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LEFT MAIN CORONARY ARTERY COMPRESSION SYNDROME IN PATIENT WITH PULMONARY ARTERIAL HYPERTENSION. FIRST CLINICAL EXPERIENCE

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SUMMARY

Chest pain remains a common complaint in patients with pulmonary arterial hypertension (PAH). Compression of the coronary arteries is rare and probably underestimated syndrome being a typical cause of angina pectoris in patients with severe pulmonary arterial hypertension. Compression of the left main coronary artery (LMCA) by an enlarged pulmonary trunk is oftentimes associated with angina pectoris, but appropriate approaches to diagnosis and treatment remain poorly defined. This is a clinical case of a 38 years-old woman with idiopathic pulmonary arterial hypertension (IPAH) who has suffered from myocardial ischemia due to compression of the LMCA by a pulmonary artery aneurysm. The diagnosis of LMCA compression was made by coronary angiography (CA) and multispiral computed tomography (MSCT), which confirmed the pulmonary artery aneurysm as a source of external compression. LMCA stenting and changing in the PAH-specific therapy led to a significant improvement in angina, heart function and quality of life. Percutaneous coronary intervention appears to be feasible, safe and effective treatment for patients with external compression of the left coronary artery from pulmonary artery enlargement.

Key words: *idiopathic pulmonary arterial hypertension, left main coronary artery, pulmonary artery aneurysm, pulmonary hypertension.*

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Pulmonary hypertension (PH) is a group of diseases characterized by progressive hypertension in the pulmonary artery and increased pulmonary vascular resistance, eventually resulting in the right heart ventricle insufficiency and early death of patients [7,8].

The PH diagnostics criterion is elevated medium pressure in the pulmonary artery (mPAP – mean pulmonary arterial pressure) ≥ 25 mm Hg at rest according to the data of manometry performed during right heart catheterization (RHC). In order to determine

a hemodynamic type of the PH during catheterization, we also measure such indicators as wedge pressure (PCWP), pulmonary vascular resistance (PVR) and diastolic pressure gradient (DPG) [8].

The PH is a rare progressive and life-threatening disease. One of the key aspects of the PH pathogenesis is the loss of adequate constriction and dilation ability by the pulmonary vessels. According to the vascular remodeling, when the pulmonary artery wall is thickening and becomes rigid, the right heart is forced to overcome a higher resistance to transfer blood through the narrowed arteries. The process results in dilation of the right heart, deteriorating its pumping ability more, and eventually in the right heart ventricle insufficiency and death [1,2,9-12].

The term "Pulmonary Artery Hypertension (PAH)" describes the group of patients with PH whose hemodynamics is characterized by precapillary PH as determined at the PCWP ≤15 mm Hg and PVR >3 Wood Units without any other causes of precapillary PH, such as PH caused by pulmonary diseases, chronic thromboembolic pulmonary hypertension (CTPH) or other rare diseases [7,8,14].

Based on the principle of similarity of pathogenesis peculiarities, clinical picture, diagnostics and treatment philosophy, 5 PH groups can distinguished [13]:

1. Pulmonary arterial hypertension (PAH);
2. Pulmonary hypertension caused by the left heart pathology;
3. Pulmonary hypertension caused by pulmonary diseases or/and hypoxia;
4. Chronical thromboembolic pulmonary hypertension (CTPH) and other pulmonary artery obstructions;
5. Pulmonary hypertension with unclear and/or multifactor mechanisms.

The PH is accompanied not only by elevated blood pressure in the pulmonary artery and alternation of other hemodynamics parameters, but also it may be accompanied by increase of the diameter thereof, which in some cases could result in the left coronary artery (LCA) trunk compression syndrome. Pulmonary artery dilation is a common feature of the group of patients with severe pulmonary hypertension, which, according to some studies, is associated with 76.6 % of cases [67].

The PAH symptoms are related to development of the right heart ventricle insufficiency and include inspiratory dyspnea, weakness and rapid fatigability, heart beating, syncope, cough, thoracalgia, peripheral edema and eventually, life impairment [13].

Thoracalgia with PH usually is of an indefinite nature. The analysis of idiopathic PAH patients' complaints has shown that 53.4 % of them have thoracalgia, at the same time 12.1 % of patients suffered from typical angina attacks [13].

The following pain factors could be present [13]:

- reduction of the cardiac output (CO) and reduction of coronary artery pressure, especially during physical exercises, when the one-minute heart volume is increased inadequately to the load;
- expressed hypertrophy of the right ventricle with the development of relative coronary insufficiency due to low one-minute volume and increased myocardial oxygen demand, as well as relatively poor development of coronary collaterals;
- hyperextension of pulmonary artery due to expressed PH, which results in the coronary arteries compression.

Despite the recent success in PAH treatment, the forecast for the patients remains unfavorable, especially in case of severe disease progress [16].

Early diagnostics may be difficult, because typical PAH symptoms, such as dyspnea, fatigue and thoracalgia at effort are not specific.

Usually, the patients suffer from thoracalgia in 29 % of cases [18-21]. In some cases the thoracalgia has classic angina-like symptoms (these are described as a precardiac discomfort) that are caused by efforts and rapidly degrade at rest [17].

Gomez et al. describe a classic angina and angina symptoms of patients with PAH, which symptoms usually take place in case of hypertrophy and overloaded right ventricle, as well as in case of the coronary artery stenosis [22].

