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CASE REPORT
Heart failure

A case report of a 37-year-old woman with pulmonary arterial hypertension first presented during her 3rd pregnancy and favourable long-term vasoreactive response

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Background Pulmonary arterial hypertension is a rare disease associated with high rates of mortality and can significantly complicate pregnancy posing health risks for the mother and child alike.

Case summary We present the case of a 37-year-old female patient with World Health Organisation functional Class IV symptoms during the 34th week of her 3rd pregnancy. Initial echocardiography showed a significantly elevated estimated systolic pulmonary artery pressure of 86 mmHg + central vein pressure as well as signs of chronic pulmonary hypertension. After a successful emergent caesarean section, pulmonary hypertension was confirmed via right heart catheterization. After exclusion of secondary aetiologies of pulmonary hypertension, the diagnosis of Class 1 pulmonary artery hypertension was made. We initially treated the patient with the phosphodiesterase-5 inhibitor sildenafil (20 mg oral bid trice daily) and later extended the medication with the dual endothelin receptor antagonist Macicentan (10 mg daily). Since the patient remained symptomatic vasodilator testing was performed and showed a significant response to intravenous Epoprostenol. We initiated a high-dose calcium channel blocker (CCB) therapy with amlodipine (20 mg daily) which led to symptomatic relief, increased exercise capacity as well as reduction in mean pulmonary artery pressure and pulmonary vascular resistance as confirmed by another right heart catheterization after therapy initiation.

Discussion Since the presentation is usually non-specific, the diagnosis of pulmonary artery hypertension can be challenging and cause a delay in treatment initiation. Even though rare vasodilator testing and invasive haemodynamic measurements should be performed to identify patients with favourable long-term response to high-dose CCB.

Keywords Case report • Pulmonary arterial hypertension • Pulmonary hypertension • Pregnancy • Vasodilator testing

ESC Curriculum 6.4 Acute heart failure • 6.7 Right heart dysfunction • 9.8 Pregnancy with cardiac symptoms or disease • 6.1 Symptoms and signs of heart failure

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Learning points

- Pulmonary arterial hypertension (PAH) is a rare disease with a high latency from symptom onset to diagnosis causing relevant delay in therapy initiation
- Vasodilator testing should be performed in patients with PAH to identify patients that can be treated safely and efficiently with calcium channel blocker over a long period of time

Introduction

Pulmonary arterial hypertension (PAH) is a rare disease manifesting usually between the 3rd and 6th decade.[1] Younger women seem to be more frequently affected.[2] Epidemiological data vary according to region, registry used, and time investigated and is estimated between 15 and 60 subjects per million population.[3] Data on survival are also variable but generally report a 5-year mortality rate of almost 40%.[4] Earliest symptoms are associated with exertion as patients suffer from dyspnoea, dizziness/syncope, weakness, and fatigue.[5] Late symptom onset and unspecific initial presentation frequently lead to a delayed diagnosis, negatively impacting patient prognosis. The time from the first presentation to diagnosis is roughly 2 years.[6] Since especially younger women are affected by PAH, pregnancy might occur either without knowledge of the diagnosis or while under treatment, even though becoming pregnant is generally discouraged.

