transition with the use of interatrial Doppler in the subcostal examination; C: Positive contrast transition in the contrast examination; D: Negative contrast transition in the contrast examination.

Conclusion

Though ECG is used for the diagnosis of MI and IRA, it is not sufficient on its own in detecting IRA and the location of the underlying lesion. The pathologies changing the morphology of the heart, such as ASD, increase the margin of error of ECG. Hence, a detailed examination should be performed to determine of potential cause of mismatch between IRA and infarct location at ECG.

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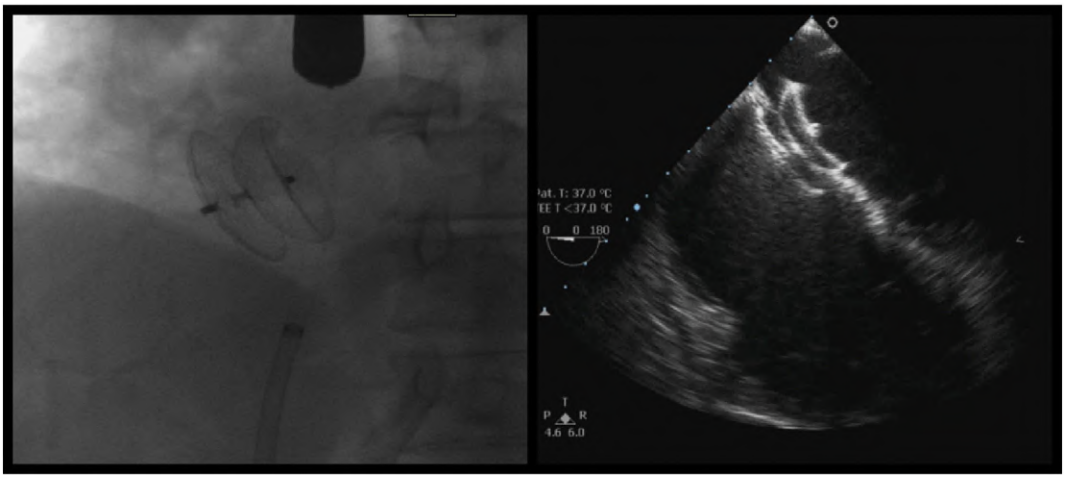


Fig. 5. Amplatz catheter was placed in the interatrial septal defect. Angiographic and TEE images are seen.

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Case report

Rare case of bilateral ductus with confluent pulmonary arteries in case of d-TGA with intact ventricular septum

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ABSTRACT

Bilateral ductus is a very rare abnormality. Here we present a rare case in which ductus was associated with confluent arteries and dextro-Transposition of the Great Arteries. The probable theory of its origin is also discussed with help of Edward's hypothetical double aortic arch system.

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Introduction

Bilateral ductus is a very rare abnormality. It is usually associated with other congenital anomalies. Bilateral ductus is frequently associated with anomalies of pulmonary arteries or arch anomalies. This is a rare case in which ductus was associated with confluent arteries and dextro-Transposition of the Great Arteries. The hypothetical reason of their origin has also been discussed.

Case details

14 day old male child with dextro-Transposition of the Great Arteries (d-TGA), intact ventricular septum was taken for Arterial switch operation. Pre op echocardiography showed dextro-transposition of great arteries with intact ventricular septum and left sided patent ductus arteriosus. Intra-operatively, there was d-TGA with aorta and main pulmonary artery related antero-posteriorly, aorta being anterior to pulmonary artery. There was left aortic arch. Pulmonary arteries were confluent and good sized. Bilateral ductus arteriosus were present. Right ductus was connected to right

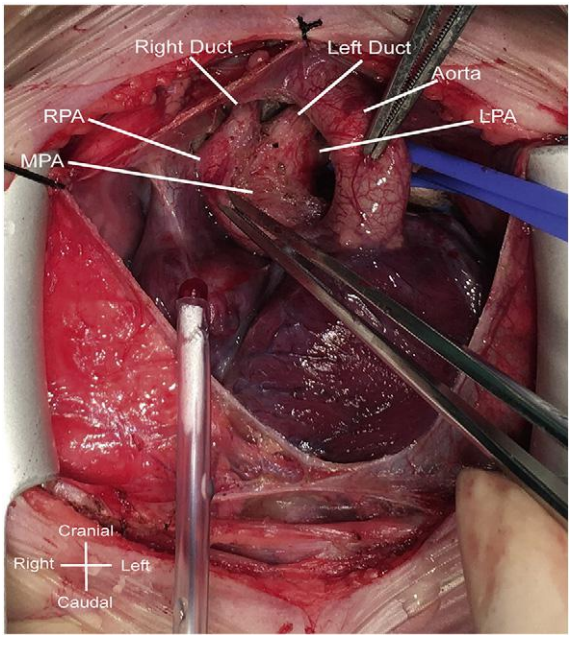


Fig. 1. Intra-operative photograph showing bilateral ductus. MPA is retracted to right and aorta to left with forceps for better view. RPA looped with blue tape. MPA: Main pulmonary artery, LPA: Left pulmonary artery, RPA: Right pulmonary artery.

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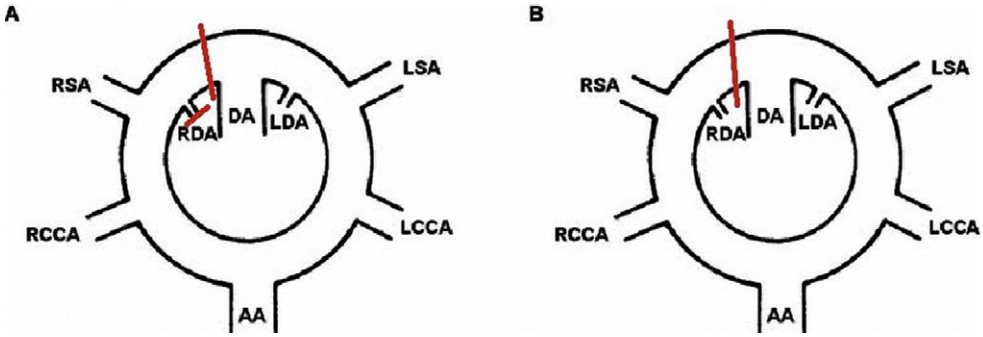


Fig. 2. A: Edward's hypothetical double aortic arch with bilateral PDA. Red lines show normal points of discontinuation of arch components. B: red line shows point of disconnection of arch component in present case. Notice there is no disconnection of right ductus with normal disconnection of right sided arch.

pulmonary artery and right brachicephalic artery. Left ductus was connected to left pulmonary artery and descending thoracic aorta (Fig. 1). There was no vascular ring. After completion of dissection required for arterial switch operation, cardiopulmonary bypass was instituted between aorta and right atrium cannulae. Soon after going on bypass both ducts were ligated and divided. Rest of the surgery was performed routinely. Intra- and post-operative course was uneventful.

Discussion

A persistent bilateral PDA is an uncommon abnormality which occurs during the development of the aortic arch and the pulmonary arteries. It is most commonly seen accompanied by abnormalities of pulmonary valve, pulmonary arteries and aortic arch anomalies.[1,2] Freedom et al. in their study of 27 cases with bilateral PDA reported associated anomalies of pulmonary arteries and aortic arch in all cases.[2] In the present case bilateral PDA were associated with confluent pulmonary arteries and no associated aortic arch anomalies. However bilateral PDA is commonly associated with co-existing intra-cardiac anomalies. Its association with dextro-transposition of great arteries has been reported only once.[3] In that case there was bilateral PDA with dextro-transposition of great arteries associated with right aortic arch. Left ductus was arising from left subclavian artery forming a complete vascular ring. The present is rare because it's first of its kind in which bilateral PDA associated with dextro-transposition of great arteries with left aortic arch with normal pulmonary arteries without anomalies of aortic arch.

Extrapolating from the primitive pharyngeal arch system, there is a tremendous range of potential anomalies of the aortic arch and its branches. With help of Edward's hypothetical double aortic arch (Fig. 2) it is easy to understand origin of bilateral PDA. Normally the segment of right aortic arch and right ductus disappears forming left aortic arch with left sided ductus. But if right ductus persists with only disappearance of right aortic arch then the present anomaly of bilateral PDA with left aortic arch arises.

Bilateral PDA is readily demonstrated on echocardiography. However, because of frequent association of anomalies of pulmonary arteries and aortic arch, some other imaging modality like CT of MRI is necessary.[4] In the present case it was missed on pre-operative echocardiography. With increasing use of fetal echocardiography it can be diagnosed in utero.[5]

The treatment mainly depends on associated anomaly of pulmonary artery, aortic arch and intra-cardiac anomaly. Surgical management frequently requires extensive reconstruction of great vessels. The treatment in present case was very straight forward. Bilateral PDA were ligated and divided and arterial switch operation was done. Absence of associated anomalies of great vessels reduced complexity of procedure.

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Case report

Is it possible? Invasion of the heart with hepatocellular carcinoma in a short time

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ABSTRACT

Primary and secondary cardiac tumors are a very rare entity, but secondary heart tumors are more common. Cardiac metastases occur in 10% all cancer patients. Hepatocellular carcinoma (HCC) is a very aggressive tumor. Intra-cardiac involvement with HCC rarely develops in a patient with HCC, and it has very poor prognosis. The clinical course of these patients may be complicated by many fatal cardiovascular complications. After the diagnosis of the heart involvement, median survival range is 1–4 months. Early diagnosis of cardiac involvement is very important and its easy way is performing echocardiography. We describe here a rare case of a 65-year-old man with HCC that invaded the heart in 3 months.

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Introduction

Cardiac tumors are very rare entity.[1] In contrast to primary malignant cardiac tumors, metastatic involvement of the heart is relatively common. Malignant melanomas are likely to metastasize to the heart. Other solid tumors commonly associated with cardiac involvement include lung cancer, breast cancer, soft tissue sarcomas, renal carcinoma, esophageal cancer, hepatocellular carcinoma, and thyroid cancer.[2] Cardiac involvement with other tumors may arise from hematogenous metastases, direct invasion from the mediastinum, or tumor growth into the vena cava and extension into the right atrium (RA).[3] Primary hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and the third-leading cause of cancer-related death.[4,5] HCC metastases tend to spread through intrahepatic blood vessels, lymphatics, or direct infiltration. HCCs frequently invade the vascular system at points such as the portal and hepatic veins. Intra-cardiac involvement of HCC rarely develops and the main mechanism of metastasis into the cardiac cavity is direct extension the tumor to the heart via hepatic vein and vena cava inferior.[2] The results of autopsy studies indicate a 2.7–4.1% incidence of atrial metastases of HCC.[6] A correct diagnosis is important in the clinical setting since cardiac metastases are able to induce sudden cardiac arrest.

Case report

A 65-year-old man with a history of hepatocellular carcinoma for 1 year presented to the cardiology clinic for dyspnea and new onset bilateral lower extremity edema rapidly progressing over 2 weeks. The diagnosis was made by hepatic biopsy and he was followed by medical oncology for 1 year with the treatment of sorafenib (multikinase inhibitor).

On physical examination, the heart rhythm was sinus, 2/6 systolic murmur in cardiac auscultation. There was pitting edema in lower extremities bilaterally and approximately 10 cm palpable mass at right upper quadrant of the abdomen.

2-D transthoracic echocardiography demonstrated a large mass in the right atrium extending to the tricuspid valve without significant obstruction (Fig. 1). Thoracic and upper abdominal computer tomography (CT) showed expansile liver mass with the extension of the tumor into the right atrium via invasion of the inferior vena cava (Fig. 2).

Compared with the previous CT and echocardiography images made 3 months ago, the hepatic mass of the liver was smaller and there was no VCI or intra-cardiac extension of HCC (Fig. 2). During this 3 months the liver mass got enlarged and invaded inferior vena cava thus reached the RA.

The patient was followed up conservatively because of the end-staged metastatic HCC and high mortality risk of the heart surgery. He died in 76 days after the diagnosis of intra-cardiac tumor because of liver and multi-organ failure. We did not identify left ventricular systolic failure during this follow-up time.

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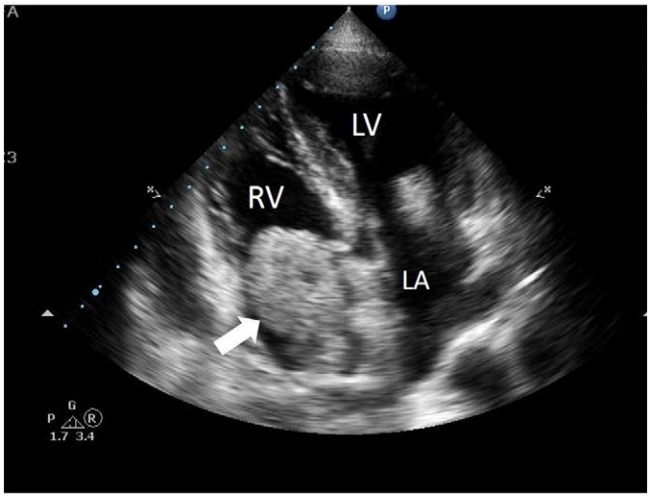


Fig. 1. 2-D and color Doppler transthoracic echocardiography in apical four chamber view. Echocardiography demonstrated a huge mobile mass that fills all the right atrium space (arrow). The mass was very mobile and protruding into the RV. LV, left ventricle; LA, left atrium; RV, right ventricle.

Discussion

The majority of HCC arises from viral hepatitis. Intra-cardiac involvement rarely occurs in patients with HCC, and its frequency was found around 2% in various series.[7] A literature search for case reports was performed on PubMed. We found 28 case reports or literature reviews of HCC with cardiac involvement that were published in the literature. Most of the cardiac metastases are direct and contiguous extensions of the intrahepatic HCC via hepatic vein and inferior vena cava.[8] Various cardiac symptoms or findings such as dyspnea, lower extremity edema, sudden death, or dilatation of the jugular veins are generally seen in HCC patients with intra-cardiac involvement.[1,7] Echocardiography is widely available and provides a simple, noninvasive technique for the initial evaluation of cardiac involvement of any tumor. Echocardiography images both the myocardium and the cardiac chambers and can usually identify the presence of a mass, its mobility and its functional effects. Both computed tomography (CT) and magnetic resonance imaging (MRI) provide noninvasive, high-resolution images of the heart and the liver, MRI generally is preferred. In addition to furnishing detailed anatomic images, MRI offers clues as to the type of tumor that is present.[9] However, CT scanning is still useful when MRI is not immediately available or is contraindicated.

The prognosis of HCC with intra-cardiac involvement is very poor, with a median survival range of 1–4 months.[10] The risk for cardiopulmonary collapse is high in such patients. Possible cardiopulmonary complications include heart failure, tricuspid stenosis or insufficiency, ventricular outflow tract obstruction, sudden cardiac death, pulmonary embolism, and pulmonary metastasis.[8] Multidisciplinary treatments to control the growth of HCC and cardiac surgery in young patients offer patients with cardiac involvement a useful chance of cure. However, such therapeutic modalities may not be feasible, especially if the patient has a poor general performance, metastatic disease, or underlying hepatic dysfunction.[10] A cardiac surgery for cardiac involvement of HCC to remove the mass can have high mortality.

This case report showed that intrahepatic HCC can disseminate and invade the heart in a short time. Even there are no curative treatments for metastatic HCC, following these patients with echocardiography periodically may give notice about cardiac involvement. We want to emphasize the importance of monitoring the patient with HCC by echocardiography with short time intervals not only for side effects of chemotherapy, but also to detect heart involvement of HCC.

Disclosures

The authors have no conflicts of interest to disclose.