However, external LCA trunk compression by an expanded main pulmonary artery trunk is increasingly recognized as the cause for angina in case of PAH [17]. The frequency of the LCA trunk compression for the patients with PAH is not reliably known [23,24]. It was reported that of 26 patients with idiopathic PAH and angina clinical picture, 7 of them had LCA trunk compression [25].

Along with angina, the LCA trunk compression could be the reason for complications of severe myocardial ischemia, such as myocardial infarction [26], dysrhythmia and, finally, sudden death [28-30].

Among all deaths of patients with PAH, the sudden death portion is >25% [31], some of them could be related to the LCA trunk compression, being a complication that potentially could be corrected [17].

The left coronary artery trunk compression by the expanded pulmonary artery (PA) trunk is a rare complication for the patients with pulmonary hypertension, which for the first time was described by Corday et al. in 1957 as the cause of the coronary insufficiency for the patients with PH [33, 84]. The LCA trunk compression syndrome is the cause of the angina-like thoracalgia and results in disfunction of the left ventricle and even in sudden heart death of patients with PH. In case of the LCA trunk compression the angina attacks are observed for 41% of patients with PAH [23].

Despite the fact that the pulmonary hypertension and the LCA trunk compression syndrome are rare pathologic conditions, these are of great interest, because may occur in persons of working age, progress rapidly, deteriorating the life quality and threatening life.

EPIDEMIOLOGY

The lowest evaluation of the PAH and idiopathic PAH occurrence is 15 cases and 5.9 cases per million of adult population, respectively, whereas the lowest PAH diseases morbidity is 2.4 cases per million of the adult population per year. In Europe the morbidity and occurrence of PAH is within 15-60 patients per million people and 5-10 patients per million per year, respectively [8].

In Sverdlovsk Region, the idiopathic PAH patients register is kept since 2013, according to which the idiopathic PAH occurrence is 6.2 cases per million of the adult population. However, while today in Sverdlovsk Regional University Hospital No.1 we have sufficient experience and certain epidemiological data on morbidity and occurrence of PAH, the actual occurrence of the LCA trunk compression syndrome for the patients with PAH still remains unknown.

According to a small-scale prospective study, the majority of patients with PAH with angina-like attacks have the left coronary artery trunk compression by aneurism of the pulmonary artery [25].

Kajita et al. report on the group of patients with severe stenosis of the LCA main trunk (≥50%) by the expanded PA [30].

External compression of the LCA trunk by the PA trunk is a rare and poorly studied phenomenon, usually associated with the congenital heart defect (CHD).

Also similar cases of combined pathology are described for children and teenagers. In both cases it was PH in combination with the atrial septal defect of the patients. Hemodynamic studies confirmed the diagnosis and demonstrated external LCA compression by expanded pulmonary artery. Surgical closure of the defect in addition to the plastics of main pulmonary artery was

successful, improving the hemodynamics values and eliminating the angina symptoms [34,35].

Other authors' papers describe the patients with Eisenmenger's disease with the LCA trunk compression syndrome. In both cases the patients underwent successful surgery with the placement of stents into the LCA trunk [36,37].

DIAGNOSTIC ASPECTS

While today we have the International and Russian recommendations as to diagnostics and treatment of PH [7,8], there are no algorithms for diagnostics of the LCA trunk compression syndrome with PH.

External compression of the left coronary artery by the dilated pulmonary artery is a rare syndrome. In the most of cases PAH is not accompanied by ischemic heart disease, therefore coronary angiography is done seldom. This is why final diagnosis and correct treatment often are late for such patients [51].

The diagnosis requires a special attention from a doctor, especially to the patients with PH and complaints for angina-like pain. The thoracalgia is a common complaint of the patients with PH and often it is explained by increase of the pulmonary artery dimensions or myocardial ischemia [23,30]. The diagnostic and treatment philosophy remains poorly studied [23,30,68].

Perez et al. in their clinical cases of angina in patients with PAH caused by the LCA trunk compression by the expanded pulmonary artery, confirmed the LCA trunk stenosis diagnosis by coronary angiography with further confirmation by the CT-coronary angiography, which confirmed expansion of the pulmonary artery being the cause of the external compression. Recovery of the LCA clearance by percutaneous coronarography intervention and treatment of the pulmonary hypertension resulted in a significant improvement of the heart function and life quality of the patients, as well as in low angina-like symptoms. The authors recommend to consider this syndrome in the differential diagnosis of angina or systolic disfunction of the left ventricle of the patients with severe PH [23].

In their clinical case Choi et al. describe the patient with PH, clinical angina and LCA trunk compression by the pulmonary artery trunk, who successfully underwent percutaneous coronarography intervention (PCI) with the stent implantation, thus demonstrating the need for the coronary angiography with perspective of PCI for the patients having pulmonary hypertension and suffering from angina or disfunction of the left ventricle [51].

Dilation of the pulmonary artery trunk is a severe consequence of PH and usually is found during the echocardiographic examination, as well as during the computer tomography [28]. Rapid diagnostics can be done by non-invasive methods, such as CT coronary angiography and transthoracic echocardiography.

In case of considerable dilation of the pulmonary artery trunk it is necessary to carry out additional assessment in order to exclude the LCA trunk compression syndrome [57], especially for the patients with angina, because the probability of the left coronary artery compression of the patients with PAH directly correlates both with the pulmonary artery diameter and with relation of the pulmonary artery diameter to the aorta diameter [30].

In a series of cases described by Kajita et al. [30], where it always was the LCA trunk compression syndrome, the average value of the pulmonary trunk diameter relation to the aortic root was 2.0.