Timeline

Date	Event
Since early 2015	3rd pregnancy (One healthy child) with gradually worsening symptoms of dyspnoea on exertion
21st of September 2015	Initial presentation in a primary care facility (Bad Langensalza) during the 34th week of pregnancy with clinical deterioration (WHO functional Class IV), pulmonary embolism was ruled out, echocardiographic diagnosis of severe pulmonary hypertension was made (estimated systolic PA pressure 100 mmHg)
21st of September 2015	Transfer to intensive care unit of tertiary centre (University hospital Jena), Initiation of Sildenafil medication
21st to 27th of September 2015	Symptomatic improvement. Estimated systolic PA-pressure was lowered to 55 mmHg
28th of September 2015	Emergent caesarean section with stand-by mechanical circulatory support, healthy child was delivered without complications
29th of September 2015	Transfer to standard cardiology ward for diagnosis
7th of October 2015	Right and left heart catheterization: Coronary artery disease was ruled out as well as arteriovenous shunts. Right heart catheterization showed elevated mean PA pressure and pulmonary vascular resistance. Left ventricular end diastolic pressure was only slightly elevated.
29th of September to 16th of October 2015	Secondary aetiologies (systemic rheumatic or pulmonary disease, chronic thrombo-embolic events, chronic infectious disease etc.) were ruled out, diagnosis of idiopathic pulmonary hypertension was established. Sequential therapy with Macicentan was initiated
17th of October 2015	Discharge from hospital in stable condition with combination therapy of Sildenafil and Macicentan
November and December of 2015	Out-patient follow-up showed a symptomatic patient (WHO functional Class III) with still elevated systolic PA pressure values of about 60 mmHg
24th of May 2016	Sequentially right heart catheterization with vasodilator testing showed elevated mean PA pressure and pulmonary vascular resistance. Vasodilator testing was performed with a significant positive result at a dose of 15 ng/kg/min intravenous Epoprostenol
25th of May 2016	High-dose calcium channel blocker (CCB) therapy was initiated, sildenafil was discontinued
13th of December 2016	The therapy was well tolerated. Symptoms improved significantly. Sequential right heart

Continued

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Date	Event
	catheterization showed normal values for pulmonary vascular resistance and only slightly increased values for mean PA pressure
Since December 2016	Stable patient with regular out-patient visits to our department. WHO functional class improved to I, natriuretic peptides were in normal range. Estimated systolic PA pressure decreased to 40 mmHg. Patient showed improvements in 6 min walk test and cardiopulmonary exercise testing results. Overall the patient could be classified as low risk (<5%). Until presentation of this report no adverse events occurred and the high-dose CCB therapy was well tolerated

Case presentation

We report on a 37-year-old female Caucasian patient who was initially referred during the 34th week of her 3rd pregnancy to our maximum-care institution from a peripheral hospital. She was admitted since she was experiencing shortness of breath (SoB) currently in World Health Organisation functional class (WHO FC) IV. Symptom onset was during the 1st trimester of her pregnancy with mild SoB—a transthoracic echocardiogram at the time reported no abnormalities. Initial electrocardiogram (see Supplementary material online, *Figure S1*) showed signs of right heart strain or pulmonary embolism. Computed tomography (CT) ruled out pulmonary embolism but also showed signs of right heart stress (*Figure 1*). A ventilation/perfusion (V/Q) scan was not performed since it was not readily available at the institution of primary care. The patient already had one healthy child and one abortion due to acute toxoplasmosis in the past. Otherwise, the medical history was unremarkable.

The initial echocardiography showed a left ventricle of normal size, but signs of chronic right heart pressure overload (*Figure 2*). The estimated systolic pulmonary artery pressure (sPAP 86 mmHg + central vein pressure) was elevated (*Table 1*). The patient experienced chest pain, was in need of oxygen supply (2 L/min), had sinus tachycardia (110/min), tachypnoea (28/min), and brain natriuretic peptide (BNP) values above 300 pg/mL.

The patient was transferred to an intensive care unit and a therapy with the phosphodiesterase type 5 inhibitor (PDE-5i) Sildenafil (20 mg oral bid trice daily) was initiated. The estimated sPAP was gradually reduced to 60 mmHg plus central vein pressure. Emergent caesarean section was performed without complication. Following birth, a pulmonary hypertension workup was performed. A V/Q scan excluded acute or chronic pulmonary embolic disease. Blood work for vasculitis, connective tissue disease, or overlap syndromes showed no significant elevated specific antibodies. There were no signs of chronic infectious disease especially HIV or hepatitis. Chronic pulmonary disease was ruled out by high-resolution CT and function tests (including transfer factor for carbon monoxide) which excluded interstitial lung disease or restrictive/obstructive ventilatory dysfunction. Abdominal ultrasound could rule out portal hypertension.

Overall, the diagnosis of Idiopathic PAH aggravated by pregnancy was likely and for confirmation a left (LHC) and right heart catheterization (RHC) was performed. An elevated mean PA pressure of 66 mmHg with a left ventricular end-diastolic pressure (LVEDP) of 16 mmHg and an elevated pulmonary vascular resistance (PVR) of 608 dyn s/cm^5 confirmed the diagnosis (*Table 2*). Since PA pressure was still elevated and the patient was classified in intermediate risk (ESC/ERS score 1.55), we decided to add the endothelin receptor antagonist (ERA) Macitentan in a dose of 10mg once daily. The patient was discharged in stable condition.