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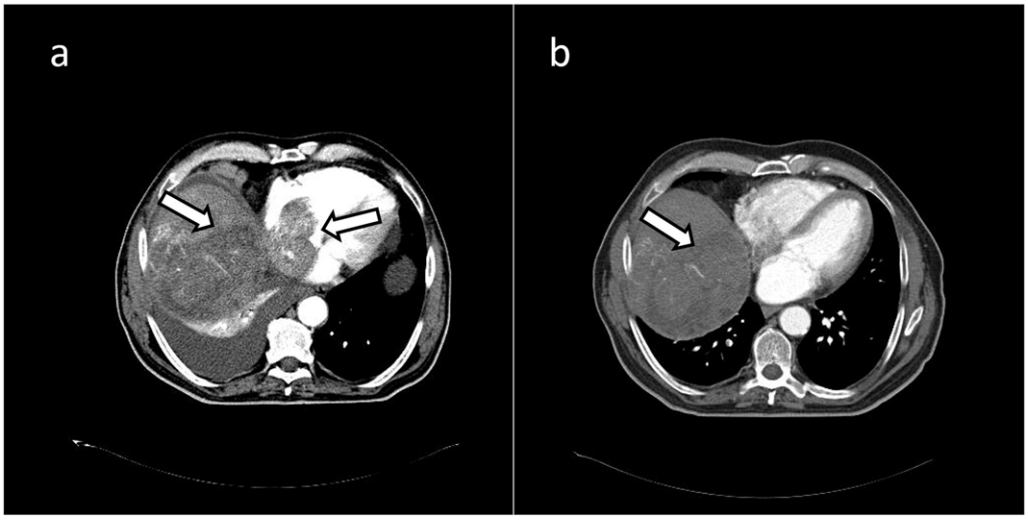


Fig. 2. Chest computed tomography image. (a) Axial image showing a mass in the liver and other mass in the right atrium (arrows). (b) This image is the control scan after chemotherapy that has been taken 3 months before the diagnosis of the cardiac involvement with hepatocellular carcinoma. This image shows the hepatic mass but there is no mass in the right atrium.

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Case report

Relationship between spontaneous echo contrast and hematological markers in patients with rheumatic mitral stenosis

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ABSTRACT

Introduction: Systemic thromboembolism is a serious morbidity and mortality cause for patients with rheumatic mitral stenosis (RMS). Previously conducted researches showed that spontaneous echo contrast (SEC) found in the left atrium can constitute a risk factor for thrombus formation. The aim of this study is to evaluate the role of echocardiographic and hematologic parameters in anticipating the presence of SEC in the left atrium of patients with moderate–severe RMS.

Methods: This retrospective study includes all patients who were diagnosed with moderate–severe RMS and underwent a transesophageal echocardiography between 2011 and 2014. They were then divided in two groups depending on SEC presence; a SEC negative group and a SEC positive group.

Results: There were 33 patients (32%) in the SEC negative group and 71 patients (68%) in the SEC positive group. The mean platelet volume was found to be significantly higher in the SEC positive group (10.0 ± 1.3 vs. 11.6 ± 1.4, $p < 0.001$). To identify the factors affecting the presence of SEC, a multivariate analysis of the hematologic parameters was conducted and the mean platelet volume was found to be an independent predictor (odds ratio 1.913, 95% confidence interval 1.300–2.814; $p = 0.001$). In the receiver operating characteristics curve analysis, a mean platelet volume >11.8 fl had a 55% sensitivity and 92% specificity in predicting SEC in patients with mitral stenosis.

Conclusion: Mean platelet volume constitutes an independent risk factor for the presence of left atrial SEC in patients with moderate–severe mitral valve stenosis.

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Introduction

Especially in developing countries, rheumatic mitral stenosis (RMS) is still a major health concern.[1] Patients with RMS show an elevated risk for systemic thromboembolism, which becomes a primary mortality and morbidity cause.[2] Among the suggested mechanisms leading to the disease are autoimmunity, inflammation and increased thrombotic activity.[3–5]

Spontaneous echo contrast (SEC) is the presence of smoke – like echoes with a characteristic swirling motion of blood found during echocardiography.[6] Previously conducted researches showed that presence of SEC in the left atrium can constitute a risk factor for thrombus formation.[7] In patients with RMS the risk of thrombosis and left atrial SEC development is eventually higher.[8] The aim of this study is to investigate the relationship between the presence of SEC and related hematologic parameters in patients with moderate–severe RMS.

Methods

In this retrospective study all moderate–severe RMS patients, who had a percutaneous mitral balloon valvuloplasty between 2011 and 2014 in our clinic were included (mitral valve area < 1.5 cm^2). Their respective electrocardiograms were inspected and the rhythm defined.

The exclusion criteria for the present study were left atrial thrombus formation, significant mitral regurgitation (grade > 1), other moderate or severe valve disease, history of malignancy, history of inflammatory disease, current therapy with corticosteroids, connective tissue disease, thyroid disease, other hematological disease and acute infectious disease. A medical history was recorded from patient anamnesis form.

Transesophageal echocardiography (TEE) and transthoracic echocardiography (TTE) records were also investigated (EPIQ 7 Ultrasound System, Philips, Heide, Netherlands). All the echocardiographic findings were carefully evaluated by two separate cardiologists. All measurements were taken according to the recommendations of the American Society of Echocardiography.[9] The mean value of 3 measurements was

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taken from patients with sinus rhythm and the mean value of 7 measurements from patients with atrial fibrillation. Routine echocardiographic measurements were also recorded. The planimetric measurements of the mitral valve area were also conducted. The mitral valve was assessed by TEE. The Wilkins score was determined by rating the severity of leaflet mobility, leaflet thickening, leaflet calcification and subvalvular thickening with a score of 0–4 and then adding the results together.[10] Left atrial SEC presence and degree was asses by TEE according to the criteria laid down by Fatkin et al.[11] The patients were then divided into two groups; a SEC positive group and a SEC negative one.

On the TEE day, the patients had blood drown from the antecubital vein and underwent routine biochemistry and complete blood count (CBC) tests, after a 12 hour fast. CBC including white blood cell (WBC), neutrophil and lymphocyte counts, mean platelet volume (MPV, normal range: 7.4–10.4 fl) were done using an automatized CBC count device (Abott Cell Dyn, Illinois USA). The C-reactive protein (CRP) levels (normal range: 0–5 mg/L) were analyzed with a Beckman Coulter Inc. (Image 800, California, USA).

Statistical analysis

Data were analyzed with the SPSS software version 21.0 for Windows (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean + SD, and categorical variables are expressed as percent. The χ^2 test and Fisher's exact test were used to compare categorical variables. The Shapiro–Wilk test was used to assess the distribution of continuous variables. Student's t-test was used for variables with normal distribution and the values were presented as mean ± SD. Continuous variables without normal distribution were analyzed using Mann–Whitney U test. Receiver operating characteristic (ROC) curve analysis was performed to identify optimal cutoff values for MPV. The effects of different variables on SEC were calculated in univariate analysis for each. The variables for which the unadjusted P-value was 0.10 in logistic regression analysis were identified as potential risk markers and included in the full model. The odds ratios (OR) and 95% confidence intervals (CI) were calculated. A two-tailed p-value of <0.05 was considered statistically significant.

Results

104 patients were included in this study of which 80 (77%) were female. 33 of them (32%) were in the SEC negative group (mean age 43.6 + 14.5) and 71 (68%) in the SEC positive group (mean age 47.0 + 11.3). Mean age, diabetes mellitus, hypertension, hyperlipidemia presence and aspirin or warfarin usage was similar among the groups. Atrial fibrillation (AF) was detected in 11 (33%) of the SEC negative group patients and 28 (40%) in the SEC positive one ($p = 0.634$). Also, in 31 of the 39 patients who had AF (79%) and in 48 of the 65 patients who did not have AF (73%), SEC presence was detected ($p = 0.632$). The groups' baseline characteristics are shown in Table 1.

The Wilkins score (9.6 ± 2.8 vs. 7.0 ± 2.2, $p < 0.001$) and the left atrial diameter (46.3 ± 2.7 mm vs. 44.7 ± 2.2 mm, $p = 0.010$) were found to be significantly higher in the SEC positive group. There was no significant difference among groups with regard to the mitral valve area (1.0 + 0.2 vs. 1.1 + 0.2, $p = 0.423$). TTE and TEE findings are shown in Table 2.

There was no significant difference among the groups with respect to some hematologic parameters like WBC count, platelet count, red cell distribution width and CRP (Table 3). However, MPV (11.6 ± 1.4 vs 10.0 ± 1.3, $p < 0.001$) was found to be significantly higher in the SEC positive group (Fig. 1). A univariate logistic regression analysis was performed in order to determine the factors leading to SEC presence and MPV (OR = 1.972, 95% CI: 1.411–2.758; $p < 0.001$), Wilkins score (OR = 1.409, 95% CI: 1.172–1.693, $p < 0.001$) and left atrial diameter (OR = 1.265, 95% CI: 1.051–1.522; $p = 0.013$) were shown to be risk factors. Also, a multivariate logistic regression analysis was performed in order to determine the factors leading to SEC presence and MPV value was found to be an independent predictor (OR = 1.913, 95% CI: 1.300–2.814, $p = 0.001$) (Table 4). In the ROC curve analysis, a MPV > 11.8 fl had a 55% sensitivity and 92% specificity in predicting SEC in patients with mitral stenosis (area under the curve 0.780, $p < 0.001$)(Fig. 2).

Table 1
Demographic characteristics of the groups according to the SEC presence.

Variable	SEC negative (n = 33)	SEC positive (n = 71)	P value
Age, years	43.6 ± 14.5	47.0 ± 11.3	0.286
Female, n (%)	28 (84%)	52 (73%)	0.062
DM, n (%)	3 (11.5%)	13 (16.7%)	0.755
Hypertension, n (%)	11 (42.3%)	37 (47.4%)	0.650
TC, mg/dl	189.0 ± 42.9	184.3 ± 36.5	0.417
LDL, mg/dl	125.5 ± 34.5	115.0 ± 34.6	0.106
HDL, mg/dl	45.0 ± 9.3	42.2 ± 8.3	0.119
Trygliceride, mg/dl	98.9 ± 43.3	122.2 ± 59.1	0.072
AF, n (%)	11 (33%)	28 (40%)	0.634
Aspirin, n (%)	17 (51%)	38 (53%)	0.248
Warfarin, n (%)	12 (38%)	29 (41%)	0.228
Beta blocker, n (%)	16 (48%)	36 (51%)	0.728

(Data are expressed as mean ± standard deviation for normally distributed data and percentage for categorical variables).
(AF: atrial fibrillation, DM: diabetes mellitus, HDL: high density lipoprotein, LDL: low density lipoprotein, TC: total cholesterol).

Discussion

Patients with moderate–severe RMS were included in this study and 23% of them were found to have SEC presence in their left atrium. Univariate and multivariate analysis showed that Wilkins echo score, MPV and left atrium diameter were risk factors related to left atrial SEC presence. In addition to that, MPV > 11.8 fl was found to have a 55% sensitivity and 92% specificity in predicting SEC presence in patients with mitral stenosis.

SEC is a dynamic smoke-like echo with a characteristic swirling motion of blood detected by echocardiography.[12] In RMS patients there is an increase in general inflammatory and prothrombotic state and therefore the risk of stasis in the left atrium that will eventually lead to left atrial SEC or thrombus, is significantly higher than the normal population.[13,14] In previous studies SEC was found to have a frequency of 21–67% in RMS patients and systemic thromboembolism was reported as an independent predictor of SEC presence.[6,15,16] Some

Table 2
Echocardiographic characteristics of the groups according to the SEC presence (variables with normal distribution were expressed as mean ± SD).

Variable	SEC negative (n = 33)	SEC positive (n = 71)	P value
LVEF, %	62.1 ± 4.2	62.0 ± 4.4	0.682
LA diameter, mm	44.7 ± 2.2	46.3 ± 2.7	0.010
LAVI, ml/m^2	32.1 ± 8.2	33.4 ± 7.2	0.378
LVEDD, mm	44.0 ± 4.0	46.1 ± 5.0	0.128
LVESD, mm	28.3 ± 4.4	30.1 ± 5.0	0.090
MVA, cm^2	1.1 ± 0.2	1.0 ± 0.2	0.423
Peak gradient, mm Hg	24.5 ± 9.2	21.9 ± 7.7	0.679
Mean gradient, mm Hg	14.5 ± 6.2	13.1 ± 6.2	0.317
WS	7.0 ± 2.2	9.6 ± 2.8	<0.001
Valve mobility	1.7 ± 0.6	2.4 ± 0.7	<0.001
Subvalvular	1.6 ± 0.6	2.4 ± 0.9	<0.001
Valve thickness	1.9 ± 0.7	2.5 ± 0.8	0.004
Calcification	1.7 ± 0.9	2.3 ± 0.9	0.010
sPAP, mm Hg	43.9 ± 13.4	40.7 ± 8.7	0.365

(LA: left atrium, LAVI: left atrial volume index, LVEF: left ventricular ejection fraction, LVEDD: left ventricular end diastolic diameter, LVESD: left ventricular end systolic diameter, MVA: mitral valve area, SEC: spontaneous echo contrast, WS: Wilkins score).

Table 3
Common hemogram and inflammatory parameters of the groups according to the SEC presence.

Variable	SEC negative (n = 33)	SEC positive (n = 71)	P value
Hemoglobin, g/dl	12.2 ± 1.2	13.0 ± 1.3	0.023
WBC, (× 10^3/μL)	7.8 ± 2.0	7.9 ± 2.3	0.892
Platelet count, (× 10^3/μL)	221.2 ± 69.3	236.6 ± 59.9	0.276
MPV, fl	10.0 ± 1.3	11.6 ± 1.4	<0.001
RDW, %	15.2 ± 2.2	14.4 ± 1.9	0.073
CRP, mg/l	6.1 ± 5.5	6.1 ± 5.2	0.703

Variables with normal distribution were expressed as mean ± SD.
CRP: C-reactive protein, MPV: mean platelet volume, RDW: red blood cell distribution width, WBC: white blood cells count.

Table 4
Evaluation of the factors affecting the presence of the SEC by univariate and multivariate logistic regression analysis.

	Univariate		Multivariate	
Variable	OR (95% CI)	P value	Adjusted OR (95%CI)	P value
Sex	0.123 (0.016–0.959)	0.046		
Hemoglobin	1.552 (1.072–2.246)	0.020	1.424 (0.950–2.134)	0.087
MPV	1.972 (1.411–2.758)	<0.001	1.913 (1.300–2.814)	0.001
RDW	0.835 (0.677–1.031)	0.093		
CRP	0.996 (0.919–1.079)	0.926		
Trygliceride	1.009 (0.999–1.019)	0.072		
LA diameter	1.265 (1.051–1.522)	0.013	1.007 (0.997–1.017)	0.026
WS	1.409 (1.172–1.693)	<0.001	1.345 (1.092–1.657)	0.005
LVEF	9.992 (0.894–1.100)	0.876		
LVESD	1.126 (1.018–1.246)	0.022		
Mean gradient	0.967 (0.903–1.036)	0.335		
MVA	0.418 (0.050–3.476)	0.420		

CRP: C-reactive protein, LA: left atrium, LVEF: left ventricle ejection fraction, MPV: mean platelet volume, MVA: mitral valve area, RDW: red blood cell distribution width, WS: Wilkins score.

of the reported clinic and echocardiographic risk factor of SEC in RMS patients are atrial fibrillation, high Wilkins score, small mitral valve area, increased mitral gradient, left atrial dilation without severe mitral insufficiency.[4,17] In a similar way, our study found that Wilkins score was significantly higher in the SEC positive group, but couldn't find a significant association with mitral valve area and mitral gradient.