This also was confirmed by Mesquita et al. [25], who reported that in the group of patients with pulmonary hypertension the average diameter of the pulmonary artery was 55 mm, and the average relation of the pulmonary trunk root diameter to aorta was 1.98 for the patients with the LCA trunk compression syndrome, whereas in those patients who had no such a syndrome, the values were 37 mm and 1.46, respectively. The study included 36 patients with PAH (idiopathic, associated with congenital heart defect). The LCA main trunk compression syndrome was confirmed by the angiography as the LCA obstruction of ≥50%. The pulmonary artery and aorta diameters were measured by transthoracic echocardiography. Of 26 patients with the angina-like clinical picture, 7 patients had the LCA trunk compression. The compression was related to the pulmonary artery diameter (p=0.002) and the relation of the pulmonary artery trunk diameter to the aorta diameter (p=0.02). No compression was observed with the diameter of the pulmonary artery of <40 mm; among 19 patients with the PA diameter ≥40 mm the compression occurrence was 37%. Similarly, there was no compression in case of the PA trunk diameter relation to the aorta of <1.21; among 27 patients with the coefficient ≥1.21 the compression occurrence was 26%. The authors concluded that non-invasive methods of the pulmonary artery trunk diameter measurement in the patients with PH could be useful in determination of the LCA trunk compression probability, as well as for selection of the patients for further examination within the scope of coronary angiography.

Computer tomography or magnet-resonance angiography are useful means for non-invasive screening [47]; however, coronary angiography [57] is considered to be the must for final diagnostics of the LCA trunk compression syndrome [60].

To assess the severity and LCA trunk compression degree, also intravascular ultrasonic survey was done, as well as the assessment of the fractional blood flow reserve [56,60,61].

It seems that the myocardial perfusion methods are helpless for the diagnostics. According to the cases presented in the literature, only 4 of 10 patients with the evidenced LCA trunk compression syndrome had the developments of regional ischemia according to the myocardial magnet-resonance tomography data [30,62,63].

Seabra L et al. describe the application of ultrasonic diagnostics for the patients with PH, which allows visualization of the intermittent angina symptoms occurrence mechanism and confirms usefulness of application of the PCI method with further stent placement for the patients with PH [40].

Previous analyses of similar clinical events allow us to suppose that the LCA trunk compression syndrome events could be associated with high location of the LCA trunk mouth on the right side of left sinus of Valsalva, and the angle of bifurcation of <45° is associated with the sudden death cases [30,69]. These observations show that mutual location of the LCA trunk and the pulmonary artery trunk is a significant aspect of that syndrome.

In their study Lee et al. concluded that the coronary angiography with intravascular ultrasonic study is the must for diagnostics of that syndrome, while CT coronary angiography and magnet-resonance angiography are non-invasive instrumental methods of examination for screening of such patients [47].

TREATMENT

It should be noted, that currently there are specific medical treatment methods for the pulmonary hypertension only of certain subtypes of the 1st and 4th PH groups according to the clinical classification.

Without specific treatment the expected life duration of the patients with idiopathic PAH is decreased to 2.8 years from the moment of diagnostics, while according to the actual registers, due to modern PAH-specific treatment, the survivability upon expiration of 1 and 3 years has increased to 83% and 58%, correspondingly [3,4].

Today there is no uniform approach to the problem of treatment of the patients with PAH with the LCA trunk compression syndrome. A number of studies show the angina symptoms regress after taking sildenafil and prostanoids [23], while other studies reported on the need for coronary revascularization due to the absence of the angina symptoms regress after treatment by using such medicines

as bosentan [23,56]. Prior to the beginning of the therapy it is important to confirm the myocardial ischemia caused certainly by the stenosis due to the LCA trunk compression [60], which will play a significant part in selection of the treatment tactics.

Available PAH-specific therapy variants include sGC stimulator, prostacyclin analogs, endothelin receptor antagonists and PDE-5 inhibitors. Despite the success in treatment of such patients due to the PH therapy medicines' development, a medical care for such patients still remains important, because there is still a high number of deaths of PH patients (15% for the first year and 32% for three years) [6].

Notwithstanding that the majority of the authors say that there is no certain conclusion as to which method of treatment of such pathology is the optimum one, many publications describe successful application of the percutaneous coronarography intervention [44-47] with subsequent stent placement [36,37,40,48-51].

Some authors suppose that surgical coronary revascularization should be done only in cases of considerable LCA trunk stenosis [58]. In case of the LCA trunk compression syndrome it is of very high importance to recover free coronary flow; this apparently results in reduction of sudden heart death occurrences. The treatment is prescribed in case of the evidenced angiographic compression; it seems that non-invasive evaluation of the myocardial ischemia is not of interest in this situation [60].

In 2001 Rich et al [64] reported on successful stent placement into the LCA trunk for two patients with idiopathic PAH with the LCA trunk compression syndrome. Later on, other authors [26,29,65,66] also reported on successful angiographic and short-term clinical results.

Ogiso et al. [44] have used USI and MSCT to demonstrate successful stent placement for the female patient of 60 years old with depression of the ST segment with idiopathic PAH and LCA trunk compression by expanded pulmonary artery trunk. Subcutaneous administration of epoprostenol in increasing doses was begun immediately after the stent placement. One year of observation has shown stable hemodynamics without the episodes of the LCA trunk compression aggravation.

