Primary aldosteronism and coronary-pulmonary artery fistula: coincidence or causal link? A case report and literature review

Luigi Marzano

Internal Medicine Unit, St. Bortolo General Hospital, Vincenza — Veneto Region, Italy

Abstract

Background: Primary aldosteronism (PA) is the most frequent form of potentially reversible hypertension and coronary-pulmonary fistulas are increasingly recognized during routine coronary angiography or multidetector computed tomography for analysis of chest pain in hypertensive patients. Aldosterone hypersecretion has been associated with endothelial proliferation and pathological remodeling of the heart and arteries, though coronary artery fistulas have never been reported in patients with PA.

Case presentation: The authors report the first case of PA with dilated cardiomyopathy unusually associated with electrocardiographic changes after normalization of hypokalemia and with the finding of a coronary-pulmonary fistula during coronary angiography. The clinical presentation and our diagnosis and treatment decision-making in the COVID-19 era are discussed below.

Conclusions: Our case suggests a potential link between hypertensive patients with coronary artery fistulas and PA.

Key words: aldosterone; cardiomyopathy; coronary-pulmonary fistula; hyperaldosteronism; hypertension; ECG

Arterial Hypertens. 2021, vol. 25, no. 1, pages: 47–52
DOI: 10.5603/AH.a2021.0006

Introduction

Although primary aldosteronism (PA) was initially considered a rarity, now it is one of the most common causes of secondary hypertension in which aldosterone production is inappropriately high and partially autonomous from the renin-angiotensin system. Broadly, PA can be dichotomized to unilateral aldosterone production from the left or right adrenal gland (aldosterone-producing adenoma; APA, or Conn's syndrome) or bilateral hyperaldosteronism (BHA). APA can be cured surgically and it is therefore important to distinguish it from BHA, which is managed medically with mineralocorticoid receptor antagonists. Appropriate diagnostic management of PA consists of three consecutive steps: first, screening test with the aldosterone to renin ratio, then case confirmation through the aldosterone suppression tests and last, discrimination of unilateral from bilateral forms of PA by adrenal venous sampling.

Our case highlights an atypical clinical presentation of PA and our choice of a diagnostic therapeutic decision-making plan amid the delicate and complex first spread of COVID-19 in Italy.

Address for correspondence: Mr. Luigi Marzano, MD, MSc, 8, via Del Fabbro, 36100, Vicenza, Italy, tel. (+39) 320 7922260; e-mail: marzanoluigimd@gmail.com

Case presentation

A 53-year-old Caucasian obese man with a history of modest fatigue and subjective dyspnea was admitted to our hospital after undergoing an outpatient transthoracic echocardiography (TTE) that showed cardiac dysfunction in March 2020, amid the pandemic of COVID-19. The patient had been in good health until 2 months before the current admission, when he saw his primary care physician for the first time presenting an asthenia lasting some weeks. Blood pressure (BP) taken in office was repeatedly noted to be 210/110 mm Hg regardless ongoing therapy with three blood-lowering drugs

Owing to his recent history of fatigue and frequently reoccurring atrial and ventricular extrasystoles (the patient was scheduled for 24-hour ECG monitoring, TTE and exercise stress test (EST).

As the TTE documented moderately dilated and hypertrophic left ventricle with a decreased contractility of the inferior and septal walls as well as modestly reduced ejection fraction (Tab. 1) the patient after the negative result for SARS-CoV-2 RNA testing was admitted in our department for detailed evaluation.