The pathophysiological mechanism of RMS is related to the antigenic similarity of the streptococcal M protein with cardiac tissue and to the related autoimmune response that follows. In the chronic state of the disease, inflammation is persistent even without the presence of an infectious agent.[3,18] According to previous studies, inflammatory predictors were found to be elevated in RMS patients.[4,19] Kaya et al. studied the systemic inflammatory state predictors in RMS patients with SEC presence and reported significantly elevated values of high sensitive CRP and neutrophil/lymphocyte ratio. Also, a neutrophil/lymphocyte ratio >3.1 was found to have a specificity of 72% and a sensitivity of 80% in detecting left atrial SEC presence in this study.[20]

Increased prothrombotic state has also been reported, alongside increased inflammation, in RMS patients. Previous studies have reported increased MPV, P-selectin, fibrinogen and D-dimer levels as conditions related to the increased prothrombotic state in these patients.[5,21,22] It has also been shown that MPV values, in RMS patients, tend to decrease after percutaneous mitral balloon valvuloplasty.[22] MPV is one of the indicators of platelet function. Bigger platelets are hemostatically more reactive that smaller ones and an increase in MPV values, reflect an increase in platelet function.[23–25] Akpek et al. included 232 RMS patients in their study and found that MPV values were correlated to left atrial SEC presence and SEC degree.[14] In a study conducted by İleri et al., examined 84 patients with RMS, severe MR and left atrium SEC presence have been shown to be associated with increased in MPV.[26]

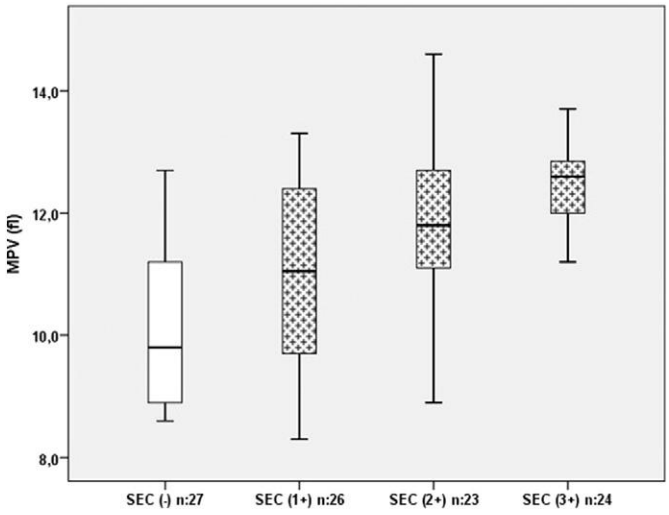


Fig. 1. MPV levels in the SEC negative and SEC positive patients.

In a similar way, our study found that MPV values were higher in SEC positive patients, compared to SEC negative patients. In addition to this, our study found that a MPV > 11.8 fl value was an independent predictor of SEC presence.

Atrial fibrillation is an important risk factor for the development of left atrial SEC or thrombus.[7] In addition to patients with AF, previous studies have reported an increased hypercoagulable state in RMS patients with sinus rhythm too.[27] Risk factors associated with left atrial thrombus are advanced age, atrial fibrillation, small mitral valve area, dilated left atrium and SEC presence.[17,28] Munjunath et al. studied 848 RMS patients with sinus rhythm and reported that left atrial thrombus did not form without a SEC presence.[27] Therefore it is important to detect SEC positive patients. Our study did not detect any significant difference among the groups with respect to atrial fibrillation but reported increased MPV values as independent predictors of SEC presence. Despite being on sinus rhythm, patients with MPV > 11.8 fl had a higher probability of developing SEC and therefore should be regularly monitored with TEE. To investigate the need and effectiveness of

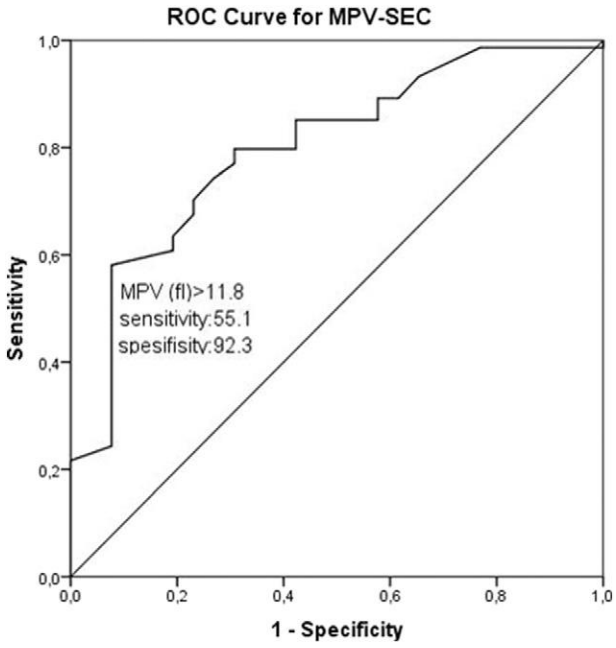


Fig. 2. ROC curve analysis for MPV in prediction of SEC (area under the curve 0.780, p < 0.001).

anti-inflammatory, antiplatelet and anticoagulant therapy in these patients, large randomized trials results are needed.

Study limitations

This study was a retrospective one. The possible limitations of the present study include that it was a single-center experience and included a small number of patients. Possibility of intermittent atrial fibrillation cannot be ruled out. Measures of thromboembolic risk like left atrial appendage size, and filling and emptying velocities were not studied. Because the majority of the included patients were expecting a percutaneous mitral balloon valvuloplasty, those with severe mitral insufficiency were not included. Therefore these results may not represent patients with severe mitral insufficiency.

Conclusion

Independently from cardiac rhythm, MPV value was found to be independently related to left atrial SEC presence in RMS patients.

Conflict of interest

None declared.

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Case report

The potential role of scar mapping in assessing of paroxysmal atrial fibrillation recurrence after cryoballoon application

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ABSTRACT

Cryoballoon ablation for atrial fibrillation (AF) has become a frequently used therapy after failure of at least one antiarrhythmic drug. The main target of AF ablation has been durable pulmonary vein isolation. However, it is unclear if ablation strategies need to be modified after recurrence. Herein, we presented a female patient undergoing successful pulmonary vein re-connection ablation after left atrial scar mapping. In electroanatomical mapping, gray area shows intense scar tissue. Gray, red, and purple areas indicate atrial potentials <0.5 mV, 0.5–1.5 mV, and >1.5 mV, respectively. Please note that there is a non-scar area in the bottom of right inferior pulmonary vein (arrow).

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Introduction

At this time, pulmonary vein isolation (PVI) is the recommended treatment for patients with drug-resistant paroxysmal atrial fibrillation (PAF). Cryoballoon ablation may be used as an alternative to radiofrequency (RF) ablation with similar success rates in patients with PAF. In nearly all cases in which AF recurs after PVI, 1 or more of the pulmonary veins (PVs) is found to have re-established electrical connection to the atria.[1–3] Gaps in the line of ablations[4] or failure to produce completely transmural lesions[5] are thought to be the main responsible mechanism of PV reconnection. If the actual mechanism of electrical reconnection is understood, it may increase to ratio of more durable PVI or may cause modification of current ablation approach. To discuss possible mechanisms of PV reconnection, we presented a female patient in whom left atrial scar mapping was performed to define cause of PV re-connection.

Case

A 64 year old female patient had undergone PVI with cryoballoon in our center 14 months ago. The patient was being followed as part of a research project. The patient was asymptomatic and Holter monitoring showed no new episode during 1, 3, 6 and 12 months follow-up visits. During previous cryoballoon application, PV potentials had been detected in each of the 4 pulmonary veins and isolated successfully. She admitted to our emergency department with haemodynamically intolerable palpitation two weeks ago. Atrial fibrillation with high ventricular response was detected on her admission ECG. Restoration of sinus rhythm was achieved by electrical cardioversion with 150 J biphasic shock. Due to previous ablation procedure, we decided to perform new procedure to define and treat the arrhythmia. Transthoracic echocardiography showed that left atrial diameter is 4.5 cm and left ventricular EF is 55%. To determine recurrence probability of new ablation procedure, we decided to define left atrial scar by using Ensite Velocity scar mapping system. The atrial potentials which are smaller than 0.5 mV accepted as intense scar on sinus rhythm. As expected, wide antral scar area was detected due to previous cryoapplication (Figs. 1 and 2). However, there was only one region demonstrating atrial potentials greater than 1 mV in the bottom of right inferior PV (Figs. 1 and 2). Not surprisingly, intracardiac recordings showed re-connection only in this region. Intense scar tissue was not detected in the rest of the left atrium and the other 3 pulmonary vein still seems isolated. So, we decided to perform RF ablation in only that site. After ablation and at 3 months follow-up, no further tachycardia was noted.

Discussion

In the present case, we used scar mapping feature of electroanatomical mapping system to define the actual cause of recurrence. It has been known over longer time periods that there are some possible

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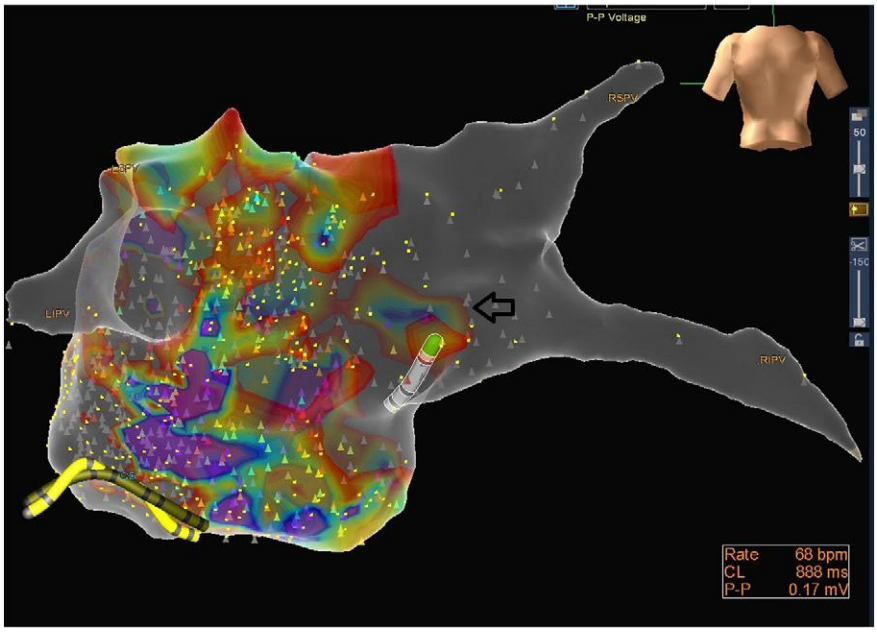


Fig. 1. Electroanatomical mapping. Ensite Velocity endocardial bipolar voltage maps in a posteroanterior view. Gray area shows intense scar tissue. Gray, red, and purple areas indicate atrial potentials <0.5 mV, 0.5–1.5 mV, and >1.5 mV, respectively. Please note that there is a non-scar area in the bottom of right inferior pulmonary vein (arrow).

mechanisms related with reconnection of PV conduction. Kowalski et al.[6] demonstrated that scar tissue due to PVI may exhibit nuclear pyknosis and myocytolysis after the index ablation, suggesting that some of left atrial tissue may remain viable and capable of recovery over a prolonged period of time. However, recurrence of AF may occur despite of durable PVI. As a potential explanation, recurrent AF might be triggered and maintained by tissue outside the PVs in these patients.[7,8] Surprisingly, reconnection of PVs may be seen even in patients without recurrent AF. So, clinical importance of reconnection remains uncertain.

It is well known that consistent PVI can be obtained if transmural and contiguous lesions are achieved. To indicate transmural damage, late gadolinium enhancement with magnetic resonance imaging may be used which can identify transmural level of scar tissue[5] even also distinguish scar from edema.[9] Although there are some contradictory thoughts, Kowalski et al.[6] have provided objective pathological evidence supporting the hypothesis that PV reconnection may be caused by a failure to achieve a transmural lesion despite acute evidence for isolation.

In our case, we detected healthy tissue in the bottom of right inferior PV. When we investigated this site for PV potentials, we defined PV reconnection. So, we speculated that the main reason of PV re-connection may be non-transmural nature of previous ablation lesion. The evaluation of scar tissue by using electroanatomical mapping systems may show main responsible mechanism whether PV reconnection or ineffective lesion. In the relevant literature, scar mapping was used as a tool to assess overall extension of left atrial scarring. However, in our case, we used scar mapping to demonstrate nature and cause of gap in PV ablation line. This may be an important difference from previous studies.

For today, independently whether AF paroxysmal or persistent, quantity of left atrial scar tissue may determine clinical success rate of ablation procedure. Therefore, the determination of scar quantity by

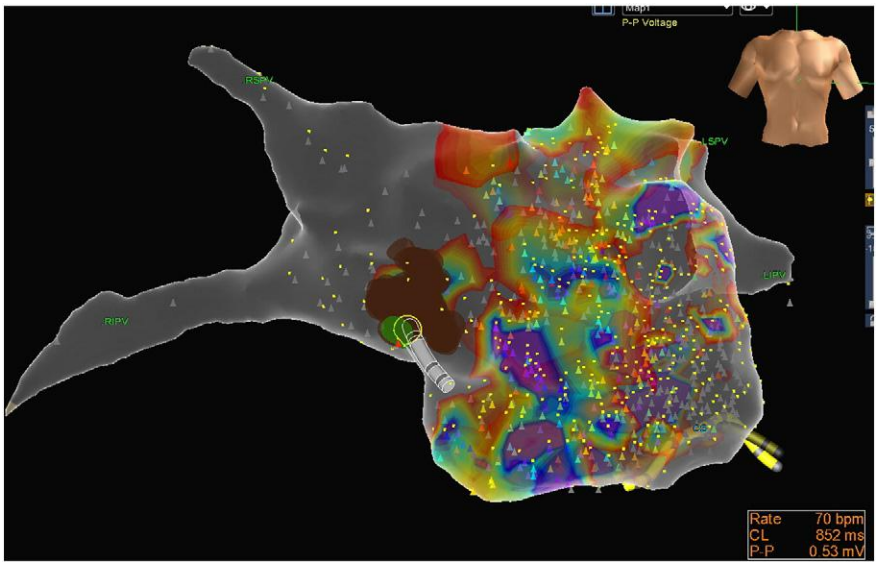


Fig. 2. Electroanatomical mapping. Ensite Velocity endocardial bipolar voltage maps in an anteroposterior view. Gray area shows intense scar tissue. Gray, red, and purple areas indicate atrial potentials <0.5 mV, 0.5–1.5 mV, and >1.5 mV, respectively. Brown spheres indicate radiofrequency ablation lesions.

using scar mapping or magnetic resonance imaging must be kept in mind especially in patients presenting with recurrence after cryoballoon application.

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Case report

A rare cause of non-ST elevation myocardial infarction related to total coronary artery occlusion: Dual RCA

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ABSTRACT

Dual right coronary artery (RCA) is one of the rarest coronary anomalies. We presented a 61-year-old male referred with non-ST-segment elevation myocardial infarction. Angiogram revealed a stenosis-free RCA and another RCA with total occlusion of the proximal segment and originating from the same aortic sinus was also found. Total coronary occlusion increases mortality in patients with NSTEMI. In this paper we discussed that the presence of dual RCA may actually prevent undesired cardiac events.

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Introduction

The prevalence of coronary anomalies is reported to be 0.2–1.4% of the general population,[1] and dual right coronary artery (RCA) is one of the rarest coronary anomalies. The incidence of dual RCA varies from 0.01% in conventional coronary angiography to 0.07% in coronary angiography.[2]

Acute coronary occlusion (ACO) is responsible for ST-segment elevation myocardial infarction; however, ACO may also cause non-ST-segment elevation myocardial infarction (NSTEMI).[3] Previous studies have reported that ACO increases mortality in patients with NSTEMI.[4] However, there is no consensus about how to predict which patients are at the highest risk. Some studies have suggested that electrocardiograms may help identify NSTEMI related to total coronary artery occlusion.[5,6] In this report, we discuss a case of dual RCA, a rare cause of NSTEMI related to RCA occlusion. Dual RCA may prevent undesired cardiac events when the second RCA is patent.