We followed up about 6 months after. Risk stratification suggested low risk (ESC/ERS score 1.27) but the patient was still in WHO FC III. Echocardiography showed an elevated sPAP of 58 mmHg+ central vein pressure (*Table 1*). We performed another RHC where PVR and mean PA pressure were still elevated (*Table 2*). Vasodilator testing showed a significant response at a dose of 15 ng/kg/min intravenous Epoprostenol (see Supplementary material online, *Table S3*). We initiated high-dose calcium channel blocker (CCB) therapy with amlodipine and discontinued Sildenafil due to intermittent hypotension and to achieve a high CCB dose during up-titration.

Another 6 months later the patient showed improvement regarding her symptoms, with a WHO FC II (Supplementary material online, *Table S4*). A good response to the CCB therapy could be demonstrated in RHC that showed a decrease of the mean PA pressure to 25 mmHg as well as a reduction of PVR (*Figure 2*). Despite current guideline recommendations[5] to assess the disease by RHC every 6–12 months the patient declined further invasive measurement. The non-invasive estimation of sPAP showed values of less than 40 mmHg+ central vein pressure in all further visits. As of today (5.5 years after diagnosis) the patient is in stable clinical condition. At the latest visit, the patient presented in WHO FC I with BNP values of <100 pg/mL and is scheduled for follow-up every 6 months.

Discussion

Even though pulmonary hypertension (PH) is common and might be caused by a number of disorders including left heart, lung, and chronic thrombo-embolic disease, PAH is rare and associated with a poor prognosis.[6] Pulmonary hypertension is defined by an elevated mean PA pressure above 25 mmHg measured by RHC.[7] The pathophysiology of PH is multifactorial and can be classified into five groups.[7] Performing RHC is critical for confirming the

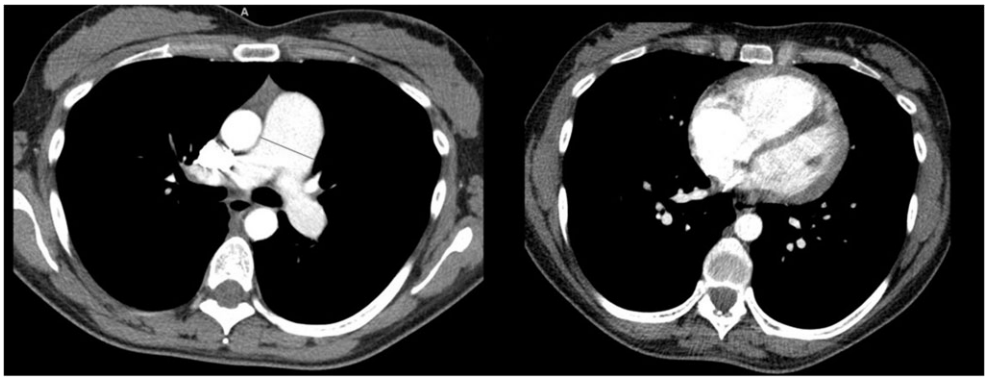


Figure 1 Left: Contrast enhanced computed tomography ruled out acute pulmonary embolism. The pulmonary trunk was dilated (37 mm, red line); right: atypical computed tomography four-chamber view showing enlargement of the right ventricle.

