Pulmonary hypertension (PH) is a frequent complication and one of the leading causes of mortality in patients with hemolytic disorders. The pathophysiology of PH in hemoglobinopathies is multifactorial including chronic tissue hypoxia, high cardiac output, hemolysis, hypercoagulopathy, splenectomy, iron overload and chronic lung injury. Chronic hemolytic anaemias have been included in group 1–pulmonary arterial hypertension (PAH) in the updated clinical classification of PH (Dana Point, 2008). Although the efficacy of the PAH-specific therapy has been established in group 1, its role in patients with hemoglobinopathies remains unclear. Most data regarding the use of the PAH-specific therapy in this patient population come from studies in patients with sickle cell disease, while the relevant data in thalassemic patients are very limited. The pathophysiology of PH in hemoglobinopathies is multifactorial including chronic tissue hypoxia, high cardiac output, hemolysis, hypercoagulopathy, splenectomy, iron overload and chronic lung injury.

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### Treatment with bosentan in a patient with thalassemia intermedia and pulmonary arterial hypertension

A 46-year-old female with TI, diagnosed at 10 years of age, presented to the Attikon University Hospital PH clinic with an 8-month history of progressive shortness of breath on exertion. In the past, she had mild symptoms and was independent from transfusions until 40 years of age, when she underwent splenectomy and started receiving occasional blood transfusions. At that time prophylactic anticoagulation therapy was initiated. Three years later, at 43 years of age, the patient started a program of regular blood transfusions (2 units of packed red blood cells per month) and iron chelation therapy that continued without change over the next 3 years maintaining stable hemoglobin levels (9-10 g/dL). She never received hydroxyurea therapy. No thrombotic event was ever diagnosed.

On presentation, she was in functional class III, her 6-minute-walk-test was 480 m and plasma NT-proBNP level was at 235 pg/mL. Transthoracic echocardiography revealed a tricuspid regurgitant jet velocity of 4.6 m/s, and left ventricular ejection fraction of 55%. PVR was 3.6 units. Svo2 % was 61.6.

| Table 1. Patient’s data before and 1 year after treatment with bosentan |
|--------------------------|--------------------------|
| Hemoglobin, g/dL | Baseline | 1 y follow-up |
| 10 | 9.8 | |
| Hematocit (%) | 31 | 30.5 |
| Fetal hemoglobin (%) | 5.8 | N/A |
| Transfusions, units of PRBC/mo | 2 | 2 |
| Lactate dehydrogenase, U/L | 302 | 259 |
| Aspartate aminotransferase, U/L | 14 | 31 |
| Alanine aminotransferase, U/L | 15 | 21 |
| Alkaline phosphatase, U/L | 47 | 62 |
| Total Bilirubin, mg/dL | 2 | 1.9 |
| Direct Bilirubin, mg/dL | 0.5 | 0.5 |
| Ferritin, ng/mL | 927 | 808 |
| NT-pro BNP, pg/mL | 235 | 225 |
| NYHA class | III | II |
| 6 MWT, m | 480 | 625 |
| RAP, mmHg | 1 | 1 |
| PAP(S/D,M), mmHg | 45/24/31 | 37/14/22 |
| PCWP, mmHg | 6 | 3 |
| CO, L/min | 6.9 | 6 |
| CI, L/min/m² | 4.4 | 3.8 |
| PVR, wood units | 3.6 | 3.2 |
| Svo2 % | 61 | 60 |

The starting dose of bosentan was 62.5 mg twice daily and increased after 4 weeks to 125 mg twice daily.

### Conflict-of-interest disclosure
The authors declare no competing financial interests.

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### References
70%. Pulmonary function testing and gas exchange were normal. A subtle mosaic pattern limited to the lower-posterior parts of the lower lobes was the only finding at the high-resolution computerized tomography (CT) of the lungs. The perfusion lung scan showed patchy defects in both lungs and a CT pulmonary angiography revealed enlarged main, right and left pulmonary arteries without signs of intraluminal thrombosis. Cardiac MRI revealed a D-shaped left ventricle and there was no evidence of iron overload. The patient underwent a RHC that confirmed the presence of pre-capillary PH (mean pulmonary artery pressure: 31 mmHg, pulmonary capillary wedge pressure: 6 mmHg).

Based on the patient’s symptoms, hemodynamic confirmation of pre-capillary PH and the absence of left heart disease or operable pulmonary thromboembolic disease, the use of PAH-specific therapy was considered and the patient was started on oral bosentan. Hematologic-biochemical monitoring during 12 months of treatment was without significant change from the baseline measurements, and therapy was well tolerated. Moreover, the transfusion requirements remained unchanged throughout the study period. Patient’s data before and 1 year after initiation of therapy including the effects of treatment on the functional capacity and invasive hemodynamics are shown in Table 1.

We believe that the positive response to therapy was partly because of the clear hemodynamic characterization before any specific therapeutic consideration targeting PAH. Patients with hemoglobinopathies have significant reduction in exercise capacity despite mild to moderate pulmonary hypertension,12 thus the substantial improvement of functional capacity in this case, while not leading to conclusions, highlights the need for further studies in symptomatic patients with hemoglobinopathies and PAH confirmed by RHC.

References

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