Case report

A 61-year-old male had a history of hypertension, smoking, and chronic obstructive pulmonary disease who admitted to hospital. He had no history of coronary artery disease and was only taking diltiazem for hypertension. He admitted to the hospital with acute chest pain. He has been experiencing angina pectoris for 10 h. Electrocardiography (ECG) was not remarkable except for minimal ST-segment depression in leads V5 and V6 (Fig. 1). Serum biochemistry was normal except for mildly increased cardiac enzymes and troponin. The level of troponin I was 0.1 ng/ml (0–0.03 ng/ml). He was referred to our center for coronary angiography due to NSTEMI. Echocardiography revealed hypokinesia of septum and normal left ventricular systolic function. Coronary angiogram was planned at the same day. The left anterior descending (LAD) artery showed intermediate stenosis in the middle segment, and the RCA was determined to have a retrograde collateral supply from the LAD artery, as identified by angiography (Fig. 2a). A plaque in the proximal segment of the major obtuse marginal branch of the left circumflex (LCx) artery was showed by angiography (Fig. 2b). Fluoroscopy (the left anterior oblique [LAO] projection) also revealed a stenosis-free RCA (RCA1) originating from the right aortic sinus (Fig. 3a). However, another RCA (RCA2) with total occlusion of the proximal segment and originating from the same aortic sinus was also found (Fig. 3b). RCA2 had just a small conus branch. Left ventriculography showed hypokinesia of inferior segment. Echocardiography revealed decreased systolic function (ejection fraction 40%) and hypokinesia of inferior segment. He had new onset angina and high troponin level. Therefore we decided to perform percutaneous coronary intervention for the stenotic RCA. However, the patient refused, so we instead followed him medically.

Discussion

Dual RCA is one of the rarest coronary anomalies, and until now there has been no consensus on the definition of dual RCA. To understand more about dual RCA, we searched the literature using the following keywords: “double right coronary artery,” “duplicated right coronary artery,” “dual right coronary artery,” and “split right coronary artery”.[1] According to Sawaya et al.[7] a split or double RCA is the same

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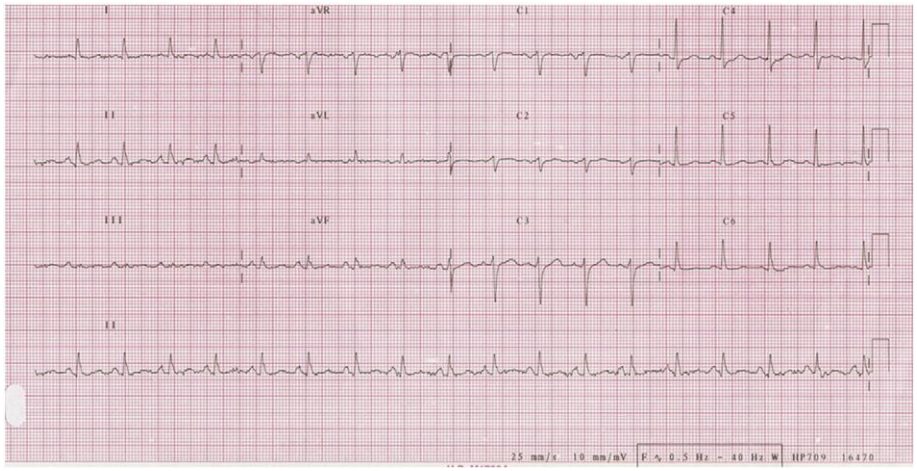


Fig. 1. The results of ECG were unremarkable except for minimal ST-segment depression in leads V5 and V6.

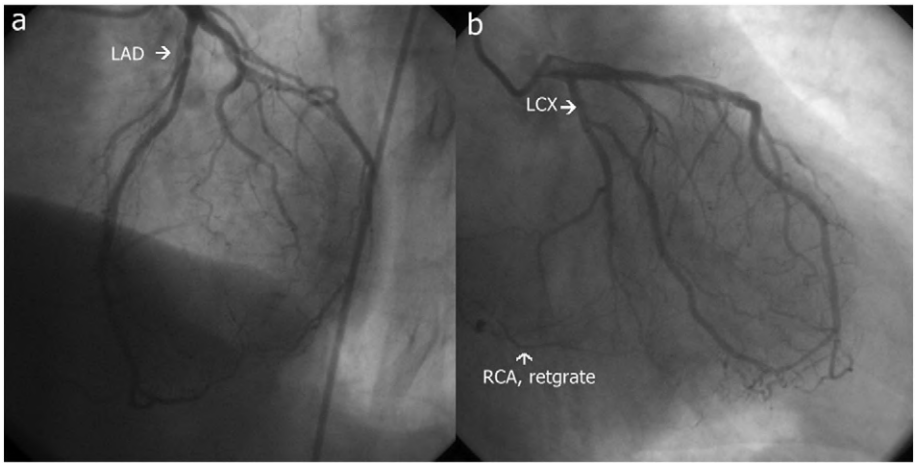


Fig. 2. (a) LAO projection fluoroscopic images revealed that the LAD artery had an intermediate occlusion in the midsegment. (b) The LCx artery showed moderate occlusion (50%) in the proximal segment on the major obtuse marginal branch in the right caudal projection.

anomaly, and in reality there is only one RCA. Other authors define "double RCA" as RCAs that originate separately from two different ostia.[8] However, most cases are reported as double RCAs whether they originate from the same ostia or not.

Bahrmann et al.[6] showed that patients with NSTEMI related to ACO had more frequent inferolateral or posterolateral lesions, more collaterals, larger infarcts, and more non-fatal reinfarctions compared with non-AOC patients. In general, there are angiographically visible

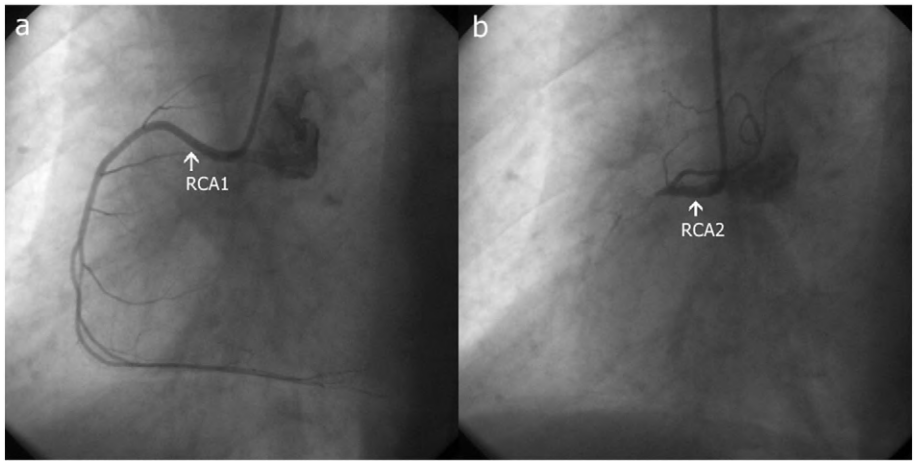


Fig. 3. (a) The RCA originated normally from the right aortic sinus as seen by LAO projection fluoroscopy. (b) The other RCA (RCA2) originated from the same aortic sinus but a different ostium with total occlusion.

collaterals in these patients, and patients with NSTEMI related to ACO and absent collaterals had a significantly higher risk of major cardiac events within six months.[6] Predicting which patients with NSTEMI related to ACO are at increased risk for additional infractions is complicated and requires further investigation.

One case was reported previously, and the patient presented with an atypical double RCA and acute inferior myocardial infarction.[9] However, a dual RCA has not been reported in a patient with NSTEMI related to right coronary total occlusion. Patients with NSTEMI are at increased risk of acute coronary occlusion, and the presence of dual RCA may actually prevent undesired cardiac events. In our case he had new onset angina and high troponin level. So we decided to perform percutaneous coronary intervention for the stenotic RCA because of his ongoing angina. That stenotic RCA might be chronic total occlusion and the culprit lesion may be a different coronary artery. In this case we needed to know the presence of viable myocardium in RCA segments and after that we decided the therapy of the patient. But he refused our medical advises.

Conclusions

We reported a patient with dual RCA originating from the same right aortic sinus from two ostia, and that presented with NSTEMI related to RCA occlusion. In this case, the dual RCA may have prevented ST-segment elevation myocardial infarction. However, this hypothesis requires further investigation and testing.

The English in this document has been checked by at least two professional editors, both native speakers of English. For a certificate, please see: http://www.textcheck.com/certificate/0HZp28.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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Case report

Anomalous origin of the right coronary artery from the left anterior descending artery: A rare variant of single coronary artery☆

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ABSTRACT

Anomalous origin of the right coronary artery (RCA) arising from the left anterior descending artery (LAD) is a very rare coronary anomaly and discovered incidentally during a coronary angiography. We, herein, experienced two cases with anomalous origin of the RCA from the LAD.
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Introduction

Congenital coronary artery anomalies (CAA) are present at birth but are usually asymptomatic and are found incidentally during coronary angiography. Their prevalence is less than 1.3% based on published series.[1–2] Of the benign anomalies, the three most common are 1) separate origination of the left anterior descending artery (LAD) and left circumflex (CX) arteries from the left sinus of Valsalva (LSV), 2) origination of the CX artery from the right coronary artery (RCA) or right sinus of Valsalva (RSV), and 3) ectopic origin of RCA from the aorta.[1] Of the malignant abnormalities, the most common anomaly, by a wide margin, is the ectopic origin of RCA from the LSV. Single coronary artery (SCA) is a rare CAA where only one coronary artery arises from the aortic trunk by a single coronary ostium, supplying the entire heart and has different subtypes depending on the course of anomaly artery. We present here a rare type of SCA with the anomalous origin of the RCA from mid-LAD in two patients.

Case report

Case 1. A 46-year-old female with hypertension, hyperlipidemia, and obstructive sleep apnea was evaluated for worsening shortness of breath. She had a strongly positive family history of premature coronary heart disease. Physical examination was unremarkable and resting electrocardiogram (ECG) was normal. The patient was referred for a stress testing that revealed the suspicious stress-induced ST changes. Coronary angiography was performed through the right femoral artery using the Judkin's technique. Cannulation of the left main coronary artery (LMCA) displayed normal courses of the left main, CX, and LAD (Fig. 1). An anomalous RCA as a separate small branch arose from the mid-LAD just after the first diagonal branch, then coursed anteriorly down the right atrioventricular groove. There was no significant coronary narrowing, and the patient was discharged with medical therapy.

Case 2. A 57-year-old male with a subacute anterolateral myocardial infarction referred to our clinic for coronary angiography due to worsening angina. He had a history of systemic hypertension, type 2 diabetes, and current smoking as coronary risk factors. Physical examination was unremarkable. Coronary angiography demonstrated that all three major coronary arteries were originating from the same ostium in the LSV (Fig. 2). An anomalous RCA as a separate small branch arose from the mid-LAD just after the first diagonal branch, then coursed anteriorly down the right atrioventricular groove. There was a high-grade 90% stenosis in the proximal first diagonal branch and thrombosed total functional occlusion at the level of mid-LAD (Fig. 2). The patient underwent successful coronary artery bypass operation and was discharged with conventional medical therapy.

Discussion

The coronary circulation arising from a single coronary ostium has little clinical significance, except for cases in which a coronary artery

☆ There is no conflict of interest.

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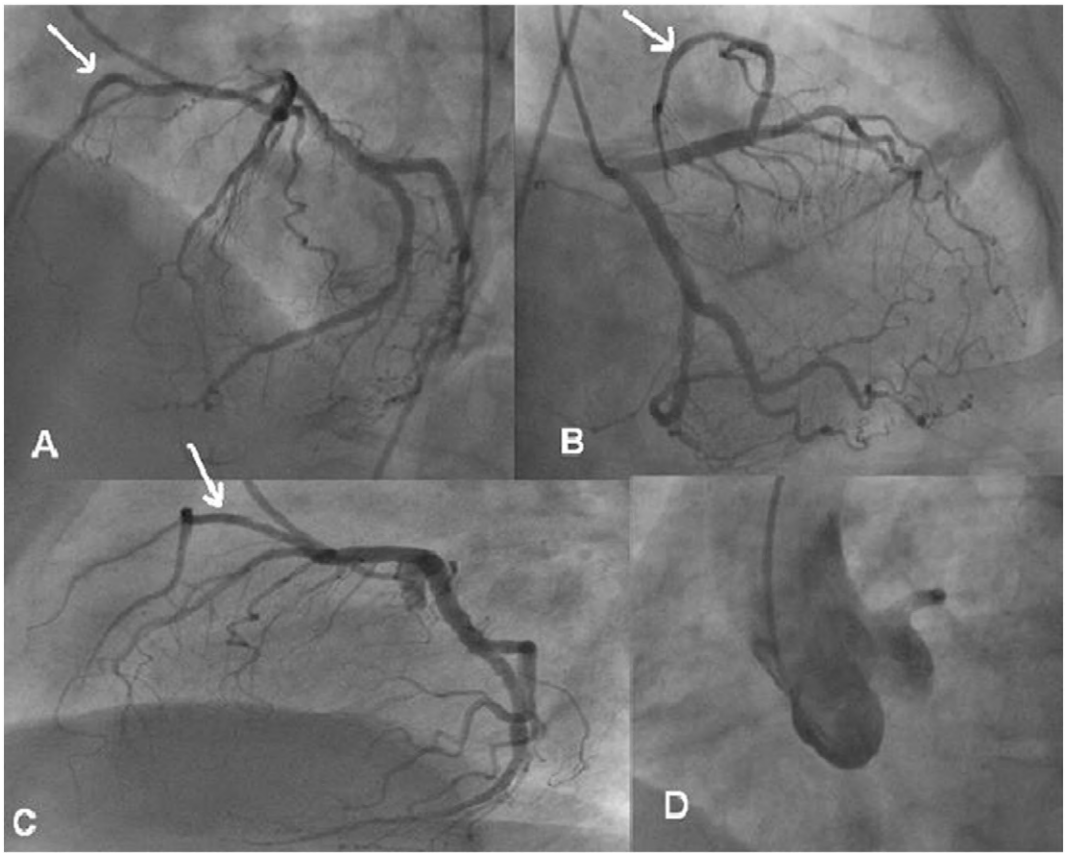


Fig. 1. LAO cranial (A), RAO caudal (B), and lateral (C) views showing the origin of the anomalous right coronary artery (white arrows). Aortography view (D) showing right coronary artery ostium was absent.

traverses between the pulmonary artery and aorta, which can cause sudden death at a young age due to extrinsic coronary arterial occlusion. The anomalous origin of the RCA as a branch of the LAD artery is a very rare variation of SCA.[3–5]

The classifications of CAA are often fragmental and difficult to remember because they combine anatomical, angiographic, and clinical elements.[6–8] Therefore, the knowledge of the common anatomic variants of CAA is of great help for their identification. The SCA has been classified according to the current classification system proposed by Lipton et al.[8] in 1979 who reorganized 2 previous systems that include the classification systems of Smith[6] and Ogden-Goodyear.[7] The Smith's system was based on three groups according to the types of the coronary arteries involved.[6] In group I, the artery follows the anatomical course of either a left or a right coronary artery. In the other words, the SCA follows the course of the RCA, continues into the CX and then as the LAD artery, or there may be a single LMCA artery that branches into the LAD and CX, the latter extending across the crux to form the RCA. In group II, after its origin, the main trunk divides into the right and left main arteries or into RCA, LAD, and CX artery. In group III, the SCA branches atypically and there is little similarity between the coursing of the three major arteries.[6]

Ogden and Goodyear's system offered five letters to classify the single coronary artery.[7] Two of them symbolized the side of the ostial origin of the SCA and three of them symbolized the anatomic course and distribution of the branches.[6]

Finally, the Lipton's classification begins with a division into the “R” (right) and the “L” (left)-type, depending upon whether the SCA originates from the right or the LSV. After that, every case is designated

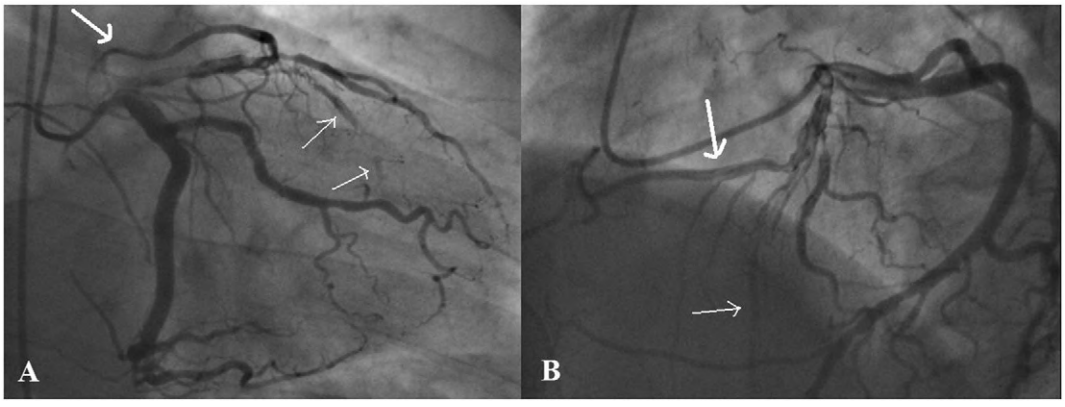


Fig. 2. RAO caudal (A) and LAO cranial (B) views are showing the origin of the anomalous right coronary artery (thick white arrows) and thrombosed total functional occlusion of the mid-left anterior descending artery (thin white arrows).

as belonging to group I, II, or III, depending on the anatomical course of the artery. The final designation describes the relationship between the anomalous artery, the aorta, and the pulmonary artery with the letters "A," "B,", and "P,", where A stands for an anterior course, P stands for a posterior course, and B represents a course between the aorta and pulmonary artery.