Galie et al. [17] performed a study aimed at assessing the frequency of the LCA trunk compression by the expanded pulmonary artery in the patients with PAH and angina or angina-like symptoms, assessing the need for CT coronary angiography screening and evaluating the efficiency and safety of PCI with further stent placement. Of 765 PAH patients covered by the study, 121 had angina symptoms. 94 patients had PA and LCA alterations according to the data of CT coronary angiography and had to undergo selective coronary angiography. LCA trunk stenosis of ≥50% was found for 48 patients of 94. Forty five patients underwent coronary stent placement, of which 41 demonstrated regress of the angina symptoms. Other three patients underwent plastic surgery of PA. Nine months after the performed PCI, 5 patients had relapse of the LCA trunk stenosis (they have undergone PCI repeatedly). The best LCA ≥50% stenosis predictor is the PA trunk diameter of ≥40 mm. The authors concluded that the LCA trunk stenosis occurrence for patients with PAH and angina-like clinical picture was high. These results evidence that the patients with PAH and angina or angina-like symptoms should undergo CT coronary angiography. PCI was tolerated well by the patients, which contributed to regress of the symptoms and good long-term results.

Lee et al. made the following conclusions based on the results of their study: treatment of the patients with external LCA trunk compressed by expanded PA using the PCI method seems to be feasible, safe and efficient. Taking into account the high risk of post-surgery complications (right heart insufficiency and death) as observed in case of surgical revascularization in such patients, the authors recommend for doctors to consider the percutaneous coronarography intervention with subsequent stent placement as the preferred method of revascularization for certain patients with the LCA trunk compression syndrome with PH [47].

Albadri K et al. [50] described successful treatment of the female PAH patient with the LCA trunk compression syndrome by using the PCI method with the stent implantation into the LCA trunk.

CLINICAL CASE

Clinical case. Today, in the regional PAH center of State Budgetary Healthcare Institution of Sverdlovsk Region "Sverdlovsk Region University Hospital No.1" 26 adult patients are observed with the idiopathic pulmonary arterial hypertension diagnosis.

For the period from 2015 to 2018 all patients were investigated for potential myocardial ischemia. 19 of 32 patients were found to have the myocardial ischemia developments (by clinical picture, according to the daily monitoring of ECG).

These patients underwent CT coronary angiography (there were no data obtained on atherosclerotic stenosis of arteries) and coronary angiography (CA), according to which 6 patients were found with the LCA compression by the expanded PA trunk.

Case description. A female patient M. (38 years old), based on the integrated survey performed in the State Budgetary Healthcare Institution of Sverdlovsk Region "Sverdlovsk Region University Hospital No.1" in the city of Yekaterinburg in 2009, received the diagnosis idiopathic PAH, FC III according to the World Health Organization.

According to the data of right heart catheterization (2009): cardiac output 4.8 l/min., mPAP 92 mm Hg, pulmonary wedge pressure 5 mm Hg, PVR 1442 dyn x s/sm5, heart index 2.8 l/min/m2. No data on the congenital heart defect were obtained. The results of pharmacological stress testing are negative. Testing with 6MWD test 280 m.

Previously performed PAH therapy included only warfarin and diuretics. Participation in the international randomized controlled trial (RCT SERAPHIN NCT00660179) of non-selective ERA allowed administration of the PAH-specific therapy as a monotherapy by using Macitentan since 2009.

Despite positive dynamics of the performed PAH-specific therapy (2013) as seen from the data of RHC, when there was improvement of a number of indicators: reduction of mPAP to 72 mm Hg, PVR 998 dyn x s/cm5, and also positive dynamics in the trial by using 6MWD test (310 m) and general improvement of the patient condition, according to the data of ECHO-CG, there was PA trunk dilation progress. For almost 4 years of observations, since 2009 to 2013, the diameter increased from 38 to 42 mm.

End of the patient participation in the SERAPHIN and start of the Sverdlovsk Regional Orphan Program in 2013 changed the PAH-specific therapy approach radically. Macitentan was cancelled, which was followed by the three-component therapy by using bosentan, sildenafil and inhaled iloprost. At the moment of administration of the three-component therapy, the patient was in the FC III as per WHO; no LCA compression developments were observed. There was no angina clinical picture at this stage.

Further, iloprost was cancelled due to low tolerance (express cough and hyperemia of face). On the double-component therapy background (bosentan+sildenafil), according to the data of RHC in 2015, there was a clinical deterioration of the patient condition in terms of a number of hemodynamic and functional indicators: increase of mPAP 98 mm Hg and PVR 1642 dyn x s/cm5, decrease of distance in the 6MWD 290 m and CO to 4.2 l/min. Based on a judgement, the patient had FC III as per WHO. In addition to deterioration of basic indicators, we noted increase of the PA trunk diameter, which according to ECHO-CG is 53 mm, and developments of myocardial ischemia by clinical picture and according to the data of daily monitoring of ECG.

Since 2015 there were a clinical picture of myocardial ischemia in

the form of angina attacks at the effort peak, enforcing to stop, and intermittently - precordialgia when the patient lied on back.

At the time of hospitalization in the Cardiology Unit of the Sverdlovsk Region University Hospital No. 1 in May of 2015, the patient had complaints of express shortness of breath at low efforts, weakness, rapid fatigability, frequent heart rate, thoracalgia at the effort peak, dizziness. During examination: tachypnoea (respiration rate 22 per minute), arterial hypotension (AP 90/55 mm Hg), tachycardia (110 beats per minute), acrocyanosis and jugular venous distention, by auscultation – loud second heart sound above the pulmonary artery, Graham Steell's murmur.