On admission, the patient was obese (BMI = 37 kg/m^2) and had a two-month history of poorly controlled hypertension, treated with amlodipine 10 mg, ramipril 5 mg and bisoprolol 1.25 mg a day. His father had ischemic cardiomyopathy but there was no family history of sudden cardiac death. He did not drink alcohol, smoke tobacco or use illegal drugs and reported drinking about 2.5 liters of water a day and snoring during the night without experiencing daytime sleepiness. On physical examination, heart rate was 104 beats per minute and the BP was 140/110 mm Hg, respiratory rate of 16 breaths per minute and the oxygen saturation 97% while the patient was breathing ambient air. Laboratory tests (Fig. 1) revealed mild to moderate hypokalemia and the arterial blood gas showed hypoxemia and primary metabolic alkalosis with a secondary respiratory alkalosis. HbA_{1c} levels were diagnostic for new onset type 2 diabetes mellitus. A chest X-ray and ECG performed at the time of admission were unremarkable as well (Fig. 2A).

Investigations

During the wide spread of coronavirus, it was necessary to invest few resources in a targeted manner and to contain the risk of hospital infections with rapid and effective hospitalizations. In such circumstances, we studied the renin-angiotensin-aldosterone system after only one week of therapy with a calcium channel blocker and a serum potassium > 4 mmol/L with oral potassium supplements.

The aldosterone/renin ratio screening test was compatible with a suspected PA, later proved by the lack of aldosterone suppression after intravenous saline load (2 L of 0.9% saline infused over 4 h) (Fig. 1). The subtype diagnosis of PA was made by means of abdomen CT scan, which showed an adenoma of 7 mm in diameter in the lateral limb of the right adrenal gland and a slight thickening of the contralateral gland (Fig. 3A).

It was surprising to notice that, 18 hours after hospitalization and oral potassium supplementation, in the absence of symptoms or secondary causes, significant changes were observed in the ventricular repolarization on ECG (Fig. 2B) with indications by the cardiologist to perform a coronary angiography and start dual antiplatelet therapy with aspirin and clopidogrel. Selective coronary angiography showed a right dominant coronary circulation and a slightly reduced left ventricular function due to diffuse hypokinesia, without evidence of significant stenoses. Furthermore, the presence of a fistula from the left anterior descending coronary draining into the pulmonary branch was detected (Fig. 3B). After a week from admission, we observed a progressive and complete normalization of ventricular repolarization on the ECG and a twenty-four hour Holter monitoring showed a sinus rhythm with no significant arrhythmias.

Table 1. Change in echocardiogram parameters before and after 9 weeks of medical treatment†

	Before treatment March 9, 2020	After treatment May 15, 2020	Reference range, Adults
LVEDVI [mL/m^2]	95	67	< 75
LVEF (%)	43	51	≥ 52
LAVI [mL/m^2]	39	25	≤ 34
PWT [mm]	12	10	< 11
IVS [mm]	13	12	< 11

†Spironolactone 100 mg, amlodipine 5 mg and bisoprolol 2.5 mg daily. LVEDVI indicates LV end-diastolic volume index; LVEF — LV ejection fraction; LAVI — LA volume index; PWT — posterior wall thickness; IVS — interventricular septal thickness