In groups II and III, an important characteristic of this classification is the path followed by the anomalous arteries from one side of the heart to the other. When the LMCA originates from the proximal RCA or vice versa, the anomalous artery takes 1 of 4 aberrant pathways to reach its proper vascular territory. These pathways are designated as type A (*A*nterior to the right ventricular outflow tract—"anterior or prepulmonic course"), type B (*B*etween the aorta and pulmonary trunk—"interarterial course"), type C (Cristal, coursing through the crista supraventricularis portion of the interventricular septum—"septal course"), and type D (*D*orsal or posterior to the aorta—"retroaortic course").[9] Both presented case were compatible with L2A type SCA.

Conclusion

There is no consensus regarding the risk for atherosclerosis in cases of SCA. Some reports claim that there is an increased risk of atherosclerosis in the case of a SCA, which may result from the acute takeoff angle and/or slit-like orifice, the others reported that SCA is not associated with increased risk for the development of atherosclerotic coronary artery disease.[2] Whereas the presented first case has only minimal coronary narrowing, the second case presented with acute coronary syndrome. The vast majority of previously reported anomalies demonstrated the RCA arising from the mid-LAD after the first septal perforator branch,[3–5] as did in presented cases, and only a few had RCA arising from the proximal segment of the LAD.[4,5]

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Case report

A rare cause of myocardial infarction: Vegetation embolism

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ABSTRACT

Coronary artery septic embolization resulting in cardioembolic myocardial infarction is a rare complication of infective endocarditis. Diagnosis requires a combination of high clinical suspicion, echocardiography, coronary angiography and cultures of peripheral blood and/or embolic material. Optimal therapy is unknown. We present a case of ST segment elevation myocardial infarction resulting from coronary artery septic embolization.

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Introduction

Acute myocardial infarction (MI) due to intracoronary septic emboli is a rare complication of infective endocarditis (IE). Autopsy studies which investigate patients with IE suggest coronary embolism is more prevalent than surviving case reports would suggest.[1] We present a case of ST segment elevation MI resulting from coronary artery septic embolization.

Case report

A 40-year-old woman presented to our emergency department with squeezing substernal chest pain more than 4 h. In initial evaluation, systolic pressure was 110/70 mmHg and pulse rate was 110 beats per minute. Physical examination revealed apical systolic murmur and crackles at the basal segment of the lungs. Patient's temperature was 36.7 °C. She had no known cardiac risk factors and had no history of cardiovascular disease. Her admission electrocardiogram (ECG) showed acute ST segment elevation in leads V3–V6 and D2–D3–AVF (Fig. 1). Acetylsalicylic acid 300 mg and clopidogrel 600 mg was given. After initial evaluation in the emergency department, the patient was taken to the catheter laboratory for primary percutaneous coronary intervention (PCI). Coronary angiography showed total occlusion of left anterior descending artery after the second diagonal branch. Right coronary artery and left circumflex artery was normal (Fig. 2). Unfractionated heparin (7500 U) was administered intravenously and PCI was planned. Despite balloon support, our guide wire failed to cross the lesion. The patient was taken to the coronary care unit for thrombolytic therapy (TT). In the intensive care unit, the patient's detailed history was taken. We learned that she was being investigated for anemia, weight loss and history of fever at the hematology unit in the last four months. During this period, she was using antibiotics occasionally. The patient had no history of oral contraceptive use. Before TT, transthoracic echocardiography was performed and showed that rheumatic severe mitral regurgitation, mobile mass compatible with vegetation at the edge of the anterior leaflet of mitral valve, partial chordae rupture and moderate tricuspid regurgitation. Pulmonary artery systolic pressure was 90 mmHg. Left ventricular systolic function and cardiac chamber size was normal. For this reason, we did not give TT. Diuretic therapy and nitroglycerin infusion was begun. Blood culture samples were taken and then an infectious disease specialist recommended prophylactic intravenous antibiotic therapy (gentamicin 240 mg/day, ampiciline 4 g/day). In laboratory tests, hemoglobin was 5.6 g/dl, white blood cell was 11.7×10^3 per μL and platelet was 319×10^3 per μL. Lipid parameters, tests associated with connective tissue disease, liver and kidney function tests were normal but erythrocyte sedimentation rate was 74 mm/h, C-reactive protein was 92 mg/dl and troponins were elevated at 3.4 ng/ml. Hemoglobin level increased to 9.1 g/dl after two units of erythrocyte suspension. The next day after clinical stabilization, the patient's three-dimensional and transesophageal echocardiography (TEE) was performed. Severe mitral regurgitation, 11×15 mm-sized mobile mass compatible with vegetation on the edge of the anterior leaflet of mitral valve and partial rupture of chordae were observed (Fig. 3). There was no lesion suggestive of septic emboli in abdominal ultrasound and brain tomography. IE associated with underlying rheumatic mitral valve and ST elevation MI due to septic emboli was considered for the patient. The blood cultures did not reveal any microorganisms. After the ninth day, the patient had been stabilized with medical treatment. Mitral valve replacement and coronary artery bypass grafting was performed by the Department of Cardiovascular

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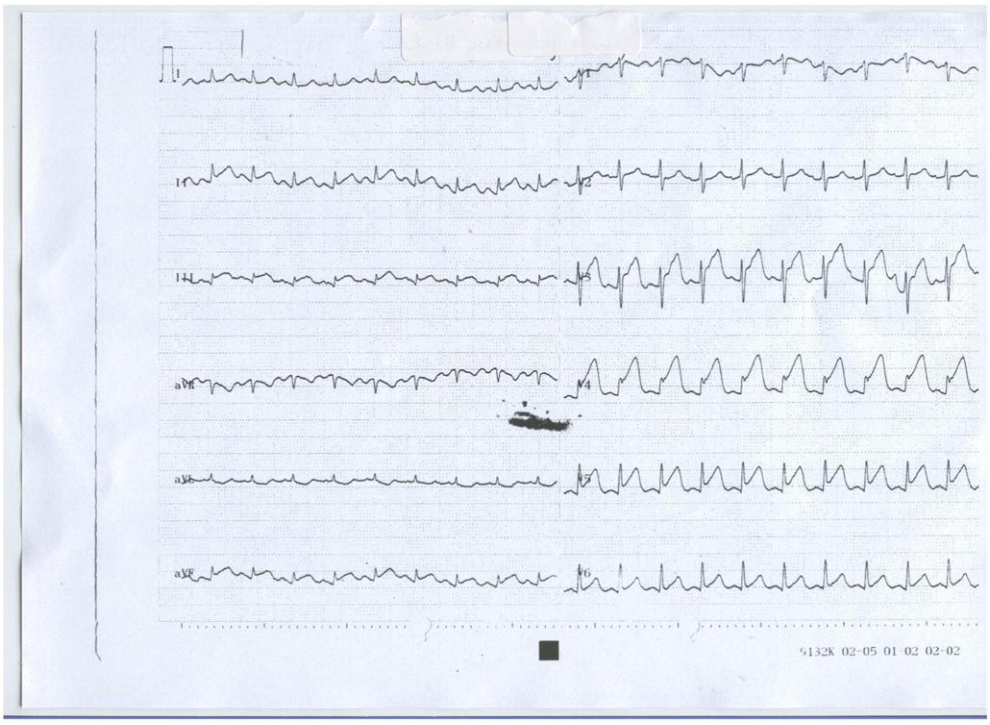


Fig. 1. Her admission electrocardiogram (ECG) showed acute ST segment elevation in leads V3–V6 and D2–D3–AVF.

Surgery. Vegetation that involved fibrin, neutrophils, plasma cells, lymphocytes and histiocytes were observed in the pathological examination of the resected mitral valve.

Discussion

MI associated with IE can occur due to septic embolization or compression of the coronary arteries by enlarging of aortic root abscess.[2] Most embolization occurs on the left main coronary artery and left anterior descending artery due to favorable anatomy regarding the larger and downward course than the right coronary system which is angled significantly.[3]

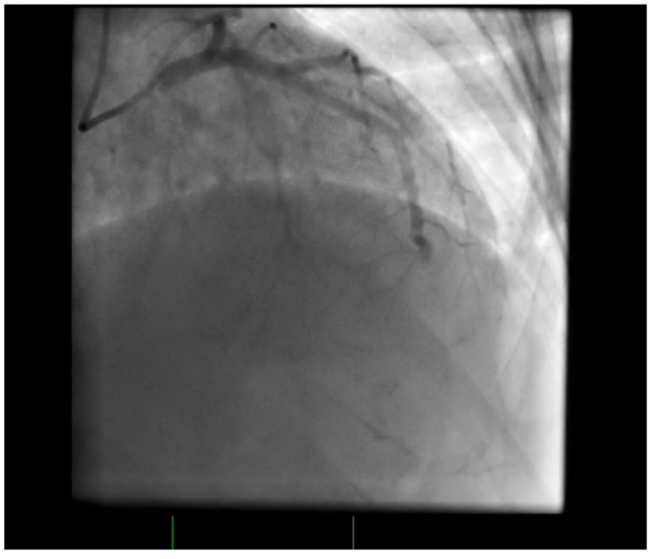


Fig. 2. Left coronary angiography showed total occlusion of the left anterior descending artery after the second diagonal artery.

On the left side of the endocarditis, risk of septic embolization to cerebral or peripheral organs is higher than coronary arteries. Septic embolization of coronary arteries is very rare but it may result in acute coronary syndrome.[4] In some cases, high risk of embolization due to IE has been reported. Accordingly, the risk of complication is higher in the cases of IE that affected the anterior leaflet of mitral valve. Also, IE due to *Staphylococcus aureus*, *Candida*, HACEK organisms and abiotrophia are at higher risk for embolization.[3,5,6] In our case, vegetation was observed in the anterior leaflet of the mitral valve. In spite of the circumflex and right coronary arteries being normal, observation of severe mitral regurgitation and chordal rupture was thought to be a result of local destruction caused by infection. In our case, the absence of positive blood cultures could be due to previous antibiotic usage.

Coronary embolism may cause ischemic chest pain, arrhythmias, valvular defects, pulmonary edema or sudden death. Severe valve regurgitation in the setting of endocarditis may be owing to destruction of valve or result of ischemia and infarction at the valvular apparatus. Anterolateral papillary muscle rupture as a result of embolic occlusion of the circumflex artery due to vegetation has been reported in the literature.[7] In our case, bedside transthoracic echocardiography findings were consistent with IE. TEE was performed to evaluate the possible complications and mitral valve vegetations were shown clearly by three-dimensional echocardiography.

The optimal treatment of MI in the setting of IE is controversial. Anticoagulation is not recommended to prevent embolization. There are a small number of cases where successful TT in the setting of ST segment elevation MI was associated with IE. Despite this, TT is not recommended due to a high risk of intracranial bleeding related with therapy.[8] Because lesions have a high risk of hemorrhage in cerebral vessels, such as mycotic aneurysms, which are more prevalent in IE. Also, septic conditions can increase the risk of intracranial hemorrhage leading to hemostasis disorders.

It seems safe to perform coronary angiography in the setting of IE. Abrupt occlusion of a coronary artery on angiography, despite the patency of other vessels and the absence of collaterals, should suggest the possibility of embolism.[9] In our case, we did not think septic emboli

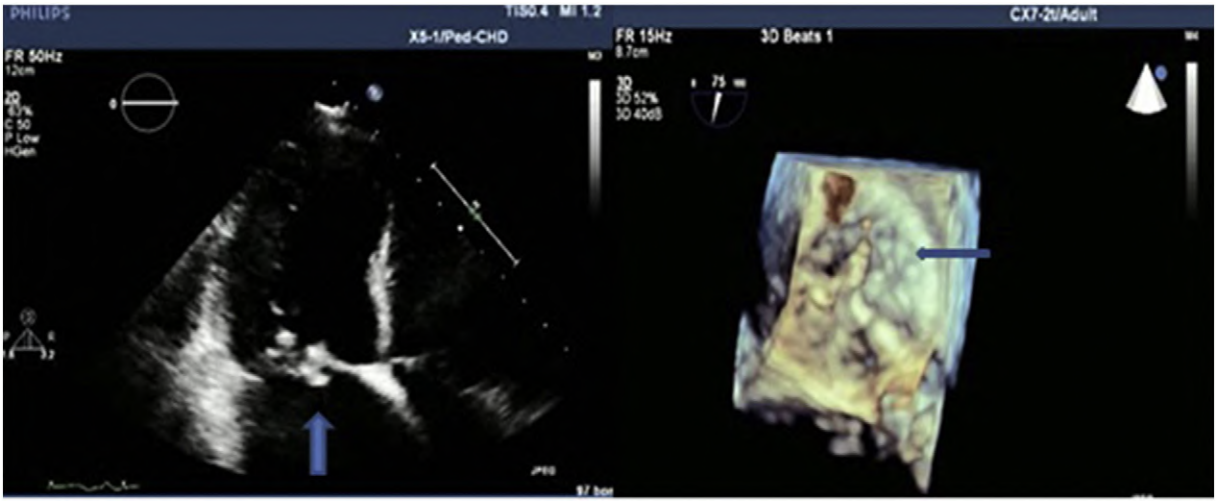


Fig. 3. Mobile mass (11 × 15 mm in size) compatible with vegetation on the edge of the anterior leaflet of mitral valve, partial rupture of chordae demonstrated by transthoracic echocardiography and three-dimensional echocardiography.

in the first evaluation because of no known heart disease, fever or diagnosis of IE. The patient was transferred to the catheter laboratory for primary PCI from the emergency department without losing time. However, the echocardiography, which was performed before TT due to detection lesion compatible with emboli in coronary angiography, murmur on physical examination and the young age of the patient changed our treatment decision.

Primary percutaneous coronary intervention can be performed for emergency revascularization in patients with IE. However, there are conflicting results regarding safety and efficacy of PCI in these patients. Furthermore, PCI due to bacterial thrombotic lesion is more difficult than atherothrombotic lesions. If the coronary arterial wall is compliant as in younger patients, full expansion of the balloon may cause distal embolism. However, if the embolus is rigid, the lesion may not be cross with the guide wire or reocclusion of the vessel can occur after balloon angioplasty. In such patients, intracoronary stent placement is recommended to ensure vessel patency. Also, in these cases, there are some risks because of stent implantation in the infected area. Localized mycotic aneurysm can originate from the stent implanted area.[10] If PCI cannot be performed, surgery and replacement of the infected valve should be performed to eliminate sources of embolism. Due to atherosclerotic changes on LAD coronary artery, in our first evaluation, we thought that myocardial infarction was associated with atherosclerotic plaque and therefore we planned to perform percutaneous coronary intervention. But, despite balloon support, our guide wire could not pass the lesion. In the foreground, we consider that infective endocarditis associated with myocardial infarction owing to the presence of mobile vegetation on TTE, the young age of the patient, the normal circumflex and right coronary arteries, the absence of risk factors for CAD and the clinical findings consistent with IE. However, it is possible that myocardial infarction was associated with atherosclerotic plaque rupture in our case.