At the moment of inpatient hospitalization – FC III (WHO), distance T6MH 290 m. According to the data of ECHO-CG: hollow of the left ventricle is abruptly low-sized, significant expansion of the right heart. Expansion of the PA trunk to 59 mm. Average pressure in PA – 98 mm Hg (Fig. 1 A, 1 B).

According to the data of daily monitoring of ECG – myocardial ischemia developments. Coronary angiography (CA) revealed hemodynamically significant Pencil-tip shaped stenosis of the LCA, which was confirmed by the data of MSCT (Fig. 2B). LA diameter barrel according MSCT - 59 mm.

No atherosclerotic or other stenotic disorders of territories of other coronary arteries were revealed. As a result of integrated survey in 2015, the diagnosis was defined more exactly: Idiopathic pulmonary arterial hypertension, Fc III as per WHO. Chronic Heart Failure II A, FC III (WHO). Critical stenosis (90%) of the left coronary artery trunk compressed by expanded pulmonary artery trunk.

For the purpose of surgical LCA trunk stenosis correction, successful stent placement was performed on May 15, 2015 in the LCA trunk by using Everolimus-eluting stent of 4.0 mm (Fig. 3 A). The control angiography (Fig. 3 B) has shown elimination of the LCA trunk stenosis.

As is seen on Fig. 3B, after the stent placement into the LCA, LCA trunk compression was eliminated, coronary blood flow was recovered, a regress of the angina-like clinical picture was noted. According to the daily monitoring of ECG (May 2015): sinus rhythm 47-107 per minute, 559 single supraventricular dysrhythmia, 3 ventricular dysrhythmia. Maximum pause of 1460 ms. No ST depression episodes are revealed (Table 1).

After successful PCI PAH-specific therapy was corrected. Considering the low tolerance (nausea, vomiting, hypotension) and decreasing effectiveness (loss of the effectiveness), sildenafil was cancelled. The therapy was changed from sildenfil+bosentan to the combined double-therapy of 125 mg bosentan 2 times per day and riociguat, the dose of which was titrated according to the instruction for the medicine (the patient dosage was kept at 2 mg 3 times per day). Systolic arterial pressure at the moment of the changing from sildenafil to riociguat was 100 mm Hg. On the background of bosentan+riociguat treatment there was improvement of a number of indicators, including improvement of the distance T6MX and improvement of FC as per WHO.

The control survey in December of 2015: 6MWD test – 420 meters (FC II), at control CA – no LCA trunk compression. RHC: mPAP 96 mm Hg, CO 2.5 l/min/m^2, PVR 1632 dyn x s/cm^5.

Further surveys (2016, 2017) also noted positive dynamics due to the absence of the thoracalgia relapse, control CA – no LCA trunk compression (Fig. 4). RHC: mPAP 74 mm Hg and PVR 1048 dyn x s/cm^5, 6MWD test 435 m, CO 4.2 l/min, FC II (WHO).

Also we noted that after administration of the new double-component combined therapy riociguat+bosentan, the PA trunk diameter showed no increasing trends, and main hemodynamics parameters were comparable and slightly varied during the period of observation. It should also be noted that all PAH-specific medicines that were used for treatment of the patient, including bosentan and riociguat, were used only for the purpose of idiopathic PAH treatment, but not as a medicinal therapy of the LCA trunk stenosis.

DISCUSSION

The most known cause of the precordialgia with PH is the hypertrophy of the right heart ventricle, which results in myocardial ischemia at effort. However, one should not overlook possible compression of the LCA trunk by aneurism of the PA trunk.

External compression of the LCA trunk is a life-threatening complication, which one shall bear in mind in case of thoracalgia occurrence for the patient with PH.

Acute coronary syndrome [26,56,57] or the left heart ventricle insufficiency and cardiogenic shock [23,26,57] cases were reported in connection with LCA trunk compression syndrome. Ventricle tachyarrhythmia due to ischemia being secondary one relative to the LCA trunk compression syndrome, may contribute to the risk of sudden heart death for such patients. Therefore, in case of angina with pulmonary hypertension, the LCA trunk compression syndrome should be considered in the differential diagnosis.

The most important factor of the LCA trunk compression syndrome development must be severity and duration of the pulmonary hypertension.

Duration of disease of our patient and severity of the idiopathic PAH probably triggered the progressive dilation of the PA trunk, which, in turn, upon reaching the critical values, resulted in the LCA