	8 Wk before Current Admission		6 Wk before Current Admission	On Admission	14 hours after Admission	Hospital Day 6	
Date (year 2020)	January, 10		January, 27	March, 9	March, 10		
	Medical practitioner	**ER 1st access**	**ER 2nd access**	**ER 3rd access**	**Hospitalization**		
Symptoms and remarks	Fatigue, dyspnea		Palpitations, fever	Cardiac dysfunction			
Relevant testing	None		Laboratory, abdominal US	Echocardiography, laboratory, ECG		Abdominal CT scan, coronary angiography	
Clinical and Laboratory data							***Reference range†***
Clinic SBP/DBP (mmHg)	210/110	140/70	140/77	140/90	140/110	135/86	
Antihypertensive drugs (n)	0	0	1	3	3	1	
White-cell count (x10^9/liter)			**12.6**	9.9	7.9		*3.5 - 11.0*
Hemoglobin (g/liter)			133	149	144		*125 - 169*
C-reactive protein (mg/dL)			**26.0**		**1.9**		*0.0 - 0.5*
Creatinine (g/dL)			1.17	0.83	0.77		*< 1.30*
Sodium (mmol/liter)			136	142	145		*135 - 145*
Potassium (mmol/liter)			**2.8**	**3.0**	4.0	4.1	*3.3 - 5.0*
Magnesium (mg/dL)					2.1		*1.7 - 2.6*
Glucose (mg/dL)			**121**	97	**120**		*70 - 99*
Glycated hemoglobin (mmol/mol)					**48**		*20 - 41*
Total cholesterol (mg/dL)					178		*< 190*
LDL-cholesterol (mg/dL)					119		*<130*
Triglycerides (mg/dL)					99		*< 150*
TSH (mUI/liter)			2.2		1.1		*0.4 - 3.7*
NT pro-BNP (ng/liter)			**3681**	**4049**		**399**	*< 300*
Troponin I (ng/liter)			47	16	17		*0 - 60*
Aldosterone (ng/liter)					**294**		*30 - 150*
Renin (µU/mL)					**1.0**	**0.7**	*3.0 - 29.0*
ACTH (ng/liter)					57		*< 95*
Cortisol (µU/mL)					235		*50 - 250*
ABG: pH				**7.5**			*7.35 - 7.45*
PaO2 (mmHg)				**63**			*75 - 100*
PaCO2 (mmHg)				40			*35 - 45*
HCO3- (meq/liter)				**29**			*22 - 26*
SaO2 (%)				97			*95 - 100*
Aldosterone post SLST (ng/liter)						**114**	*<50*
Cortisol post ODST (µg/L) Hospital day 7						<10	*<50*
24-h urinary cortisol (µg/day)					222		*70 - 320*
24-h urinary metanephrine (µg/day)					107		*< 280*
24-h urinary normetanephrine (µg/day)					**534**		*< 500*
Diagnosis	Hypertensive crisis		Acute cholecystitis	PA with Dilated CMP and CPF			

Figure 1. Timeline. ER — emergency room; US — ultrasound; CT — computed tomography; PA — primary aldosteronism; CMP — cardiomyopathy; CPF — coronary-pulmonary artery fistula; SBP/DBP — systolic and diastolic blood pressure; TSH — thyroid-stimulating hormone; NT pro-BNP — N-terminal pro-B-type natriuretic peptide; ABG — arterial blood gas; ODST — overnight dexamethasone suppression test; SLST — saline load suppression test performed with calcium channel blocker and serum potassium 4 mmol/liter. To convert the values for glucose to millimoles per liter, multiply by 0.05551. To convert the values for creatinine to micromoles per liter, multiply by 88.4. †Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at our Hospital are for adults who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients

Treatment

Current guidelines suggest the use of unilateral adrenalectomy or mineralocorticoid receptor antagonists (MRA) for the treatment of PA with or without lateralized aldosterone secretion, respectively [1].

Due to the complex and delicate COVID-19 pandemic and in compliance with the WHO declaration and the United States Surgeon General's recommendations [2] suggesting to cancel elective surgeries at hospitals with the concern that elective procedures within facilities may contribute to the spreading of the coronavirus so as to utilize the medical resources needed to manage a potential increase of coronavirus cases, we discharged the patient with a MRA therapy, waiting to perform the adrenal venous sampling in order to confirm the lateralization of overproduction of aldosterone for the best treatment.