In summary, the possibility of septic embolism should be considered in patients with IE who develop chest pain and ischemic ECG findings. In addition, the probability of septic emboli and IE should be considered in patients with ST elevation MI who have fever, murmur, and coronary angiographic findings compatible with embolism. Echocardiographic evaluation should be performed before thrombolytic therapy because MI may be the first presentation of IE.

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Case report

A case of atypically located left atrial myxoma with concomitant acute myocardial infarction and severe pulmonary hypertension

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ABSTRACT

Myxomas are the most frequently seen benign cardiac tumor. They mostly originate from interatrial septum. They can lead variable signs and symptoms. Opposite to their benign structure, embolic and obstructive complications can be fatal. Myxomas can rarely lead acute myocardial infarction due to coronary embolism. In this article, we presented a left atrial myxoma case that originated from posterior mitral annulus with simultaneous acute inferoposterior myocardial infarction, severe pulmonary hypertension and dynamic mitral stenosis. The patient was managed with successful percutaneous transluminal coronary angioplasty of the left circumflex artery without stenting and surgical removal of the myxoma consecutively. Pulmonary hypertension dropped significantly in postoperative follow-up.

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Introduction

Myxomas are the most frequent benign cardiac tumor but they are potentially hazardous. Seventy-five percent of myxomas are found in the left atrium (LA), mostly attached to interatrial septum (IAS). Mitral valve stenosis or systemic embolization are the most commonly seen clinical presentations of left atrial myxomas along with constitutional symptoms. Systemic embolism has been reported in 30%–50% of the case series.[1] A majority of the cases are sporadic but 7% of them have familial backgrounds. The left atrial myxomas have a significant potential for systemic embolization perioperatively to both peripheric and coronary vasculature.[2,3] Detection of this kind of pathology is very important in determining the treatment strategy since underlying pathology may lead to recurrence. Additionally, stenting with dual antiplatelet can increase bleeding risk perioperatively. In this article, we presented a case of atypically originated left atrial myxoma with simultaneous acute myocardial infarction and severe pulmonary hypertension. The patient was managed with successful percutaneous tranluminal angioplasty of the left circumflex artery (LCx) without stenting and surgical removal of the myxoma consecutively. In this article, we aimed to emphasize importance of preprocedural echocardiographic examination and the combined approach of percutaneous transluminal coronary angioplasty (PTCA) and surgery for the left atrial myxoma.

Case report

The patient, a 77-year-old woman, was admitted to the emergency room with clinical presentation of acute inferoposterior myocardial infarction with a squeezing chest pain of one-hour duration radiating to the shoulders. In the history, she had no relevant prior disease or any risk factor for cardiovascular disease and she did not describe any signs of heart failure or arrhythmias previously.

Blood pressure values were 130/70 mmHg, the pulse rate was 72 beats/min, the oxygen saturation was normal. Lung fields were clear of rales or ronchi except for a decrease in respiratory sound at the base of the right lung on auscultation. Cardiac examination revealed apical diastolic murmur of moderate intensity without opening snap at the left lateral decubitis position.

An initial ECG revealed sinus rhythm and premature atrial beats with significant ST segment elevation in leads II, III and aVF consistent with transmural ischemia.

A transthoracic echocardiographic examination showed the presence of an echogenic, mobile mass stemming from the corner of the lower IAS and the LA and protruding toward the posterior mitral leaflet and orifice, compatible with myxoma. The mass, 36 × 28 mm in size, was prolapsing toward the left ventricle and producing mitral gradient of 12 mmHg (Fig. 1). Along with these findings, there were inferoposterior wall motion hypokinesia, the left ventricule ejection fraction (LVEF) was 48%, moderate to severe tricuspid regurgitation, the estimated pulmonary artery systolic pressure (PASP) was

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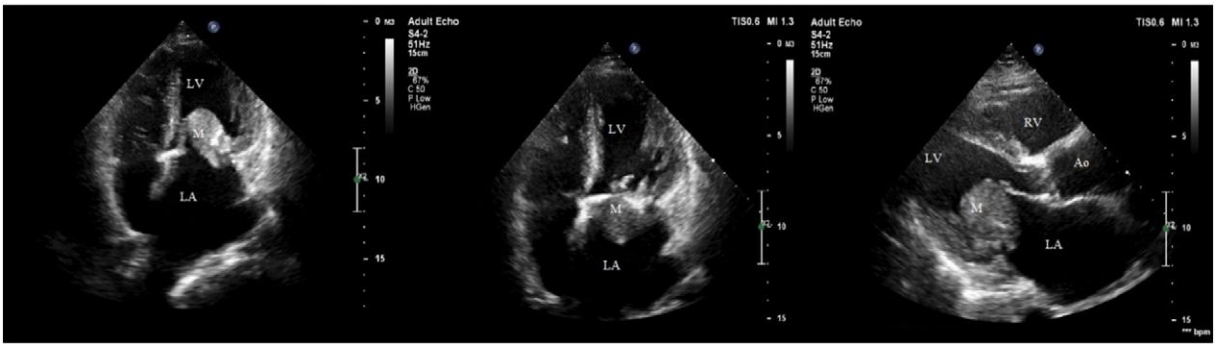


Fig. 1. Echocardiographic views of the myxoma.

90 mmHg and the LA diameter was 48 mm. Following prompt antiplatelet and anticoagulant treatment, she was transferred to the coronary angiography laboratory immediately. She had thrombotic total occlusion at the distal segment of the LCx along with non-significant, stable, atherosclerotic plaques at the left anterior descending and the right coronary arteries. Successful PTCA was performed without stenting for the LCx 30 min after her admission. Three days later, she underwent operation. A tumoral lesion of 45 × 38 × 46 mm in size with stalk stemming from posterior mitral annulus was excised via left atriotomy (Fig. 2). Under a light microscope, the tumor was composed of elongated, fusiform, stellate or polygonal cells with round to ovoid nuclei immersed in a myxoid stroma. No cytological atypia was present. Immunohistochemically, the tumor cells showed positivity for vimentin, CD34, factor VIII, calretinin and S100. They were negative for pancytokeratin and CD68. Histochemically, the myxoid stroma was positive for Alcain blue and PAS. In addition, focal calcification and excessive hemorrhage were detected in the tumor, mostly in the central area. Microscopic features were diagnosed as myxoma (Fig. 3). Postoperative ECG recordings were free of ST elevations on inferior leads. Additionally, postoperative first day echocardiography revealed significant decrease in PASP to 30 mmHg without any transmitral gradient and with no change in dimensions of the LV and the LA and mild mitral regurgitation. In the following days till discharge, the echocardiographic findings were similar to the previously described ones. The patient was discharged without complication. Postoperative 30th day echocardiographic examination showed mild mitral regurgitation and mild to moderate tricuspit regurgitation with estimated PASP of 40 mmHg with the LVEF of 59%.

Discussion

Myxoma is the most common benign cardiac tumor. Left atrial myxomas mostly present with changing levels of dyspnea imitating mitral stenosis and/or systemic embolization occurring in 30% to 50% of cases.[1] The incidence of coronary embolization is 0.06%.[4] Here, we presented a case of myxoma that originated from the posterior mitral annulus with concomitant acute inferoposterior myocardial infarction.

Atrial myxomas mostly stem from the fossa ovalis portion of the interatrial septum. The next most common location for myxomas is the posterior wall of the left atrium. However, valvular involvement of myxomas is more rare.[2] To the best of our knowledge, annular involvement has not been reported. In our case, the myxoma originated from the posterior mitral annulus with a pedicle. As in our case, females are more prone to have myxomas compared to males with a peak incidence at the third and sixth decades. Additionally, 67% of the subjects develop signs and symptoms of mitral stenosis in their life course;[5] however, our case was asymptomatic previously. It may be due to the development of severe pulmonary hypertension in the long term leading to reduced blood flow through the pulmonary artery and low cardiac output.

Compared to computed tomography and magnetic resonance imaging, transthoracic echocardiography is the method of choice in the emergency setting. It gives functional and anatomical data related to the myxoma. Myxomas present their clinical outcomes in accordance with location, size and mobility. Thus, symptomatology can vary respectively. Our case was asymptomatic with advanced age till the admission with acute myocardial infarction. As known, the incidence of coronary embolization is very rare.[4] It may be explained with the perpendicular alignment of the coronary ostia with respect to the aortic blood flow and protection of coronary ostia by the opening aortic valve leaflets. Approximately half of the cases involve the RCA. There is a concrete explanation for this tendency. There have been reports indicating that papillar or villous myxomas are more brittle and embolise more easily than myxomas with a smooth surface, it is not a must for embolization. Absence of previous coronary artery and risk factors for cardiovascular disease, absence of significant atherosclerotic coronary lesions, obtaining TIMI 3 flow just after guide wire passage and sustaining it

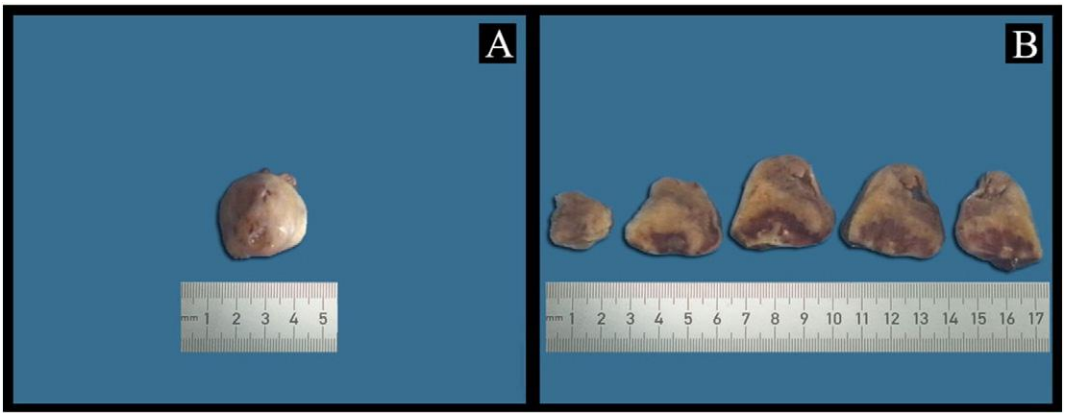


Fig. 2. Gross photographs of the lesion. (A) The rough surface of the lesion with a thin capsule. (B) The cut surfaces of the lesion containing hemorrhagic areas.

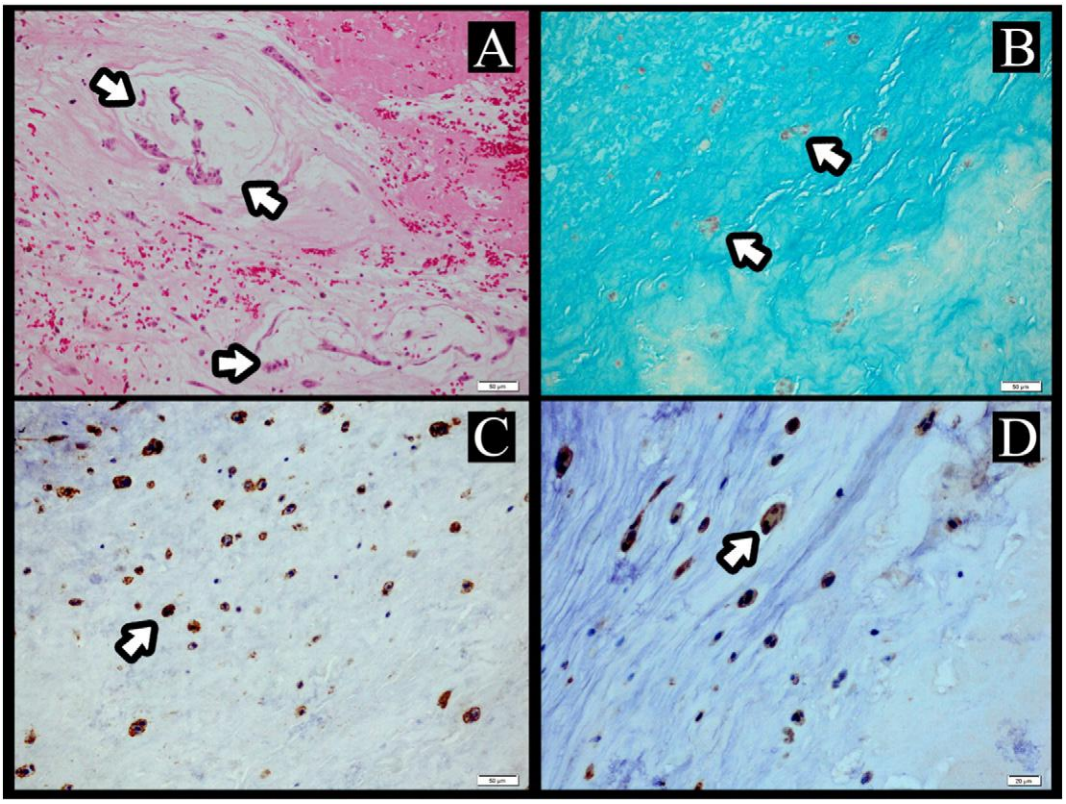


Fig. 3. The photomicrographs of the lesion. (A) The elongated, fusiform, stellate or polygonal tumor cells (arrows) in a myxoid and hemorrhagic stroma (hematoxylin and eosin stain, original magnification ×200). (B) The tumor cells (arrows) in the Alcian blue positive myxoid background (Alcian blue stain, original magnification ×200). (C) CD34 positivity in the tumor cells (arrow) (avidin–biotin–peroxidase method, original magnification ×200). (D) Calretinin positivity in the tumor cells (arrow) (avidin–biotin–peroxidase method, original magnification ×400).

with simple PTCA without stenting were suggested coronary embolism rather than atherosclerotic etiology for acute myocardial infarction. We did not perform thrombus aspiration due to the distal location of the occlusion and obtaining TIMI 3 flow as soon as the guide wire passage through the lesion. Additionally, embolism is not the sole reason for acute myocardial infarction but reduced coronary perfusion at cardiac diastole due to reduced cardiac output by tumor-related valvular stenosis may contribute to the process. Since the patient was suffering both mechanical and embolism complication of the myxoma, we preferred the surgical excision of the myxoma. Postoperative echocardiographic examination proved the dynamic nature of myxoma-related findings. Both PASP and tricuspid regurgitation were improved respectively along with symptoms. In the literature, there have been reports implying positive correlation between myxoma size and pulmonary hypertension as in our case.[6]

Percutaneous coronary intervention (PCI) of acute coronary syndromes with concomitant cardiovascular problems such as congenital abnormalities, myxoma, aortic dissection, valvular diseases, infective endocarditis are challenging. Mostly due to bleeding complications or necessity of long-term dual antiplatelet limit the use of stenting in primary PCI for acute coronary syndromes. Here, we preferred to perform PTCA alone. Another important issue in the management of the myxoma is mechanical obstruction of mitral valve by the mass. It can lead to acute pulmonary edema and termination of coronary perfusion during this period. These clinical settings can further complicate the patient status. Additionally, development of new neurological findings during and after PCI should raise suspicions of recurrent embolism or PCI-related adverse event. Differentiation can be important during surgical management. In our case, there was not any neurological deterioration.

Histopathological diagnosis of myxoma is usually straightforward due to its characteristic features similar to our case.[7,8] However, myxomas rarely include heterolog components, such as bland or atypical glandular structures (2%), thymic rests, bone formation, chondroid tissue and extramedullary hematopoiesis (7%) that might cause difficulty in the diagnosis of myxoma.[8] It should be noted that if myxoma contains glandular structures, it might be misinterpreted as metastatic adenocarcinoma.[8] Thus, the presence of a past or simultaneous history of adenocarcinoma elsewhere, presence of tumor invasion to the cardiac walls and using immunohistochemical methods for organ-specific antibodies may aid in distinguishing myxoma from metastatic adenocarcinomas.[8] The lesions in our case were processed totally, but no heterolog component was detected.