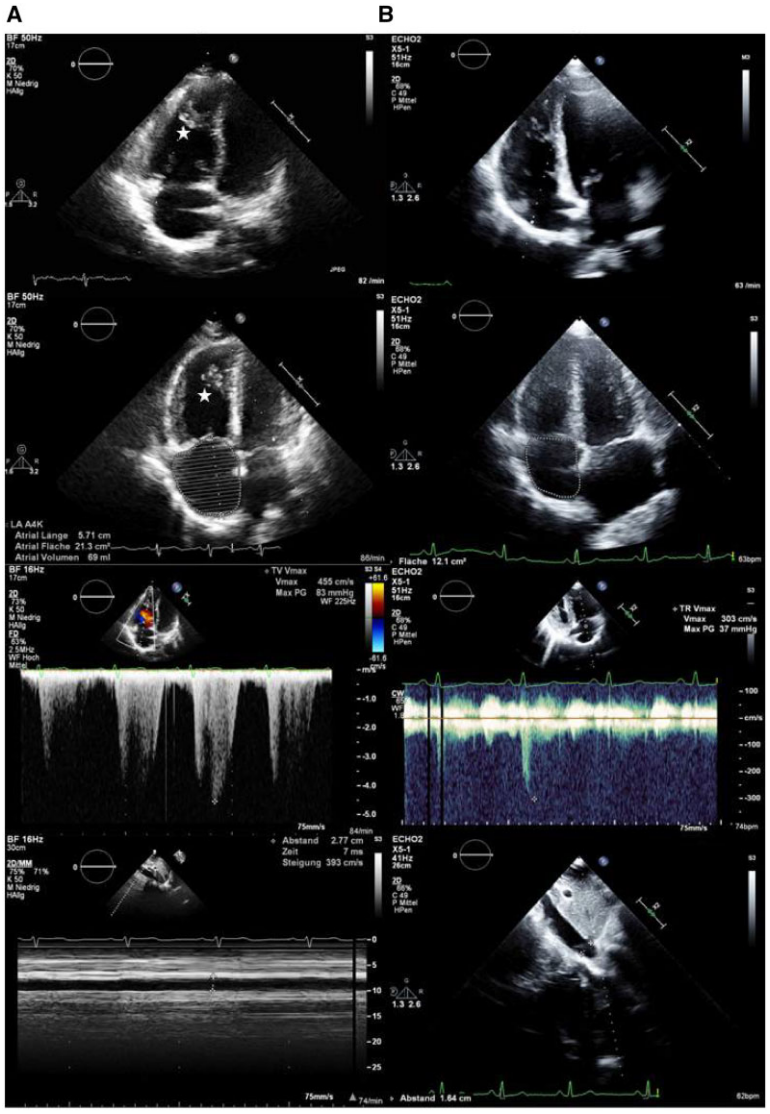


Figure 2 Transthoracic echocardiogram with echo studies before treatment initiation (column A) and after treatment initiation with calcium channel blocker and endothelin receptor antagonist (column B). First row showing right ventricle size, 2nd row showing right atrium size, 3rd row showing the gradient derived from maximum velocity of tricuspid regurgitation for estimation of systolic PA pressure (note that in 3B transducer orientation is rotated 180 degree showing right ventricle on the right side), 4th row showing the size of the inferior caval vein. ★: Prominent moderator band in the right ventricle.

Table 1 Laboratory values and echocardiographic parameters before and during the different stages of specific pulmonary artery hypertension therapy

Value	Before treatment	ERA+ PDE-5i	CCB+ERA
BNP in pg/mL	287	31	25
Creatinine in µmol/L	45	62	58
eGFR in mL/min	122.5	109.5	111.9
Bilirubin in µmol/L	40	27	23
LVEF in %	62	70	62
LVEDd in mm	41	38	45
RVEDd in mm	56	48	38
TAPSE in mm	19	17	26
TDI-Ś in cm/s	10.0	12.0	14
RAA in cm^2	21.3	15	11.5
ICV in mm	28	18	17
TR-PPG in mmHg	83	56	40

BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; ICV, inferior caval vein; LVEDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; RAA, right atrial area; RVEDd, right ventricular end-diastolic diameter (basal); TAPSE, tricuspid annular plane systolic excursion; TDI-Ś, tissue Doppler velocity of the tricuspid annulus; TR-PPG, tricuspid regurgitation peak pressure gradient.

Table 2 Right heart catheterization

Value	Before treatment	ERA+ PDE-5i	CCB+ERA
CI in $mL/min/m^2$	2.7	3.2	8.2
sPAP in mmHg	108	86	41
mPAP in mmHg	66	51	25
dPAP in mmHg	40	24	11
SVR in $dyn*s/cm^5$	1718	1075	430
PVR in $dyn*s/cm^5$	608	497	106
PCWP in mmHg	35	5	5
LVEDP in mmHg	16	—	—
SvO^2 in %	60	77	84