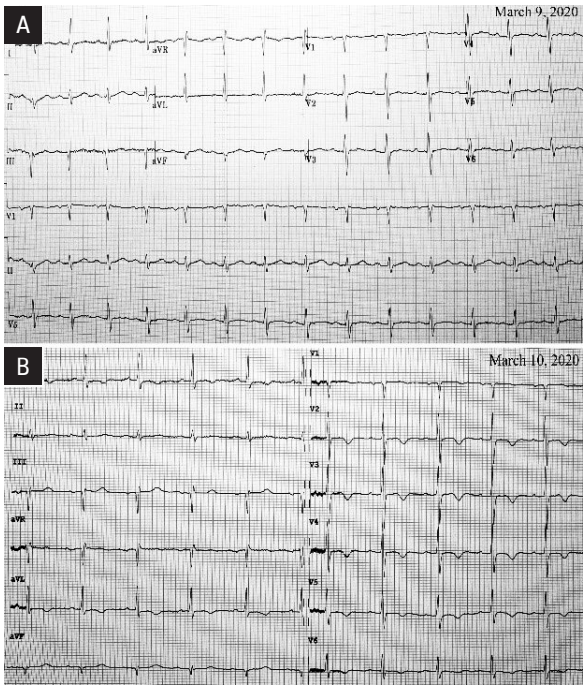

Figure 2. Twelve-lead ECG tracing done upon the arrival of the patient at the emergency room (**A**). ECG tracing showing negative T wave in the precordial leads V2-6 after 18 hours from admission and oral supplement of slow-release potassium chloride (600 mg or 8 mmol per tablet), 2 tablets every 6 hours (**B**)

Outcome and follow-up

About two weeks after discharge, we achieved the normalization of plasma potassium levels and a sufficient BP control with spironolactone 100 mg, amlodipine 5 mg and bisoprolol 2.5 mg a day. Currently in medical treatment the patient is still under follow-up in our clinic with good clinical and echocardiographic outcomes [3, 4] (Tab. 1) and no complications.

Discussion

Hypertensive patients with PA showed the increased risk of coronary artery disease, heart failure, atrial fibrillation and stroke, compared with patients with essential hypertension [5]. The classic presenting signs of PA are resistant or difficult-to-control hypertension and hypokalemia, but less than half of the cases show these two conditions [1] and also because of this the unsuppressible (primary) hypersecretion of aldosterone is often an underdiagnosed cause of hypertension.

A wide body of experimental and clinical researches has demonstrated that inappropriately increased aldosterone secretion induces a significant inflammation, remodeling and fibrosis on cardiovascular system, including endothelial proliferation and vascular remodeling, which cannot be explained only by the increased degree of blood pressure [6–10]. Yet a link between primary aldosterone hypersecretion and coronary artery fistulas has never been reported.

In 1964, James O. Davis et al. have investigated on animal models the aldosterone secretion and the mechanisms which lead to hypersecretion of aldosterone in experimental high-output heart failure secondary to an aortic-caval fistula [11]. Higher aldosterone concentrations in patients free from overt cardiovascular disease are associated with the increased risk of subclinical coronary atherosclerosis and all-cause mortality particularly among individuals with renin suppression [12]. In patients with PA, complex mechanisms may lead to functional and structural abnormalities of the blood vessels walls. Clinical evidence indicates that PA patients may have immune cell activation, increased oxidative stress,