In a review of 48 patients, they found that the average age of patients with concomitant acute myocardial infarction and myxoma was 46 years and anterior wall involvement was less common than inferior wall. Our case was 77 years old with inferior wall involvement. Also, coronary angiographic examination of these patients yielded normal coronary arteries in 48.8% of the subjects and obstructive coronary artery disease in 51.2% of the subjects. Culprit lesion was the LCx in 38.1%, the right coronary artery in 28.6% and the left anterior descending artery in 23.8%. Similar to the literature, LCx involvement was the culprit lesion in our case.[9]

Pineda et al. reported a case with the left atrial myxoma and acute inferolateral myocardial infarction. In the coronary angiographic examination, they found acute occlusion of the first obtuse marginal branch of the LCx. The other coronary arteries were normal without plaque or dissection, coronary aspiration yielded no thrombus, and thus they considered the etiology of occlusion as embolism rather than atherosclerosis. They performed PTCA to treat the patient as in our case. Our case also didn't have any significant lesions in other coronary arteries; additionally, the subject didn't have any ulceration or dissection. We did not apply aspiration for the subject due to short of time so we couldn't analyse the occlusion material.[10]

We couldn't perform transesophageal echocardiography or magnetic resonance imaging to confirm the diagnosis due to the emergency setting. However, transthoracic echocardiography was well enough to manage the case in the acute setting.

In conclusion, we presented a demonstrative case of myxoma with acute myocardial infarction and severe pulmonary hypertension. The patient was treated with PTCA without stenting followed by total surgical excision. Additionally, significant improvement was observed at the follow-up.

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Competing interests

None declared.

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Short communication

Treatment approaches to coronary artery fistulae: A single center trial

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ABSTRACT

Background: A coronary artery fistula (CAF) is a sizable communication between a coronary artery, bypassing the myocardial capillary bed and entering either a chamber of the heart or any segment of the systemic or pulmonary circulation. It accounts for 0.27–0.40% of all cardiac defects.
Patients and methods: The study included 6 CAF patients hospitalized between January 2010 and June 2016. The mean patient age was 52.6. The sites of origin of the fistulae were from the left coronary artery in 4, from the right coronary artery in 1 and from right and left coronary arteries in 1 patient/patients. In all patients the site of termination was the pulmonary artery. The fistulae were closed surgically in 4 patients who also had accompanying cardiac pathology (3 patients with coronary artery disease and 1 patient with mitral stenosis) and in 2 patients without additonal coronary pathology with coil embolization performed in the angiography unit. In the surgically treated group, with cardiopulmonary bypass the fistula opening was closed through pulmonary arteriotomy in 2 patients and fistula was ligated epicardially in 2 patients. Moreover, in the surgical group of 4 patients, coronary artery bypass grafting was performed on 3 patients with coronary artery disease, and mitral valve replacement on 1 patient with mitral stenosis.
Results: All patients had no pathological symptoms and findings in the follow-up controls one and three months after the surgery.
Conclusion: We suggest that CAF in patients with additional cardiac pathology should be treated surgically and others by performing coil embolization.
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Introduction

A coronary artery fistula (CAF) may be described as a sizable communication between a coronary artery, bypassing the myocardial capillary bed and entering either a chamber of the heart or any segment of the systemic or pulmonary circulation. It accounts for 0.27–0.40% of all cardiac defects.[1] Coronary artery fistula was first described by Krause in 1865. In 1947, Bjork and Crafoord reported the first successful surgical intervention for CAF. The first successful transcatheter closure of CAF was reported in 1983.[2] Most babies and children are asymptomatic, but adults may show symptoms of fatigue, dyspnea, and chest pain which can also be associated with congestive heart failure occurring in young ages.[3]

Patients and methods

The study included 6 CAF patients (3 males and 3 females) hospitalized between January 2010 and June 2016. The patients were diagnosed by performing echocardiography (ECHO) and coronary angiography. The age range of the patients was between 42 and 57, with a mean of 52.6. The most frequent patient symptoms were fatigue (100%), effort angina (67%), and effort dyspnea (33%). In physical examination, continuous cardiac murmurs could be heard in 2 (33%) patients (Table 1). The radiographic examinations of the lungs showed cardiomegaly in 3 and increased pulmonary vasculature in 1 patient/patients. All patients had electrocardiographic (ECG) abnormalities which were left ventricular hypertrophy in 2, negative T wave in 3, and left axial deviation in 1 patient/patients. One patient had the results of a formerly made exercise test which showed inducible ischemia and negative T wave.

The definite diagnosis was reached by performing ECHO and coronary angiography. With ECHO, the origin and course of CAF could be determined in 2 patients as well as mitral stenosis in 1 patient (mitral valve area of 1.4–1.3 cm^2) and 1–2° mitral valve regurgitation in 1 patient. Along with angiography, right and left heart catheterization procedure was performed on all patients. As additional pathologies, coronary artery disease requiring intervention was diagnosed in 3 patients and severe mitral stenosis in 1 patient. Angiographically, the origin and morphology of the fistulae were determined, and the coronary arteries were evaluated. Five patients (83%) had single fistulae; the sites of origin of the fistulae were from the left anterior descending (LAD) in

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Table 1
Clinical characteristics of the patients.

	Age/sex	Symptoms	Murmur	ECHO	Origin	Surgery	Coil
1	42/M	Fatigue, effort angina, palpitation	Thrill +		LAD		+
2	49/F	Fatigue, effort dyspnea			LAD	+ ACBG	
3	57/M	Fatigue, palpitation, effort angina			LAD	+ ACBG	
4	52/M	Fatigue, effort angina			RCA	+ ACBG	
5	68/F	Fatigue, effort angina		1–2 MR	LAD		+
6	48/F	Fatigue, palpitation, effort dyspnea	Thrill +	MVA 1.4 cm^2	RCA and LAD	+ MVR	

4 (67%) and from the right coronary artery (RCA) in 1 (17%) patient/patients. One patient had fistula originating from right and left coronary arteries (17%) (Figs. 1 and 2). In all patients the site of fistula termination was the pulmonary artery.

The appropriate modes of therapy were decided by the council formed by members from the Clinics of Cardiology and Cardiovascular Surgery, after analyzing hemodynamic and angiographic findings of the patients.

Surgical intervention

The surgery was approached via a median sternotomy on all 4 patients. Following standard aorta-bicaval cannulation, the patients were put on cardiopulmonary bypass (CPB). In 2 patients, following application of moderate hypothermia and topical cold and placing a cross-clamp, cardiac arrest was achieved by antegrade cardiac cardioplegia. The arteriotomy of the pulmonary artery was performed with a longitudinal incision. The site of drainage of the fistula coming from the coronary artery was identified and closed with 6/0 prolene suture. Followingly, the pulmonary arteriotomy incision was appropriately closed and accompanying cardiac pathologies were corrected, thus ending the surgical intervention (Fig. 3). In 1 patient the fistula originated from RCA and in 1 patient from RCA and LAD. Since the coronary fistulae in these patients could not be epicardially determined, pulmonary arteriotomy was preferred (Figs. 4 and 5). External ligation of the fistula was performed on 2 patients. The fistulae of these 2 patients were of LAD-origin, and epicardial ECHO localized the artery feeding the fistula. In these 2 patients, CAF was ligated and cardiac pathologies were corrected before and after placing a cross-clamp, respectively.

Additionally, 3 patients underwent coronary artery bypass graft (CABG) and 1 patient underwent placement of valve prosthesis with MVR operation. The operations of all patients ended without problems. Following the appropriate closure of median sternotomy, all 4 patients were held under observation in the Intensive Care Unit until postoperative day 1.

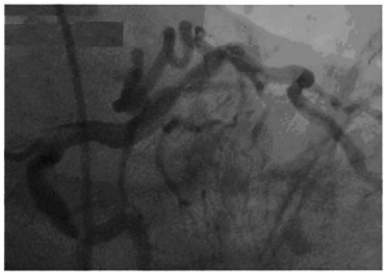


Fig. 1. Fistula from left coronary artery.



Fig. 2. Fistula from right coronary artery.

Coil embolization of the opening of coronary fistula under angiographic guidance was performed on 2 patients by the Cardiology Clinic.

Results

All patients undergoing surgery were closely followed up. There was no case of morbidity or mortality. The period of hospitalization ranged between 5 and 7 days with an average of 5.5 days. In the ECHO controls 1 and 3 months after surgery no pathology was detected, and the preoperative symptoms were resolved in all of the patients.

Conclusions

Coronary artery fistula is rare, but may present in patients at any age. Its incidence in angiographical series is 0.3–0.8%.[4] It may originate from any coronary artery including the left main trunk.[5] Major sites of origin of the fistulae are from RCA and LAD. CX is rarely affected.[6] In 55% of the cases, the site of origin is RCA or its branches. Fistulae originate from LAD in 35% and from both coronary arteries in 5% of the cases. In our study; fistulae originated from LAD in 4 (67%), from RCA in 1 (17%) and from both RCA and LAD in 1 (17%) of our patients. About 90% of the fistulae drain to venous circulation. Fistulae most commonly drain to low-pressure receiving cavities which are right cardiac chambers,



Fig. 3. Pulmonary arteriotomy and closure of the fistula.

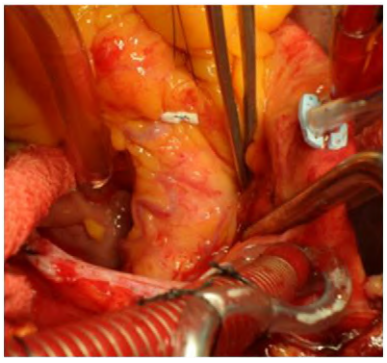


Fig. 4. External ligation to the proximal of the fistula.

pulmonary artery, superior vena cava, and coronary sinus.[7] Fistula draining to left cardiac chambers is very rare.[8] Fistulae drain to right ventricle in 41%, to right atrium in 26%, to pulmonary artery in 17%, to left ventricle in 3%, and to superior vena cava in 1% of the cases. There is only one single case in the literature draining to and causing hematoma in the pericardium.[9] Dilatation of the coronary artery may occur, but is not related to the size of the fistula.[4] Fistulous opening into a chamber or the drainage is mostly single or, rarely, multiple.[10] The probability of shunt formation is usually low if the drainage is to pulmonary artery. A left-to-right shunt exists in 90% of the cases. In all of patients, the coronary fistula drained to the pulmonary artery.

The clinical symptoms vary with the degree of left-to-right shunt.[11] Young patients are usually asymptomatic. The presenting symptoms of symptomatic cases may include fatigue, dyspnea, angina, arrythmias, paralysis, and myocardial ischemia or infarction.[11–12] All of the patients in our study were symptomatic cases; there was the complaint of fatigue in all of the patients, effort angina in 4, palpitations in 2, and effort dyspnea in 2. Myocardial ischemia or infarction may occur in the absence of atherosclerotic coronary lesion, caused by decreased coronary flow at the distal of the fistula. Rarely, pericardial effusion or sudden death may also ocur.[13] Continuous crescendo-decrescendo type systolodiastolic murmur is detected, and the murmur may have an unusual diastolic accentuation. Murmur was detected in 2 of our patients. In the presence of a major left-to-right shunt, pulmonary hypertension and congestive cardiac failure may develop as complications. Thrombosis of the ruptured fistula or fistula may be due to arterial aneurisma and coronary artery steal.

In the differential diagnosis, the disorders to be considered include persistent ductus arteriosus, pulmonary arteriovenous fistula, ruptured sinus of valsalva aneurysm, aortopulmonary window, supracristal ventricular septal defect with severe right coronary cusp prolapse, fistula originating from internal mammary artery draining into pulmonary artery, and systemic arteriovenous fistula.[14]

In ECHO, dilated coronary artery is frequently detected. Contrast-ECHO may give an idea about the site and size of the fistula.[15] Color Doppler may not reveal the flow at the distal of CAF. In such a case, transesophageal ECHO provides high quality images of the origin, course, and draining site of CAF.[4–16,17] The coronary-pulmonary artery fistulae in our 2 patients were detected by ECHO.

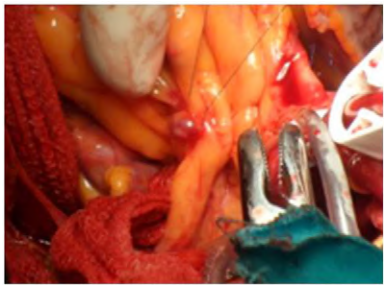


Fig. 5. External ligation of the fistula.

Selective coronary angiography, Standard aortography, and angiography made by baloon closure of aortic root supply information about the course and anatomic features of the fistulae.[18] Contrast computed tomography (CT) or contrast magnetic resonance imaging (MRI) may be performed as alternatives to coronary anigography.[19]

Spontaneously thrombolized secondary spontaneous closure is rarely reported.[10] Antiplatelet treatment is recommended for patients with distal coronary artery fistula or with abnormally dilated coronary artery.[12] Also prophylactic treatment for subacute bacterial endocarditis should be made.

The main indications for fistula closure are cardiac insufficiency, myocardial ischemia, and high-volume flow rate of fistula in asymptomatic patients.[16] Surgical and direct epicardial or endocardial ligamentation are the primary methods used in the management of CAF.[11] Surgical intervention is safe and effective, providing good results.[11–20,21] The management of young and asymptomatic patients with no significant shunt is still disputable. Some authors claim that small, asymptomatic CAF may be followed up for long term, requiring no surgery.[22] On the other hand, some authors claim that appropriate therapeutic approaches should be made as soon as CAF is diagnosed. According to the latter authors, the early closure of asymptomatic CAF might prevent the cardiac problems to occur in the future.[22]

The catheter-technique for closure of coronary fistulae is a nonsurgical alternative technique reported to provide success.[23] The transcatheter closure, started in the early 1980s, is an effective and safe method used in the management of CAF.[23] Multiple different closure devices are used including balloons, stainless steel coils, patent ductus arteriosus coils with controlled delivery systems, and plain or covered stents.[21–24] Following transcatheterization, the feeding artery is occluded distal to all normal branches to the myocardium minimizing the left-to-right shunt, which results in normalization of myocardial perfusion.[23] This technique may effectively and safely be used in the closure of significantly symptomatic CAF in children. Four of our patients underwent coil embolization in the Clinic of Cardiology.

The results of both transcatheter and surgical approaches indicate a good prognosis. Close clinical follow-up in all patients should be considered after CAF closure.[25]

Our approach to the management of CAF includes surgical closure of symptomatic fistulae that cannot be closed by coil embolization and/or fistulae with accompanying cardiac pathologies requiring correction; epicardial ligation in cases of fistula track that can be epicardially detected; and in case of no detection of epicardial track, detection and closure of the draining end of fistula by pulmonary arteriotomy and/or correction of the accompanying cardiac pathology. In cases of CAF with no accompanying cardiac pathology and requiring only epicardial ligation, we do not use CPB; on the other hand, in all other cases we perform bicaval cannulation and use CPB with intermediate hypothermia and cold blood cardioplegia. We think that median sternotomy is an appropriate technique for all patients. All patients who have undergone coronary surgical interventions should be provided with follow-up care after hospital discharge to check for evidence of ischemia or recurrence of CAF. Patients should be checked for symptoms and other findings and should have ongoing cardiac follow-up monitoring that may include ECHO and repeat angiography as needed. We are of the opinion that the surgical management of CAF is a safe and effective method with no morbidity and mortality. Asymptomatic CAF should carefully be evaluated in view of potential cardiac risks and closely followed up.

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Short communication

ECG-based atrial fibrillation detection using different orderings of Conjugate Symmetric–Complex Hadamard Transform

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ABSTRACT

Atrial Fibrillation (AF) is a classification of cardiac disrhythmia is an arrhythmia in which the heartbeat is irregular, too fast, or too slow. Because of this erratically changing behavior, effective pumping of blood by the heart to other organs results in malfunctioning of them. Generally, AF is seen commonly in elder people who are suffering from heart failure. To effectively treat AF, automatic detection methods based on electrocardiograph (ECG) monitoring is highly desirable. The objective of this study is to develop a novel algorithm able to detect atrial fibrillation episodes supervising a standard superficial ECG lead. In this discussion, AF is detected by considering the MIT/BIH arrhythmia database. The features of this database is extracted by using the different orderings of Conjugate Symmetric–Complex Hadamard Transform (CS–CHT), namely, natural order, Paley order, sequency order, and Cal–Sal order as they are fast and can be implemented with less memory usage as compared with the previous techniques in literature. The results obtained are applied to Levenberg–Marquardt Neural Network (LM NN) classifier and the performances of these techniques were estimated in terms of sensitivity, specificity, and overall detection accuracy on the datasets.

