Author’s response to reviews

Title: The multiple systemic artery to pulmonary artery fistulas resulting in severe irreversible pulmonary arterial hypertension in patient with previous history of pneumothorax.

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Author’s response to reviews:

Dear Editor,

thank you for your review. You can find our replies for the reviewers’ comments hereunder. We would like to inform you that they have been taken into account in the new version of the manuscript substantially.

Sincerely

On behalf of the co-authors

Wojciech Jacheć PhD

Review 1.
Dear Mr Andrea Lombi (Reviewer 1),

thank you for your in-depth, preliminarily positive review. Hereunder you can find our replies to your comments and questions.

1. The title has been shortened. The current version: The multiple systemic artery to pulmonary artery fistulas resulting in severe irreversible pulmonary arterial hypertension in patient with previous history of pneumothorax.

2. Corrections to grammar and to some linguistic constructions have been made:
   Control RHC, performed 5 months later - Control RHC, performed 5 months later
   A 52 year old male patient - A 52-year-old male patient
   we have not decided to replace - we did not decide to replace

3. The acronyms have been standardised.

4. PVRI in dyna\cdot cm\cdot s^5/m^2 has been altered and is now expressed in Wood Units.

5. Vasoreactivity test in pulmonary hypertension: Evidently, in accordance with the guidelines, the results produced in the first inhalation of nitric oxide indicate that it is irreversible. Subsequent measurements were performed with sildenafil oral administration and then, during the successive inhalation of nitric oxide in order to assess whether the additional impact on the NO-dependent pathway exerts greater vasodilatory effect.

6. We agree with your last suggestion about conclusion that the fact that after closing AV fistulas, patient condition went dramatically worse could be related to the loss of beneficial effect of right-left shunting with "decompress" of right ventricle, as it happens after closure of interatrial defects with R-L shunts. This valid comment was taken into consideration in the Discussion.

Dear Rocco Francesco Rinaldo (Reviewer 2),
thank you for your in-depth, preliminarily positive review. Hereunder you can find our replies to your comments and questions.

1. The title has been shortened. The current version: The multiple systemic artery to pulmonary artery fistulas resulting in severe irreversible pulmonary arterial hypertension in patient with previous history of pneumothorax.

2. The acronyms have been standardised.

3. RHC results have been rounded to the first decimal place.

4. The analysed case is, undoubtedly, clinically ambiguous, especially since it may concern a compilation of many rare diseases.

There are many clinical scenarios; you can find some of them hereunder:

Pulmonary hypertension in this patient can be primary (idiopathic, genetically determined) and the coexistence of fistulas can be accidental and they exert no influence upon the natural course of disease.

SA-PAFs can be either congenital or acquired. Both types are rare in patients with normally developed pulmonary circulation.

Pneumothorax is one of the causes of the acquired SA-PAFs.
We agree with you that the above-mentioned states are observed extremely rarely. It is our first encounter with such a case in the app. 30 years of practice in the pulmonary hypertension diagnosis and treatment.

Nevertheless, there are cases of PH in patients with SA-PAFs. At the manuscript stage we had knowledge of 2 such cases. After having received the review we examined the literature again and we found another example of a 32-year-old patient in whom medium pulmonary hypertension and numerous systemic-to-pulmonary artery fistulas were observed. Fistulas were assessed as congenital. Embolisation of the greatest fistula led to the decrease in the pressure in the pulmonary artery within the 6-month follow-up (Ji-Feng Li, Zhen-Guo Zhai, Tu-Guang Kuang, Min Liu, Zhan-Hong Ma, Yi-Dan Li, Yuan-Hua Yang. A Case of Pulmonary Hypertension Due to Fistulas Between Multiple Systemic Arteries And the Right Pulmonary Artery in an Adult Discovered for Occulted Dyspnoea. Heart, Lung and Circulation 2017; 26, e54–e58).

Before having been admitted to our Department, the patient underwent examination excluding respiratory diseases as a cause for pulmonary hypertension. Angio-CT of the pulmonary arteries had been performed twice (in each case the preserved perfusion of both lungs had been described and was reaffirmed in the post hoc analysis). HRCT of the chest, spirometry and autoimmune disease screening ruled out connective tissue disease and no hepatic impairment resulting in pulmonary hypertension was observed. Screening for HIV infection was negative. The shunt congenital heart disease was eliminated, as well.

Normal PWP (both initial and during NO-inhalation), normal chest X-ray and HRCT rule out diagnosis of veno-occlusive pulmonary disease, especially since pulmonary edema during vasodilatatory therapy (sildenafil, iloprost) was not developed in this patient.

On the basis of the clinical data we have at our disposal we assumed that the scenario presented in the manuscript is the most probable, which does not eliminate a different scenario of the increase in pulmonary arterial hypertension. This was taken into account in the current manuscript version.

5. Reasoning based on the presence of the R-L shunt is based on angio-CT of pulmonary arteries performed twice. In both tests no impairment in the perfusion of the upper lobe of the right lung was observed, which may indirectly suggest R-L shunt. The proportion of the pulmonary to the systemic pressure observed in the first heart catheterization unambiguously indicate the left-to-right direction of the shunt. Unfortunately, at that time we had no premises of any co-existing SA-PAFs, which i.a. resulted in a deficient number of blood samples for the oximetry test and therefore lack of possibility to assess the pulmonary flow in a reliable manner. What is more, the presence of fistulas causes a difficulty in the selection of a representative spot for an arterial blood sample for the oximetry test.
On the basis of the results idiopathic pulmonary arterial hypertension was diagnosed and specific therapy/treatment (sildenafil, iloprost) was initiated/applied. The clinical improvement was observed, however, in the subsequent measurement of the mean pressure in the pulmonary artery proved higher than the initial one. Can this be explained by the improvement in right ventricle function as a consequence of a partial vasodilatation of the pulmonary arteries? We find no explanation for this.

The discovery of fistulas was very surprising to us and to find explanation for the probable course of disease a retrospective data analysis had to be largely sufficient.

Eventually, the data was interpreted in the manner presented in the manuscript.

6. The results have been complemented by SaO2 values and the cardiac output index.