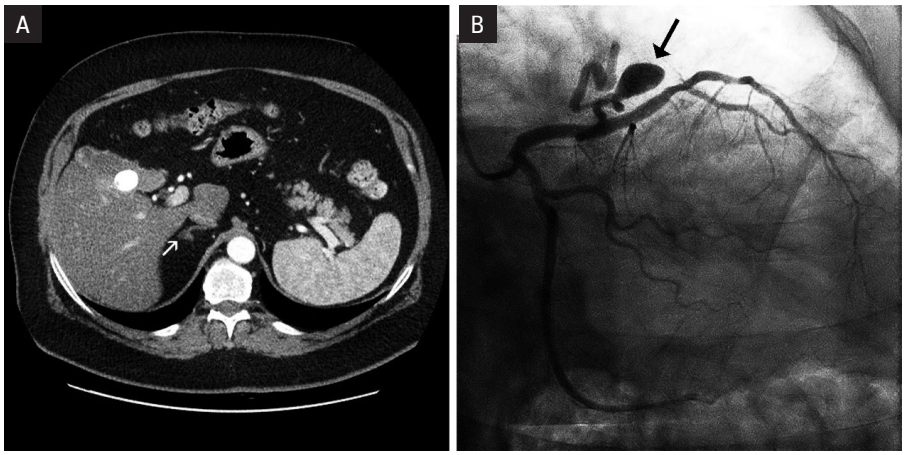

Figure 3. Transverse CT scan of the abdomen showing a nodule in the lateral limb of the right adrenal gland (*Arrow*) compatible with the adenoma measuring 7 mm (**A**). Coronary angiogram clearly showing a coronary artery fistula (*Arrow*) between the proximal left anterior descending artery and the pulmonary artery (**B**)

endothelial dysfunction and proliferation with vascular remodeling [13]. There is evidence that aldosterone via the mineralocorticoid receptor (MR) promotes angiogenesis. In vitro findings, aldosterone exacerbated retinal neovascularization in ischemic retinopathy which was attenuated with MR antagonist (MRA). The aldosterone infusion increased VEGF mRNA levels and neovascularization in mice with hindlimb ischemia, and these events were reduced with spironolactone [14]. It was also noticed that in a mouse model, a modest increase in plasma aldosterone concentration can modulate cardiac genes expression and induce the proliferation of cardiac endothelial cells in vivo. Aldosterone-induced MR-dependent proliferation was confirmed ex vivo in human endothelial cells and the pharmacological-specific blockade of the MR by eplerenone inhibited endothelial proliferation in a rat model of heart failure [7]. Recently, Rho-associated kinase (ROCK) activity has drawn attention for its crucial role in angiogenesis [15] and the treatment with eplerenone for 12 weeks improves arterial stiffness, vascular smooth muscle function and microvascular endothelial function, and inhibits ROCK activity in patients with PA [16].

Thus far, however, PA has not been reported as a clear cause for dilated cardiomyopathy [17] or coronary arteriovenous fistulas.

Coronary-pulmonary fistulas (CPFs) are rare congenital or acquired coronary artery anomalies that can originate from any of the three major coronary arteries and drain into any of the cardiac chambers and great vessels. According to a literature review, the published epidemiological data may underestimate the real prevalence of the coronary artery fistulas in the general population, while the incidence in the echocardiographic series was 0.06 to 0.2%, in the necropsy series 14%, and in the angiographic series was 0.1% to 0.67% [18]. Furthermore, with the increasing use of the coronary artery angiography and multidetector computed tomography for the analysis of chest pain, the number of incidentally detected unilateral and multilateral CPFs has been gradually rising [18]. Although they are often incidental findings, patients with CPFs may have arrhythmias, angina, dyspnea, congestive heart failure, pulmonary hypertension, endocarditis, and sudden cardiac death. Therefore, their potential clinical consequences require further investigation in order to adopt either interventional (percutaneous transcatheter closure/surgical ligation) or conservative treatment, preventing any complications such as aneurysm creation, vessel dissection, pericardial effusion, coronary arterial steal phenomenon, thrombosis and myocardial infarction [19]. The American Heart Association/American College of Cardiology guidelines suggest the transcatheter occlusion for symptomatic fistulas and for moderate or large fistulas without clinical manifestations [18]. Nevertheless, the best approach to the asymptomatic CPFs is still controversial.

The excellent echocardiographic results observed after 2 months of MRA therapy support the hypothesis that PA was the primary cause of dilated cardiomyopathy in our patient and his mild-moderate CPF currently deserves a careful follow-up for the appearance of symptoms.

Both PA and CPFs might be associated with ECG changes and arrhythmias. However, a paradoxical T-wave inversion in the precordial leads was observed in our patient after oral potassium supplementation. Changes in electrolyte levels can affect depolarization and/or repolarization and can cause ECG changes. In a recent prospective study on hospitalized hypokalemic patients, it was found that 85% of them experienced ECG changes after potassium correction and 36% of patients who showed a T-flat or T-inverted might have a T-wave inversion after potassium supplementation. In addition to this, there was no significant relationship between post-correction potassium levels and ECG changes [20].