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Introduction

AF is an arrhythmia due to the anomalous discharges of electrical signals in the atria of heart in comparison to the ventricles, leading to the potential stroke due to the clot formation in the atrium. Effective prevention of AF[2,5] is possible by detecting the heart activities through analysis of electrocardiogram (ECG).[16] Episodes of AF comprise of unbalanced heart beat interval (RR) and/or low P-wave amplitude in the QRS complex in addition to the irregular cardiac frequency. In this paper, detection of AF is carried out by the extraction of atrial activity of MIT/BIH arrhythmia database. Primarily, noise in the signal is removed using filters and then the non-uniform beats obtained are converted to uniform beats of size 128 by resampling in order to extract features of the atrial with non-linear signal processing technique of 12-lead ECG with the detection of the spectral peak detection and spectral entropy by applying Fourier transforms in order to avoid the atrial and ventricular spectrum overlapping, which cannot be removed by linear filtering. But the previous works[4] failed to achieve this detection. In this paper, this drawback in feature extraction is overcome by considering different orders of Conjugate Symmetric–Complex Hadamard Transform (CS–CHT),[3] namely, natural order, Paley or dyadic order, symmetric order, and Cal–Sal order.[6,1] These extracted features are categorized into two classes, namely, Normal signal and AF signal by applying to a Levenberg–Marquardt Neural Network (LM NN) classifier. The optimized technique from all the techniques from different orders of CS–CHT is obtained by considering the sensitivity and specificity plot.

System Modeling

The detection of AF signal,[9,10] as shown in Fig. 1. using the electrocardiograph method, is performed in this paper by considering the following processes:

A. Preprocessing

The preprocessing contains mainly three steps

- Removing noise
- Segmenting the ECG files into beats
- Converting the non-uniform beats into uniform

The noise from the ECG signal is removed by using the filters. The obtained ECG files are segmented into beats by detecting the “R” peaks. The samples obtained from these beats are non-uniform samples. By using a technique called resampling, uniform samples of size 200 are generated from these non-uniform samples in each beat. The MIT–BIH Record numbers of AF database of 26 patients and Normal Sinus

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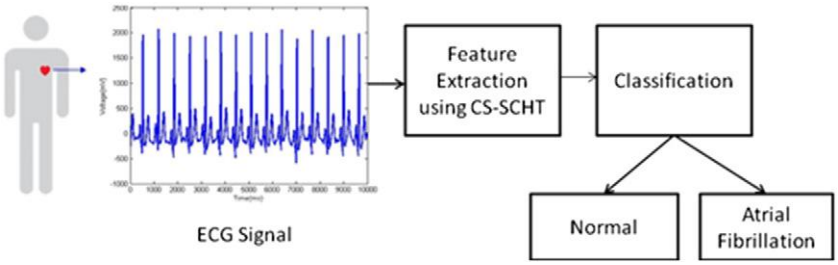


Fig. 1. ECG classification.

Rhythm database of 18 patients are used to detect AF. The sampling rate of normal signals is 128 Hz and AF signals are 250 Hz. For easy processing, they both are resampled again with the same sampling rate. De-noising of ECG signal is applied to Sgolay FIR smoothing filter. Beat is the $(2/3)^{rds}$ of the RR interval to the right of the R peak and $(1/3)^{rds}$ of the RR interval to the left of the R peak. After segmentation, each beat is resampled to 200 samples.

B. Feature Extraction

In real-time applications, Hadamard transform is used for the signals to be processed using various techniques like signal and image processing, digital logics because of uncomplicated realization of the fast algorithm. But Hadamard transform cannot be applied to complex signals, so, complex Hadamard transform is implemented, which consists of $\left\{\pm 1, \pm\sqrt{-1}\right\}$. The memory requirement for these transforms is high as compared to the DFT because DFT depends on frequency but not on sequency. Hence, a Conjugate Symmetric–Complex Hadamard Transform (CS–CHT) is introduced to reduce this memory requirement. Hadamard matrices can be ordered in different methods namely, natural, dyadic or Paley or bit–reversed, sequency,[8] and cal–sal orderings.[7]

By using the tensorial products, the rows of a natural order CS–Complex Hadamard matrices are obtained as represented below in Eq. (1).

$$H_S = \begin{bmatrix} H_{s/2} & H_{s/2} \\ H'_{S/2}T_{S/2} & -H'_{S/2}T_{S/2} \end{bmatrix} \tag{1}$$

where T_S and $H_{S/2}$ are represented using Eqs. (2) and (3).

$$T_S = \begin{bmatrix} I_{S/2} & 0 \\ 0 & jI_{S/2} \end{bmatrix} \tag{2}$$

$$H'_{S/2} = \begin{bmatrix} H'_{s/4} & H'_{s/4} \\ H'_{S/4}I'_{S/4} & -H'_{S/4}I'_{S/4} \end{bmatrix} \tag{3}$$

where $I'_{S/2}$ is defined using Eq. (4).

$$\mathrm{I}'_{S/2} = \begin{bmatrix} I_{S/4} & 0 \\ 0 & -I_{S/4} \end{bmatrix} \tag{4}$$

By placing $S=2$ in Eq. (1), we have

$$H_S = \begin{bmatrix} 1 & 1 \\ 1 & -1 \end{bmatrix}$$

CS–Complex Hadamard matrices in natural order satisfy the Good's theorem, which states the uniformity between the tensorial product and normal product with the sparse matrix as represented in Eq. (5).

$$(H_S)_{nat} = \begin{bmatrix} 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 \\ 1 & -1 & 1 & -1 & 1 & -1 & 1 & -1 \\ 1 & j & -1 & -1 & 1 & j & -1 & -j \\ 1 & -j & -1 & j & 1 & -j & -1 & j \\ 1 & 1 & j & j & -1 & -1 & -j & -j \\ 1 & -1 & j & -j & -1 & 1 & -j & j \\ 1 & -1 & -j & j & -1 & 1 & j & -j \\ 1 & 1 & -j & -j & -1 & -1 & j & j \end{bmatrix} \tag{5}$$

A CS–Complex Hadamard matrix is said to be in Paley ordered if the Rademacher functions are used to generate the Hadamard matrix. A Paley-ordered matrix is obtained from the natural ordered matrix by simply changing the row of a natural order with the bit–reverse of the row number. For example, for an 8×8 matrix, the natural row number 3 (011) is replaced by 6 (110). The FFT is similar to the fast algorithms of CS–Complex Hadamard matrix. The Paley ordered CS–Complex Hadamard matrix is represented in Eq. (6).

$$(H_S)_{pal} = \begin{bmatrix} 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 \\ 1 & 1 & j & j & -1 & -1 & -j & -j \\ 1 & j & -1 & -j & 1 & j & -1 & -j \\ 1 & -1 & -j & j & -1 & 1 & j & -j \\ 1 & -1 & 1 & -1 & 1 & -1 & 1 & -1 \\ 1 & -1 & j & -j & -1 & 1 & -j & j \\ 1 & -j & -1 & j & 1 & -j & -1 & j \\ 1 & 1 & -j & -j & -1 & -1 & j & j \end{bmatrix} \tag{6}$$

$$(\mathrm{H_S})_{\mathrm{seq}} = \begin{bmatrix} 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 \\ 1 & 1 & j & j & -1 & -1 & -j & -j \\ 1 & -1 & -j & j & -1 & 1 & j & -j \\ 1 & j & -1 & -j & 1 & j & -1 & -j \\ 1 & -j & -1 & j & 1 & -j & -1 & j \\ 1 & 1 & -j & -j & -1 & -1 & j & j \\ 1 & -1 & j & -j & -1 & 1 & -j & j \\ 1 & -1 & 1 & -1 & 1 & -1 & 1 & -1 \end{bmatrix} \tag{7}$$

$$(H_S)_{cal-sal} = \begin{bmatrix} 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 \\ 1 & -1 & -j & j & -1 & 1 & j & j \\ 1 & -j & -1 & j & 1 & -j & -1 & j \\ 1 & -1 & j & -j & -1 & 1 & -j & j \\ 1 & -1 & 1 & -1 & 1 & -1 & 1 & -1 \\ 1 & 1 & -j & -j & -1 & -1 & j & j \\ 1 & j & -1 & -j & 1 & j & -1 & -j \\ 1 & 1 & j & j & -1 & -1 & -j & -j \end{bmatrix} \tag{8}$$

Real-time applications use an ordering called sequency ordering, which is achieved by incrementing number of zero crossings. The sequency ordering is obtained from Paley ordering by simply applying gray code conversion for a row in Paley ordering. For example, for an 8×8 matrix, the Paley row number 7 (111) is replaced by 4 (100) in Sequency ordering. Eq. (7) represents the eight-order CS–Complex Hadamard Matrix in sequency order.

Another ordering algorithm proposed for CS–Complex Hadamard Matrix is Cal–Sal ordering. It can be achieved by placing even numbered

rows in the first half of the matrix in ascending order and odd numbered rows in the second half of the matrix in descending order as represented using Eq. (8). This order is more advantageous that the storage locations required are dropped by half, i.e., S storage locations required are dropped to $S/2$. Cal–Sal order matrix is symmetric.

C. Levenberg–Marquardt Neural Network (LMNN) Classifier

A back propagation Levenberg–Marquardt Neural Network (LMNN) method is used to detect the AF in this paper. Rapid execution of the network is done by using NN. A well-designed NN network comprises of 20 input neurons, 10 neurons in the hidden layer, and 3 neurons in the output layer. A comparison of these results is made with the Scalar Conjugate Gradient Neural Network (SCG NN) in which a conjugate direction search is performed instead of linear search. LMNN is a very simple and robust method for an approximating function. This network training and testing are performed by using 1800 ECG beats and 1006 ECG beats correspondingly by setting the total number of iterations to 1000 and mean square error less than 0.001 with the minimum time requirement.

Results and discussion

The convergence speed and final accuracy are increased by applying the results obtained from feature extraction as the input of a neural network. A sampling rate of 128 samples/beat is used for resampling process. In this feature, extraction techniques of CS–CHT using different orderings of natural, Paley, sequency, and Cal–Sal are used. The performance of these four techniques is compared as shown in Table 1 below.

For measuring accuracy, two parameters are used as shown in (8). They are sensitivity and specificity as represented in the Eqs. (9) and (10).

$$specificity = \frac{True_{Negative}}{True_{Negative} + False_{Positive}} \times 100 \tag{9}$$

$$sensitivity = \frac{True_{Positive}}{True_{Positive} + False_{Negative}} \times 100 \tag{10}$$

$$Accuracy = \frac{TP + TN}{TP + TN + FP + FN} \times 100 \tag{11}$$

$TP\ (True_{Positive})$ = Count of all the correctly classified Abnormal beats

$TP\ (True_{Negative})$ = Count of all the correctly classified Normal beats

$FP\ (False_{Positive})$ = Count of Normal beats classified as Normal beats

$FN\ (False_{Negative})$ = Count of Abnormal beats classified as Abnormal beats

The network performance is checked by applying a multilayer NN in training mode to decide if there is any requirement of any changes to the training progression or the data set or the system planning. The performance of different classifiers is compared as shown in Fig. 2. by plotting sensitivity ($True_{Positive}$ rate) and specificity ($False_{Positive}$ rate) and it is obtained that the cal–sal order of CS–CHT achieves the maximum performance compared to that of the remaining orders.

Table 1
Classification using LM NN classifier.

Classifier	Sensitivity	Specificity	Accuracy
$CS-NCHT+LMNN$	87.3%	89.9%	67.8%
$CS-PALEYCHT+LMNN$	89.2%	91.2%	89.3%
$CS-SCHT+LMNN$	92.2%	93.342%	93.2%
$CS-CAL-SALCHT+LMNN$	98.7%	99.97%	99.1%

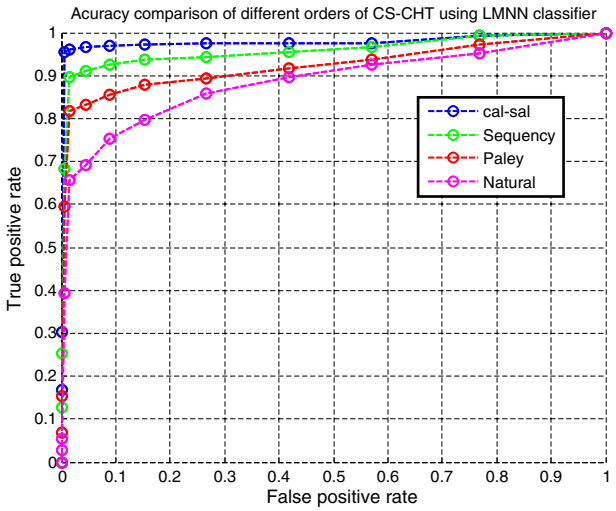


Fig. 2. Comparison of different orders of CS–CHT using LM NN classifier.

The proposed method is compared with the other four detection algorithms as shown in the Table 2 such as, RR interval (RRI), AR coefficients, symbolic dynamics (SD), and Shannon entropy and WTC features in terms of related features selected from the original database and classification accuracy obtained from different classifiers using Matlab software. The work in Ref. 14 explored an experimental study based on the difference between RR intervals for extracting relevant features for the detection of AF. The values of sensitivity and specificity are 94.4% and 97.2%, respectively. The work presented in Ref. 12 used AR coefficients as features for classification AF using three different classifiers. AR coefficients are calculated for each 15-second data sequence length. The values of specificity and sensitivity are 96.14% and 93.20%, respectively. The work proposed in Ref. 13 used three statistical methods for the detection of AF. These techniques are tested on AF database and Normal database. The values of sensitivity and specificity are 97.2% and 95.91%, respectively. The work proposed in Ref 16 used SD and entropy and computed various operations like nonlinear or linear integer filtering. Online analytical processing of the method can be achieved using this novel algorithm. The values of sensitivity, specificity, and accuracy are 96.89%, 98.27%, and 98.03% respectively.

The work proposed in Ref. 11 used WTC coefficients for the detection of AF. The WTC features for the normal and AF datasets are calculated. These features are optimized using PCA algorithm. The values of sensitivity, specificity, and accuracy are 100%, 96.9%, and 99.1%, respectively.

From the experiments, this study concludes that the proposed beat feature optimization technique with cal-sal order of CS–CHT outperformed other three algorithms with selection of minimal number of relevant features using CS–CHT. The proposed method shows the highest classification accuracy for the detection of AF. The CS–CHT has been employed intelligently to select the most relevant features that could increase the classification accuracy while ignoring noisy and redundant features.

This procedure helps us to automate a certain section or part of the diagnosis and then it will help the medical community to focus on other crucial sections. This has also increased the accuracy of diagnosis.

Conclusions

Automation of diagnosis of the human heart by measuring ECG plays a major role in saving a patient. In this paper, this life saviour is achieved in detection of AF signal with an accuracy of 99.9% by applying CS–SCHT technique to the LMNN classifier. The obtained experimental results have shown that the proposed SCHT method can extract more relevant features than the other methods proposed in the literature with highest classification accuracy for the detection of AF.

Table 2
Comparative study of detection of AF.

Studies	Approach	Sensitivity (%)	Specificity (%)	Accuracy (%)
Tateno et al. (2001)[14]	RR interval	91.20	96.08	_
Parvaresh et al. (2011)[12]	AR coefficients	96.14	93.20	90.09
Lee et al. (2013)[13]	RR interval	97.26	95.91	_
Zhou et al. (2014)[15]	SD and entropy	96.89	98.27	98.03
Padmavathi Kora et al. (2016)[11]	WTC features	100	96.9	99.1
Proposed approach	Cal–sal order of CS–CHT	99.97	98.7	99.5

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