CI, cardiac index; dPAP, diastolic pulmonary artery pressure; LVEDP, left ventricular end diastolic pressure; mPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; sPAP, systolic pulmonary artery pressure; SvO^2, central venous oxygen saturation; SVR, systemic vascular resistance.

diagnosis. Pulmonary hypertension can be suspected in the presence of pre-capillary PH, defined by a pulmonary artery wedge pressure (PAWP) ≤15 mmHg and a pulmonary vascular resistance (PVR) above 3 Wood units in the absence of other causes of pre-capillary PH. Pulmonary hypertension is diagnosed by ruling out other causes of PH.[5] Since its poor prognosis meticulous diagnostic workup as well as a comprehensive prognostic evaluation and risk assessment are paramount to charting the therapeutic course.[8]

When the diagnosis of PAH is made, vasodilator testing should be performed to identify patients who might be available for successful treatment with CCB. Vasodilator testing is recommended for patients with drug-induced, idiopathic, or hereditary PAH as responders are very rare in all other forms and testing can produce misleading results.[5] A vasoresponder is defined as a reduction of mPAP ≥10 to reach an absolute value of ≤40 mmHg with an increased or unchanged cardiac index.

Right heart catheterization plays a pivotal role in diagnosing PAH and guiding therapy. However, there are pitfalls as can be displayed in our case as PAWP and LVEDP were elevated at the time of diagnosis, formally hinting to left heart disease as an origin of PH. Pregnancy can lead to increased values of both due to the increase in circulatory volume.[9] Also PCWP might be falsely elevated as the discrepancy to the only slightly elevated LVEDP was significant, showing the importance of LHC in case of inconclusive PCWP values. Since the result was possibly misleading and pointing towards PH Class II, we decided to postpone VT in this patient to reduce risk and avoid misinterpretation even though not standard of care at our institution.[10]

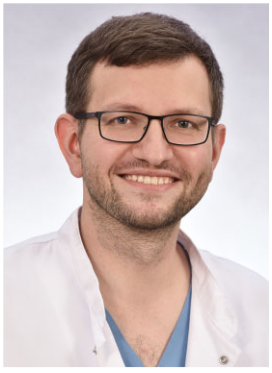
Situations which cause large fluid shifts or changes in haemodynamic (such as pregnancy, trauma, sepsis, or operation) are associated with a high mortality in PAH patients and can worsen the underlying disease or exacerbate a to this point clinical silent and untreated condition. These women are at especially high risk probably due to the late initiation of specific PAH therapy.[11] For patients with PAH, the risk of mortality conferred by right heart failure is particularly high during labour, delivery, and in the post-partum period, reflecting the volume changes that occur during these stages.[12] The vast changes in immunity and innate immune response during pregnancy might also contribute to the progression or manifestation of PAH in pregnant women.[13] When it comes to medical treatment of pregnant women with PAH data is generally scarce even though successful PAH targeted therapy has been described quite frequently.[14] Due to possible teratogenic effects, soluble Guanylate Cyclase stimulators and ERAs are discouraged. For PDE5-i such as Sildenafil reports of successful treatment during pregnancy mostly in combination with prostaglandins exist.[15] However, one still might question the choice of treatment in the presented case due to initiation of therapy before the diagnosis of PAH was formally established. Thus, the choice of therapy in this case was out of guidelines and owed to the rapid progression of clinical symptoms and fear of harm to the unborn child. Still one might argue about the course of action. In general, RHC should be performed before initiating targeted therapy. Other therapeutic options such as prostaglandins should be considered if targeted therapy is indicated. Furthermore, the compatibility of the chosen drug during breastfeeding should be taken into account as Macitentan or other ERA are not recommended. However, the patient in this case was not breastfeeding her child.

Conclusion

Pulmonary hypertension is a rare disease with unspecific symptoms and associated with a high mortality especially in pregnant women. Even though diagnosis and treatment can be complex and challenging,

a dedicated interdisciplinary team approach is key to ensure the best outcome for mother and child alike.

Lead author biography



Dr Julian Georg Westphal graduated from the Friedrich-Schiller-University of Jena in 2015. He is currently a research fellow of cardiology at the University Hospital Jena with special interest in heart failure and pulmonary hypertension.

Supplementary material

Supplementary material is available at *European Heart Journal—Case Reports online*.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidance.

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