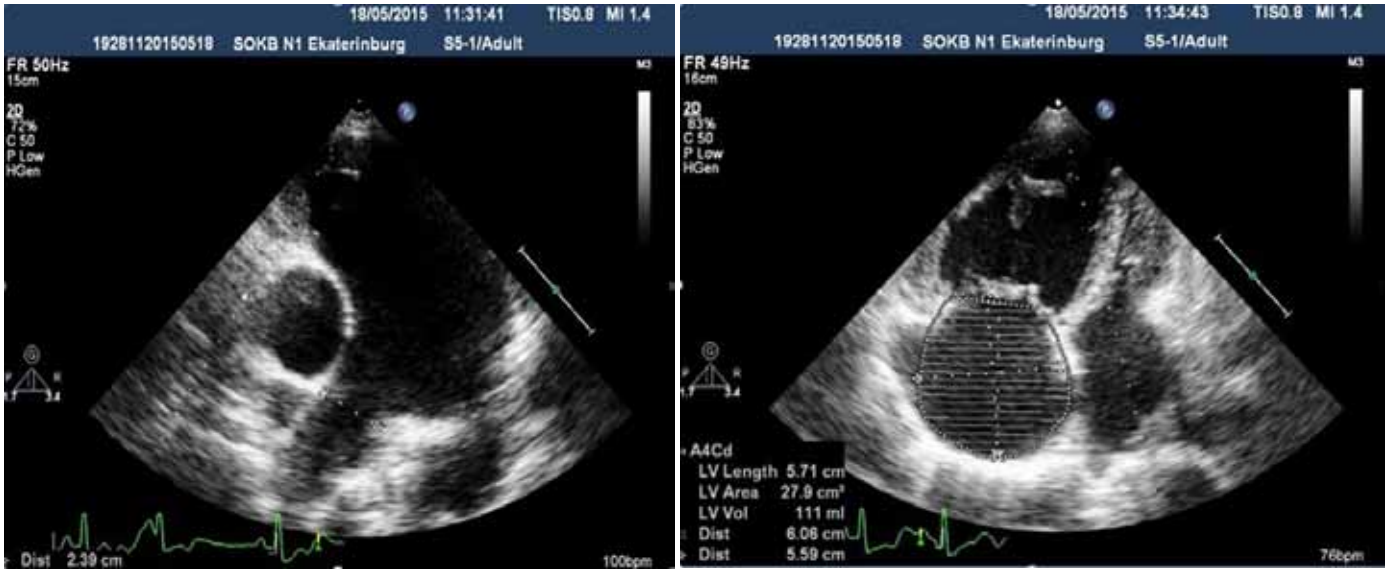

Figure 1. ECHO-CG study. PA trunk aneurism (A) and dilation of the right heart (B).

trunk compression syndrome.

The factors of risk of possible LCA trunk compression with PAH are as follows: young age, considerable PA trunk expansion (over 40 mm) and relation of the PA trunk/aorta diameters over 1.2 (normal is 1.0) [25].

According to the data of various authors, the LCA trunk compression in case of PH is observed in 5% to 44% cases (19% in case of idiopathic PAH), and in about 41% cases this compression is indicated by thoracalgia [38,51,52], with which we faced for the first time in our PH center when the myocardial ischemia clinical picture occurred for a young female patient with idiopathic PAH and long-term medical history. Angina-like clinical picture occurrence for the patient stimulated us to carry out the diagnostics of the cause of such a rare complication of PAH.

Expansion of the pulmonary artery usually is observed in echocardiographic studies, as well as in computer tomography [28]. Rapid diagnostics can be done by non-invasive methods, such as CT coronary angiography and transthoracic echocardiography.

CT or magnet-resonance angiography are useful means for non-invasive screening [47]; however, coronary angiography [57] is considered to be the must for final diagnostics of the LCA trunk compression syndrome [60]. For evaluation of the severity, LCA compression degree, as well as exclusion of atherosclerotic disorder of coronary vessels, some authors use the intravascular ultrasonic investigation [56,60,61], which was not available for us before 2018.

In our case, for making the differential diagnosis, we selected a set of instrumental non-invasive and invasive methods of survey. According to the daily monitoring of ECG, the ST segment depression was observed for the patient, which seems to be a probable indicator of the myocardial ischemia. According to the data of transthoracic ECHO-CG, dilated right heart and aneurism of the expanded PA trunk were verified (59.8 mm on the moment of occurrence of the angina clinical picture). Next step in the differential survey was MSCT-coronary angiography, which enabled to determine the relation of PA and coronary arteries without intervention. The diagnosis of LCA trunk compression by the expanded PA trunk was confirmed by meeting the gold standard - performing coronary angiography.

While according to the international literature there is no general opinion on the algorithm of diagnostics of the LCA trunk compression syndrome, the majority of the authors agree that the treatment should be aimed at recovery of the coronary blood flow by surgical coronary revascularization [58]. In case of the LCA trunk compression syndrome it is very important to recover the coronary blood flow. This apparently decreases the occurrence of sudden heart death. The treatment is prescribed for the angiography-evidenced compression [60].