Conclusions

In summary, the presented case highlights novel aspects related to PA and its diagnostic algorithms. Therefore, we strongly recommend cardiologists and clinicians to maintain a high level of suspicion of PA in hypertensive patients with finding of coronary artery fistulas (Tab. 2). Further studies will be needed to clarify this association.

Conflict of interests

The author has no conflict of interest that is relevant to the subject matter included in this work.

Patient consent

Obtained.

Acknowledgments

We thank all the medical staff, residents, and nurses of our Hospital.

Funding

None declared.

Table 2. Learning points and take-home messages

- Hypertensive crises in the emergency room are often underestimated. Patients, particularly if young and presenting spontaneous hypokalemia, should be referred initially to the Hypertension Reference Centers for screening and/or early diagnosis of secondary forms of hypertension.
- The finding of CPFs in hypertensive patients should lead to a high suspicion of underlying PA.
- In patients with PA and chronic hypokalemia, the correction of serum potassium levels might be associated with transient T-wave inversion on the ECG.
- PA should be excluded as a potential cause of dilated cardiomyopathy, because evidence suggests that there may be a probable causal relationship between dilated cardiomyopathy and PA [17].
- The clinical practice guidelines for case detection, diagnosis, and treatment of PA are an essential part of quality medical practice, though the flexibility in diagnostic and therapeutic decision-making is sometimes the only alternative available, such as during the CoViD-19 pandemic crisis.