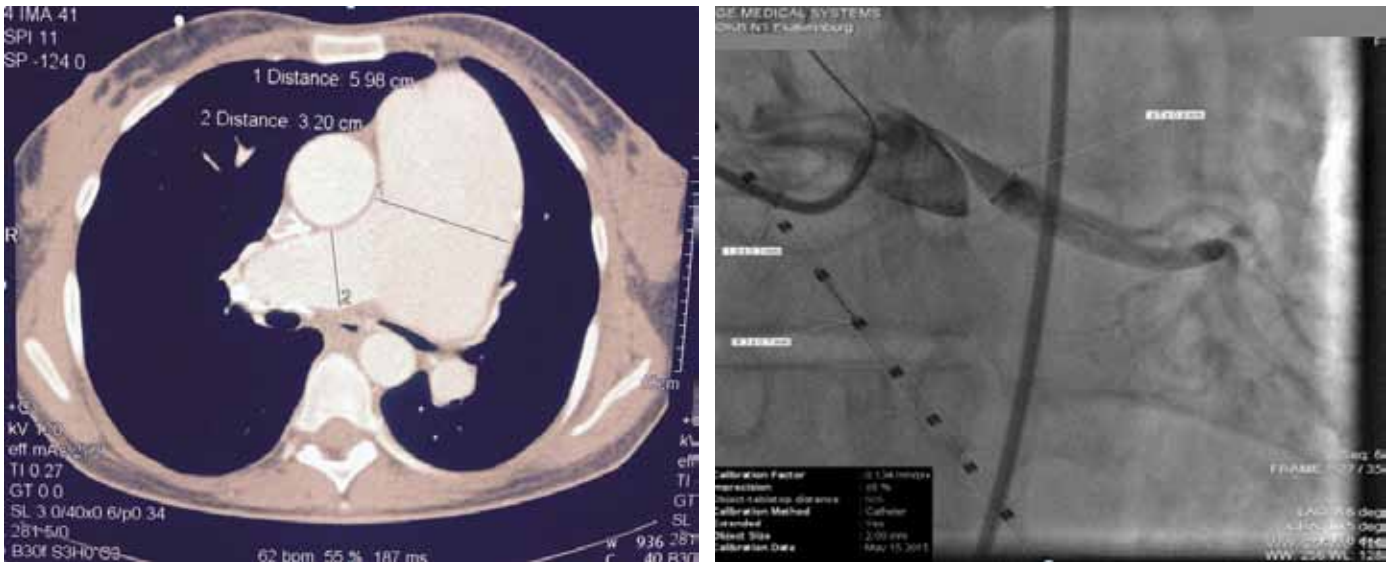

Figure 2. PA trunk aneurism (A) and LCA trunk compression by the expanded PA trunk according to the data of coronary angiography (B).

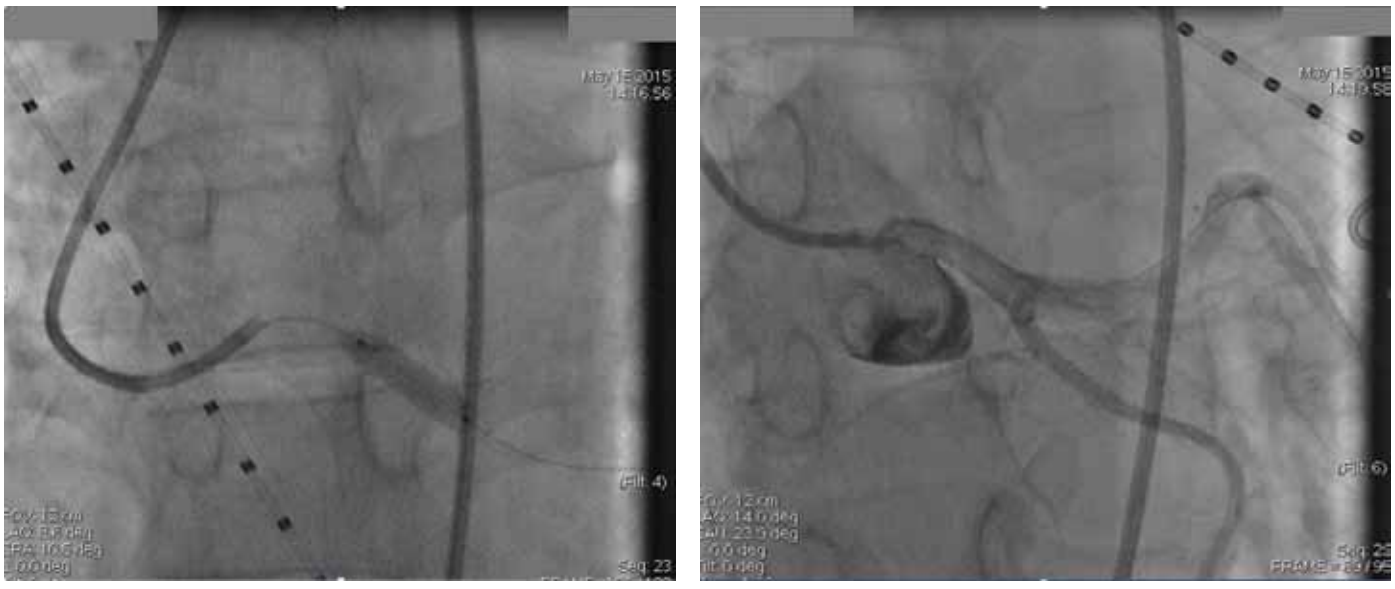

Figure 3. Coronary angiography. Stent placement into the LCA trunk (A). Control angiography after successful stent placement into the LCA trunk (B)

Table 1. Hemodynamics and functional changes during treatment and observations over the patient

	2009	2013	05.2015		2016-2017*
			before LCA stent placement	after LCA stent placement	
PAH-specific therapy and reasons for change	Macitentan	Sildenafil Bosentan Iloprost	Sildenafil Bosentan	Riociguat Bosentan	
		End of participation in the SERAPHIN study and start of the Sverdlovsk Region Orphan program. Expressed cough in response to iloprost.		Loss of the effect and dyspeptic developments in response to sildenafil. LCA trunk compression syndrome	
CO, l/min	4,8	5,8	4,2	4,4	4,2
med. PAP, mm Hg	92	72	98	96	74
PCWP, mm Hg	5	6	7	7	8
PVR, dyn x s/cm5	1442	998	1642	1632	1048
heart index, l/min/m2	2,8	3,5	2,5	2,5	2,4
FC WHO	III	III	III	II	II
Diameter of PA, mm	38	42	59	59	57
T6MH, m	280	310	290	420	435
Depression ST, daily monitoring of ECG	-	-	+	-	-

** parameters studied 7 months (December 2015) after the stent placement and during follow-up observations in 2016 and 2017 were comparable and had very low differences.*

Notwithstanding that the majority of the authors say that there is no certain conclusion as to which method of treatment of such pathology is the optimum one, many publications describe successful application of the percutaneous coronarography intervention [44-47] with subsequent stent placement [36,37,40,48-51].

According to Ayşenur Paç et al. percutaneous coronarography intervention with the stent placement shall be considered as the most optimum strategy for the myocardial revascularization in case of the LCA trunk compression for the patients with idiopathic PAH [34].

Also there is an opinion that the use of both invasive (PCI) and therapeutic methods of treatment of the PAH patients with the LCA trunk compression syndrome is possible [51].

In our case we selected pharmacological and surgical strategy of treatment of the patient. By the moment of progress of idiopathic PAH and occurrence of the angina-like clinical picture, the patient was under the combined double-component therapy by PAH-specific medicines (sildenafil, bosentan), however, soon after the stent placement, the researchers had to change the therapy because of low tolerance to sildenafil, as well as the lack of therapeutic results of such a combination. It was decided to change the PAH-specific therapy, namely add riociguat to bosentan instead of sildenafil.

For today it has been shown that a part of the PAH-patients (up to 60% according to some authors) demonstrate a weak response to the therapy with PDE-5 inhibitors [76,77,79]. The reason for this may be a low concentration of endogenic nitrogen oxide in the pulmonary vessel walls of the PH patients. Another reason of low efficiency of sildenafil could be destruction of cyclic guanosine monophosphate by PDE isozymes, relative to which the activity of sildenafil is low or absent [76,79,80]. Therefore, it was supposed that a good alternative for the PAH patients with poor response to PDE-5 inhibitors therapy could be sGC stimulators [79]. Ability of riociguat to induce the cyclic guanosine monophosphate synthesis at the deficit of nitrogen oxide, which is often observed for the P patients, seems to be a potential advantage of riociguat over PDE-5 inhibitors [79].

Riociguat represents a new class of medicines, soluble guanylate cyclase stimulators (sGC). The medicine has a double-action mechanism, on the one hand it induces sGC directly, independently on the endogenic NO level, and on the other hand increases sGC sensitivity to the endogenic NO [81,82]. Due to increase of the cyclic guanosine monophosphate level riociguat results in vasorelaxation, proliferation suppression and antifibrose effect, as was proven in the PH experimental models.

One of the riociguat advantages is potentially beneficial peculiarities of the activity mechanism, i.e. independence on the endogenic nitrogen oxide for synthesis of cyclic guanosine monophosphate [78, 83].

In our case simultaneous use of therapeutic and surgical treatment methods resulted in positive long-term results.

Stent placement enabled to recover the coronary blood flow and eliminate the myocardial ischemia picture, after which total regress of the angina-like picture has been observed.

Improvement of hemodynamic values in case of idiopathic PAH, probably, is caused partially by administration of the combined double-component therapy that included the second PAH-specific medicine, riociguat.

CONCLUSION

The left coronary artery trunk compression by the pulmonary artery trunk is associated with possible angina clinical picture, but appropriate diagnostic and treatment approaches still remain poorly studied.

There are no modern recommendations as to diagnostics of the LCA trunk compression in case of PH.

In case of angina with pulmonary hypertension, the LCA trunk compression syndrome should be considered in the differential diagnosis.

Non-invasive methods of the pulmonary artery trunk diameter measurement for the patients with PH could be useful in

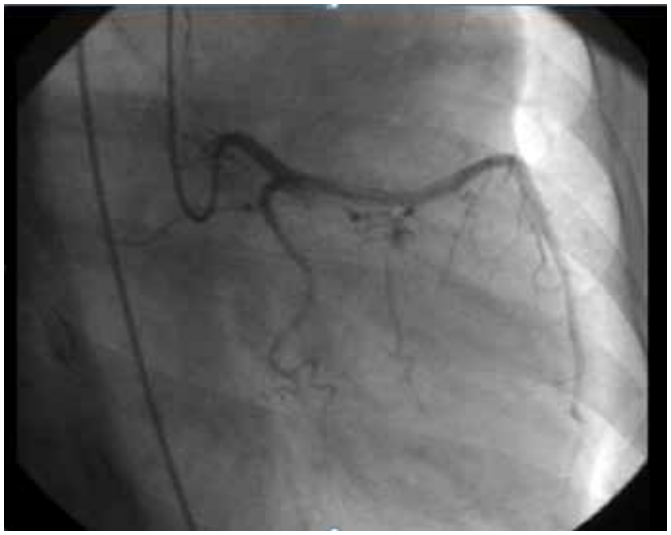

Figure 4. Control coronary angiography, December, 2015. No data on the LCA trunk compression, there is no restenosis in the stent.

determination of the LCA trunk compression probability, as well as for selection of the patients for further examination within the scope of coronary angiography.

Coronary angiography is the must for diagnostics of the LCA trunk compression syndrome, while CT coronary angiography and magnet-resonance angiography are non-invasive instrumental methods of examination for screening of such patients.

The most important factors of the risk of the LCA trunk compression development must be severity and duration of the pulmonary hypertension, as well as: young age, significant PA trunk expansion (over 40 mm) and relation of the PA trunk/aorta diameters of 1.2 (normal is 1.0).

Early revelation of the coronary artery stenosis in case of idiopathic PAH and further surgical correction thereof could improve the forecast and the patient's life quality.

Critical stenosis of the LCA trunk by the expanded PA trunk, probably shall be sufficient to prescribe the surgical treatment. Percutaneous coronarography intervention with the stent placement can be considered as the most optimum strategy for the myocardial revascularization in case of the LCA trunk compression for the patients with idiopathic PAH, which shall be carried out in parallel with the PAH medicinal treatment. Clinical research is required for revelation of additional LCA trunk stenosis predictors in case of PAH, as well as for development of the optimum approaches to the diagnostics and treatment of this syndrome.

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