CPFs — coronary-pulmonary fistulas; PA — primary aldosteronism

References

1. Funder JW, Carey RM, Mantero F, et al. The Management of Primary Aldosteronism: Case Detection, Diagnosis, and Treatment: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2016; 101(5): 1889–1916, doi: 10.1210/jc.2015-4061, indexed in Pubmed: 26934393.
2. Commins J. Surgeon general urges providers to consider stopping all elective surgeries — hospitals push back. Health Leaders Health Leaders Media, Brentwood, TN 2020.
3. Marzano L, Colussi G, Sechi LA, et al. Adrenalectomy is comparable with medical treatment for reduction of left ventricular mass in primary aldosteronism: meta-analysis of long-term studies. Am J Hypertens. 2015; 28(3): 312–318, doi: 10.1093/ajh/hpu154, indexed in Pubmed: 25336498.
4. Catena C, Colussi G, Di Fabio A, et al. Mineralocorticoid antagonists treatment versus surgery in primary aldosteronism. Horm Metab Res. 2010; 42(6): 440–445, doi: 10.1055/s-0029-1246185, indexed in Pubmed: 20119883.
5. Monticone S, D'Ascenzo F, Moretti C, et al. Cardiovascular events and target organ damage in primary aldosteronism compared with essential hypertension: a systematic review and meta-analysis. Lancet Diabetes Endocrinol. 2018; 6(1): 41–50, doi: 10.1016/S2213-8587(17)30319-4, indexed in Pubmed: 29129575.
6. Tsai CH, Pan CT, Chang YY, et al. TAIPAI Study Group. Endothelial Dysfunction in Primary Aldosteronism. Int J Mol Sci. 2019; 20(20): 131–147, doi: 10.3390/ijms20205214, indexed in Pubmed: 31640178.
7. Gravez B, Tarjus A, Pelloux V, et al. Aldosterone promotes cardiac endothelial cell proliferation in vivo. J Am Heart Assoc. 2015; 4(1): e001266, doi: 10.1161/JAHA.114.001266, indexed in Pubmed: 25564371.
8. Hung CS, Sung SH, Liao CW, et al. TAIPAI Study Group. Aldosterone Induces Vascular Damage. Hypertension. 2019; 74(3): 623–629, doi: 10.1161/HYPERTENSIONAHA.118.12342, indexed in Pubmed: 31352825.
9. Sztechman D, Czarzasta K, Cudnoch-Jedrzejewska A, et al. Aldosterone and mineralocorticoid receptors in regulation of the cardiovascular system and pathological remodelling of the heart and arteries. J Physiol Pharmacol. 2018; 69(6), doi: 10.26402/jpp.2018.6.01, indexed in Pubmed: 30898981.
10. Catena C, Colussi GL, Marzano L, et al. Predictive factors of left ventricular mass changes after treatment of primary aldosteronism. Horm Metab Res. 2012; 44(3): 188–193, doi: 10.1055/s-0032-1301902, indexed in Pubmed: 22351477.
11. Davis JO, Urquhart J, Higgins JT, et al. Hypersecretion of Aldosterone in Dogs with a Chronic Aortic-Caval Fistula and High Output Heart Failure. Circ Res. 1964; 14: 471–485, doi: 10.1161/01.res.14.6.471, indexed in Pubmed: 14169966.
12. Inoue K, Goldwater D, Allison M, et al. Serum Aldosterone Concentration, Blood Pressure, and Coronary Artery Calcium: The Multi-Ethnic Study of Atherosclerosis. Hypertension. 2020; 76(1): 113–120, doi: 10.1161/HYPERTENSIONAHA.120.15006, indexed in Pubmed: 32418495.
13. Widimsky J, Strauch B, Petrák O, et al. Vascular disturbances in primary aldosteronism: clinical evidence. Kidney Blood Press Res. 2012; 35(6): 529–533, doi: 10.1159/000340031, indexed in Pubmed: 22890049.
14. Wilkinson-Berka JL, Suphapimol V, Jerome JR, et al. Angiotensin II and aldosterone in retinal vasculopathy and inflammation. Exp Eye Res. 2019; 187: 107766, doi: 10.1016/j.exer.2019.107766, indexed in Pubmed: 31425690.
15. Liu J, Wada Y, Katsura M, et al. Rho-Associated Coiled-Coil Kinase (ROCK) in Molecular Regulation of Angiogenesis. Theranostics. 2018; 8(21): 6053–6069, doi: 10.7150/thno.30305, indexed in Pubmed: 30613282.
16. Kishimoto S, Oki K, Maruhashi T, et al. Eplerenone improves endothelial function and arterial stiffness and inhibits Rho-associated kinase activity in patients with idiopathic hyperaldosteronism: a pilot study. J Hypertens. 2019; 37(5): 1083–1095, doi: 10.1097/HJH.0000000000001989, indexed in Pubmed: 30418321.
17. Zhang J, Yang J, Li Y. Dilated cardiomyopathy and aldosteronoma: a causal link? ESC Heart Fail. 2020; 7(1): 334–336, doi: 10.1002/ehf2.12579, indexed in Pubmed: 31856419.
18. Said SAM, Nijhuis RLG, Akker JW, et al. Unilateral and multilateral congenital coronary-pulmonary fistulas in adults: clinical presentation, diagnostic modalities, and management with a brief review of the literature. Clin Cardiol. 2014; 37(9): 536–545, doi: 10.1002/clc.22297, indexed in Pubmed: 25196980.
19. Huang Z, Liu Z, Ye S. The role of the fractional flow reserve in the coronary steal phenomenon evaluation caused by the coronary-pulmonary fistulas: case report and review of the literature. J Cardiothorac Surg. 2020; 15(1): 32, doi: 10.1186/s13019-020-1073-x, indexed in Pubmed: 32013986.
20. Musa N, Tandean P, Mappangara I, et al. Electrocardiogram pattern pre and post potassium correction in hypokalemia. International Journal of Medical Reviews and Case Reports. 2019(0): 1, doi: 10.5455/ijmrcr.ecg-potassium-correction-hypokalemia.